European
Thyroid Journal

36TH ANNUAL MEETING
OF THE EUROPEAN
THYROID ASSOCIATION
PISA / CONGRESS PALACE
8/12 SEPTEMBER 2012

36th Annual Meeting of the European Thyroid Association

Programme

Pisa, Italy, September 8–12, 2012

Guest Editors
Theo Visser, Rotterdam, The Netherlands
Paolo Vitti, Pisa, Italy

KARGER
Basel · Freiburg · Paris · London · New York · New Delhi · Bangkok ·
Beijing · Tokyo · Kuala Lumpur · Singapore · Sydney

The Executive Committee of the ETA and the Local Organising Committee would like to thank the following companies for their generous support of the 36th Annual Meeting

S. Karger
Medical and Scientific Publishers
Basel · Freiburg · Paris · London · New York · New Delhi · Bangkok · Beijing · Tokyo · Kuala Lumpur · Singapore · Sydney

Published by S. Karger AG,
P.O. Box, CH–4009 Basel (Switzerland)
ISBN 978–3–318–02222–3
e-ISBN 978–3–318–02223–0

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

European
Thyroid Journal

Vol. 1, Suppl. 1, 2012

Contents

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Published by S. Karger AG, Basel
Access to full text and tables of contents,
including tentative ones for forthcoming issues:
www.karger.com/etj_issues

Scientific and Organizing Committees

Executive Committee of the ETA
Theo Visser (The Netherlands) – President
Luigi Bartalena (Italy) – Secretary
George J. Kahaly (Germany) – Treasurer

Maria Alevizaki (Greece)
Ana Aranda (Spain)
Laurence Leenhardt (France)
Simon Pearce (UK)
Robin Peeters (The Netherlands)
Agnieszka Piekielko-Witkowska (Poland)
Kris Poppe (Belgium)
Mariastella Zannini (Italy)

Local Organizing Committee
Honorary Chair
Aldo Pinchera
Enio Martino

Chair
Paolo Vitti

Members
Claudio Marcocci
Fabrizio Aghini Lombardi
Fulvio Basolo
Fausto Bogazzi
Claudia Ceccarelli
Rossella Elisei
Claudio Giani
Lucia Grasso
Ferrucio Santini
Massimo Tonacchera

ETA Standing Office
EndoScience Endokrinologie Service GmbH
Contact: Sandra Crutchley
Hopfengartenweg 19
90518 Altdorf b. Nürnberg
Germany
tel.: +49 (0) 9187-9742415
fax: +49 (0) 9187-9742475
euro-thyroid-assoc@endoscience.de

Local Conference Agency
DGMP Group
Via A. Gozzini, 4
56121 PISA
tel.: (+39) 050 989 310
fax: (+39) 050 981 264
info@dgmp.it
info@dgmpviaggi.it

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Published by S. Karger AG, Basel

Accessible online at:
www.karger.com/etj

European
Thyroid Journal

DOI: 10.1159/000341428

Published online: August 15, 2012

A Warm Welcome to the ETA Annual Meeting in the Wonderful City of Pisa

The 36th Annual Meeting of the European Thyroid Association will be held on September 8–12, 2012 at the Congress Palace in Pisa. At this meeting, the latest developments in the various areas of clinical, basic and translational thyroidology will be presented by internationally renowned researchers. In the afternoon of Saturday, September 8, the annual meeting will be kicked off by Reed Larsen, who will give the European Thyroid Journal Lecture. The meeting will last five days and include a mid-conference field trip.

Keynote speeches and oral presentations by young researchers will be given in the mornings and late afternoons, while the midday hours will be dedicated to poster sessions in which many participants will present their latest research. Several symposia will be held to present an excellent opportunity to learn about major developments in many clinical and basic areas. As the Web continues to expand, making scientific exchange a real-time daily activity, direct contact among researchers remains an irreplaceable need for strengthening the scientific community.

Three satellite conferences will precede the opening of the congress on Saturday: (1) the ICCIDD West Central Europe Regional Meeting, (2) the joint session of European Thyroid Association-Cancer Research Network and European Society of Endocrine Surgeons, and (3) an Italian symposium 'Update in Endocrinology', which will focus on the treatment of Cushing's disease and acromegaly. In addition, a thyroid ultrasound course will be held at the Department of Endocrinology of the University Hospital in Pisa.

Pisa welcomes its visitors with art, cultural events and, of course, the Leaning Tower. The Leaning Tower, however, is not the only unique point of interest Pisa has to offer, as there are many beautiful sites that deserve a visit, including just taking a walk along the historic and picturesque streets. In attending the meeting, you will have the opportunity to enjoy the beauties and spirit of Tuscany during one of the most beautiful times of the year. We have arranged several tours that will allow you to discover and appreciate Pisa.

The welcome reception will take place at the Stazione Leopolda, which was one of the first railway stations built in Italy. It is a large neo-Renaissance building designed by the architect Enrico Presenti, and is named after the Habsburg-Lorraine Grand Duke Leopold II of Tuscany, who built it in 1844.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/etj

The meeting excursion will allow you to visit the enchanting Charter House of Calci. The monumental Monastery of Calci (Certosa di Calci), just 10 km from Pisa, was founded in 1366 by Carthusian monks. It is today one of the most interesting national museums, exhibiting ancient mineralogical, palaeontological and zoological collections, with some pieces dating back to the 16th century.

The gala dinner will be held at the Cloister of the National Museum of San Matteo, one of the most important European museums in the field of medieval art. It hosts numerous masterpieces of paintings and sculptures from the early Middle Ages, as well as archaeological and ceramic treasures.

We feel sure that ETA 2012 will be a scientifically successful meeting in the friendly and welcoming city of Pisa. We look forward to seeing you here in September 2012.

Paolo Vitti
Chair of the Local
Organizing Committee

Theo Visser
President of the ETA

Registration Information

Main Conference Fees

Membership status	before 5th July	6th July – 31st August	on site
Ordinary and Senior	150 €	175 €	200 €
Junior <35 yrs	60 €	80 €	100 €
Corresponding	250 €	300 €	350 €
Non-Member	500 €	550 €	600 €
Student /Res. fellow <30 yrs	125 €	160 €	200 €
Accompanying Person	30 €	40 €	50 €

Pre-Conference Events Fees

ETA-CRN and ESES Meeting	50 €
ICCIDD	40 €
Ultrasonography Course	150 €

Social Programme

8th Sept. Welcome Reception	free for registered participants and registered accompanying persons
10th Sept. ETA Excursion to Calci Chaterhouse	50 €
11th Sept. Gala Dinner	80 €

Day Tickets (only available on site)
Saturday: 100 €
Sunday, Monday, Tuesday: 150 € per day
Wednesday: 75 €

Main Conference Registration Entitlements

Delegate registration includes:
– Access to all congress sessions and commercial exhibition
– All congress materials and a name badge
– Programme and Abstract Book
– Refreshment breaks during the congress
– Welcome Reception

Registration does not include:
– Accommodation, tickets to the social events (unless stated) or optional excursions

Accompanying person registration includes:
– Name badge
– Welcome Reception
– Access to the lecture halls and commercial exhibition is not included!

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Published by S. Karger AG, Basel

Accessible online at:
www.karger.com/etj

Pre-Conference Registration Entitlements

ETA-CRN, ICCIDD and Ultrasonography Course
Admission to the Scientific Sessions, congress material, lunch and coffee breaks

On-Site Registration / Secretariat Desk / Membership Information

The Congress Registration Desk will be located in the entrance area of the Congress Centre and will operate the following hours:

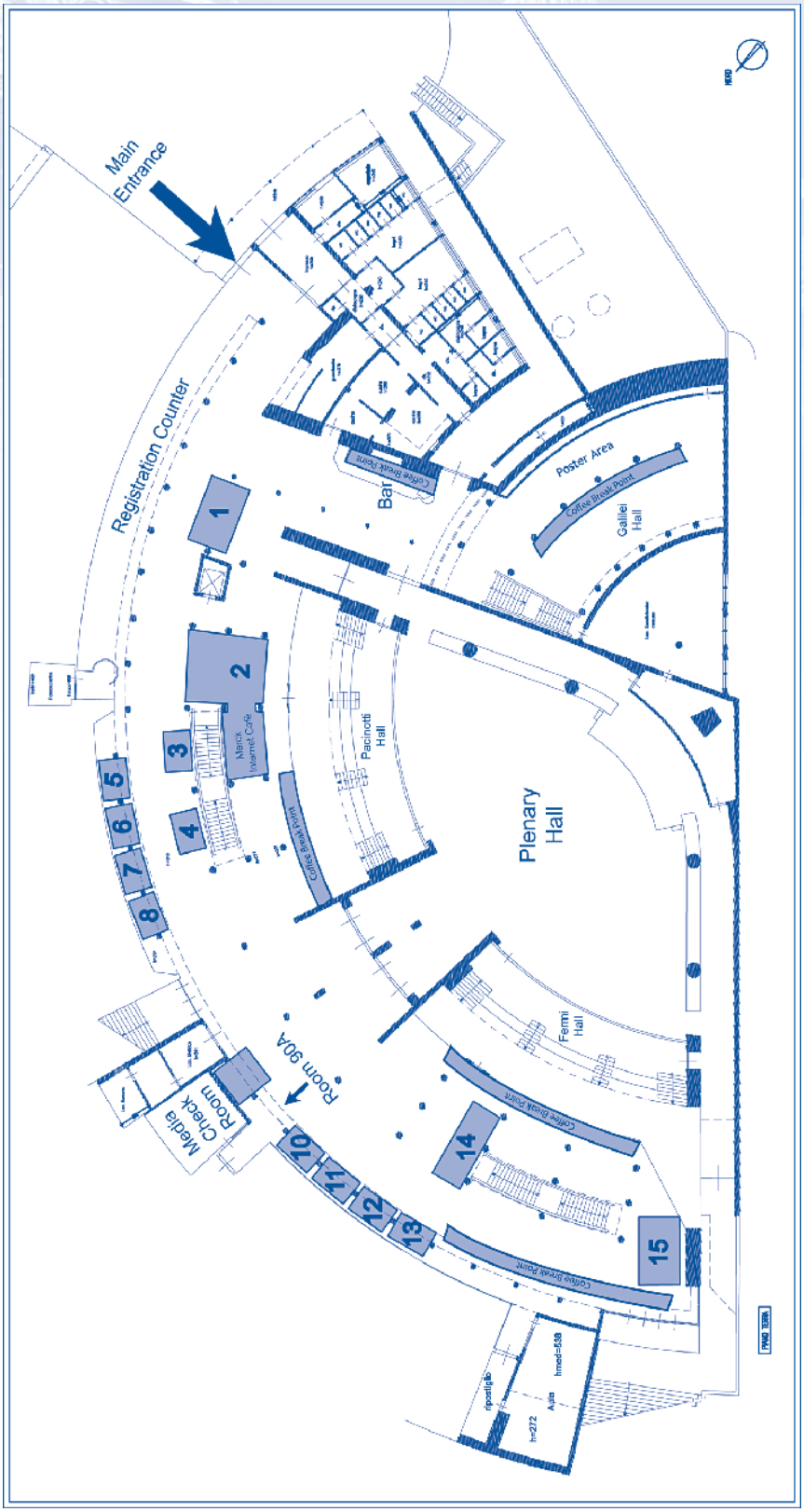
Saturday	8th September	07.30–19.00
Sunday	9th September	07.30–19.00
Monday	10th September	07.30–16.30
Tuesday	11th September	07.30–18.30
Wednesday	12th September	07.30–13.00

ETA Commercial Exhibition Opening Hours

The commercial exhibition will commence on Sunday, 9th September and finish on Tuesday, 11th September.

Set-up:	Friday, 7th September	13.00–20.00
Preliminary opening times:	Saturday, 8th September	08.30–18.00
	Sunday, 9th September	08.30–18.00
	Monday 10th September	08.30–16.00
	Tuesday, 11th September	08.30–18.00
Break-down:	Tuesday, 11th September	18.00–22.00

Ground Floor and Exhibition Plan



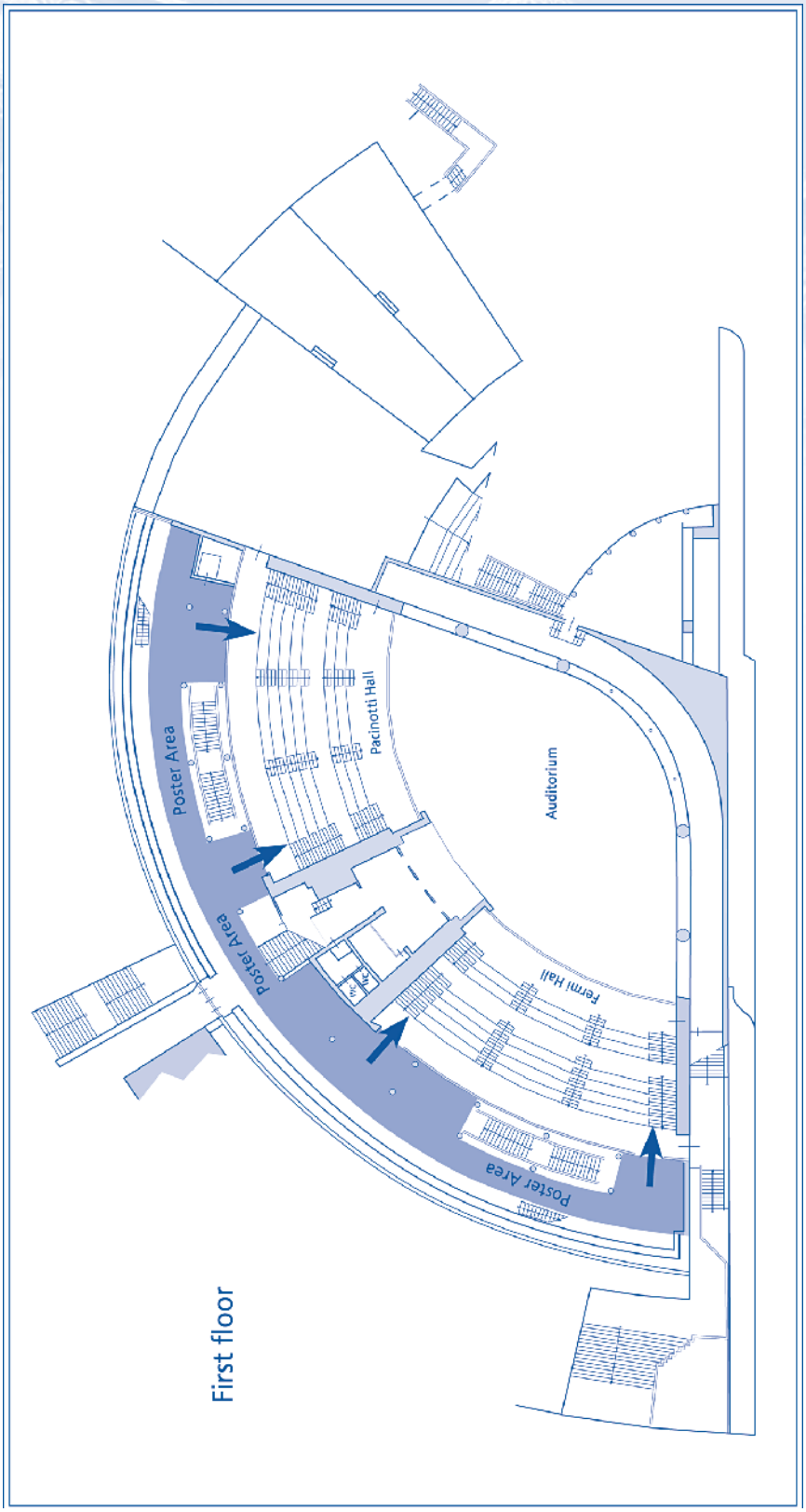
List of Exhibitors in alphabetical order	Booth no.
AstraZeneca Europe	15
DEKA srl	4
Endocrine Education Inc.	11
Esaote S.p.A.	5
Genzyme Europe	3
IBSA Institut Biochimique SA	1
Inomed Medizintechnik GmbH	10
KARGER	8
Merck Serono	2
Oxigene, Inc. (Hospitality Desk)	6
Pantec srl	7
ThermoFisher	14
Thyroid Cancer Alliance	13
Thyroid Federation International	12

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/etj

European
Thyroid Journal

First Floor Plan



KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/etj

Saturday, 8th September 2012

Main Auditorium
08.00–14.15

ETA-CRN and ESES Meeting

A joint session of the European Thyroid Association-Cancer Research Network and the European Society of Endocrine Surgeons

Department of Endocrinology, Building 8
Main Hall, Ground Floor, Via Paradisa 2
Cisanello Hospital, Pisa
08.15–15.15

Thyroid Ultrasound and Ultrasound-Assisted Procedures Satellite Meeting

Fermi Hall
08.30–16.00

ICCIDD West-Central Europe Regional Meeting

Pacinotti Hall
12.00–13.00

TFI Patient Forum

Thyroid hormone replacement therapy and quality of life
Rossella Elisei, Italy

Thyroid nodules: an epidemic disease
Laura Fugazzola, Italy

Pacinotti Hall
14.00–15.30

ETA 2012 Italian Satellite Symposium 'Update in Endocrinology'

Chairs: *Enio Martino, Marco Boscaro*

Update in Cushing

14.00–14.30 Medical treatment of Cushing's disease
Rosario Pivonello

14.30–15.00 Cushing's syndrome: a rare disease or an underdiagnosed disease?
Giorgio Arnaldi

Update in Acromegaly

15.00–15.30 Update in Acromegaly
Paola Razzore

Published by S. Karger AG, Basel

Accessible online at:
www.karger.com/etj

ETA-CRN and ESES Meeting

A joint session of the European Thyroid Association-Cancer Research Network and the European Society of Endocrine Surgeons

Unresolved questions in thyroidology:

1. Suspicion of follicular neoplasm:
   how does the Bethesda NIH reporting system of thyroid cytology results change our clinical praxis?
2. Prophylactic neck dissection in thyroid cancer:
   a beneficial surgical intervention or unnecessary burden for patients?
3. Follow up of TgAb-positive patients with thyroid carcinoma

ETA-CRN
President: *Ulla Feldt-Rasmussen*, National University Hospital, Copenhagen, DK
Secretary: *Barbara Jarząb*, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
Treasurer: *Georg Brabant*, The University of Lübeck, Germany

ESES
President: *Jean-Françoise Henry*, University Hospital La Timone, Marseille, France
Past President: *Henning Dralle*, Martin-Luther-University, Halle-Wittenberg, Germany
President Elect: *Bruno Niederle*, Medical University of Vienna, Austria
Secretary: *Jean-Louis Kraimps*, University Hospital, Poitiers, France
Treasurer: *Frederic Triponez*, University Hospital of Geneva, Switzerland

08.00–09.00	Coffee and Registration
09:00 - 09:05	Presidential ETA-CRN and ESES addresses
09:05	Bethesda NIH system in the view of European pathologist *Fulvio Basolo,* Pisa, Italy
09:30	How can molecular FNA diagnostics resolve some of the inherent limitations of thyroid FNA cytology? *Ralf Paschke,* Leipzig, Germany
10:05	TSH serum level and the risk of malignancy in follicular thyroid neoplasm *Georg Brabant,* Luebeck, Germany
10:20	Biology of follicular thyroid cancer *Rossella Elisei,* Pisa, Italy
10:50 - 11:10	Coffee break
11:10	Thyroid surgeon faced with the cytological diagnosis 'suspicion of follicular neoplasm' *Paolo Miccoli,* Pisa, Italy
10:40	Long-term outcome of patients with papillary thyroid cancer lymph node metastases *Markus Luster,* Ulm, Germany
12:10	Prophylactic central neck dissection in papillary thyroid cancer – is there a balance between the benefit and the risk? *Marcin Barczynski,* Krakow, Poland
12:40	Follow-up of DTC patients with TgAbs – clinical point of view *Frederik Verburg,* Aachen, Germany
13:10	Follow up of DTC patients with TgAbs – laboratory point of view *Luca Giovanella,* Bellinzona, Switzerland
13:30 - 13:45	Discussion
13:45	ETA-CRN as a network to organize multicenter studies in thyroid cancer field *Barbara Jarzab, Ulla Feldt-Rasmussen*
14:00 - 14:15	Discussion

Thyroid Ultrasound and Ultrasound-Assisted Procedures Satellite Meeting on Thyroid US

Venue:
Department of Endocrinology, Building 8, Main Hall, Ground Floor, Via Paradisa 2, Cisanello Hospital, 56124 Pisa

08.15–08.30 Introduction
Paolo Vitti, Italy

Thyroid Ultrasound

08.30–08.45 Neck anatomy, basics of ultrasonography, how to perform neck ultrasonography
Murat Erdogan, Turkey

08.45 – 09.00 Thyroid nodules; Chair: *Paolo Vitti*
B mode US for thyroid nodule and Sonographic risk assessment of thyroid nodules, TIRADS classification
Jennifer A. Sipos, USA

09.00 – 09.15 Doppler sonography and elastography in thyroid nodules and thyroid-itis
Teresa Rago, Italy

09.15 – 09.30 Ultrasonography in the follow up of thyroid cancer, neck lymph nodes, thyroid bed
Laurence Leenhardt, France

Live Session N°1

09.30 – 11.00 Case illustrations on volunteers. Questions and answers with real-time projection of the ultrasound examination.
All discussants (*Murat Erdogan, Laurence Leenhardt, Enrico Papini, Teresa Rago, Gilles Russ, Jennifer A. Sipos, Paolo Vitti*)

Take Home Messages N°1

11.00 -11.15 Students/senior (15 min)

11.15 – 11.30 Coffee Break

11.30 – 11.45 Fine needle aspiration biopsy (FNAB) and ultrasonography guidance
Enrico Papini, Italy

11.45–12.00 Mini-invasive treatment procedure (PEI and Thermal ablation for benign lesions)
Claudio Pacella, Italy

12.00 -12.15 Questions

12.15–13.15 Session in live FNA laser ablation
Teresa Rago, Italy

13.15 – 14.00 Lunch

Live Session N°2

14.00 – 15.00 Live session : 'Hands on US'

Conclusion

ICCIDD West-Central Europe Regional Meeting

Fermi Hall
08.30–16.00

08.30–09.00	Registration
09.00–09.10	Welcome address *Aldo Pinchera* (ICCIDD Regional Coordinator)
09.10–09.20	Introduction *Gerard Burrow* (ICCIDD Chairman) *Michael Zimmermann* (ICCIDD Executive Director)

Scientific Symposium
Section 1

Chairs: *Peter Laurberg* (Denmark)
Gerard Burrow (USA)

09.20–09.35	Global iodine status and trends over the past decade *Maria Andersson* (Switzerland)
09.35–09.40	Discussion
09.40–09.55	Iodine nutrition and pregnancy *Francesco Vermiglio* (Italy)
09.55–10.00	Discussion
10.00–10.15	Thyroid function and pregnancy *John Lazarus* (UK)
10.15–10.20	Discussion
10.25–10.45	Coffee break

Section 2

Chairs: *Leonidas Duntas* (Greece)
Michael Zimmermann (Switzerland)

10.40–10.55	Iodine intake, environment and risk for thyroid diseases: goiter, autoimmunity *Nils Knudsen* (Denmark)
10.55–11.00	Discussion
11.00–11.15	Alternative methods to USI *Massimo Tonacchera* (Italy)
11.15–11.20	Discussion
11.20–11.35	Iodine in the environment: release of gaseous iodine from seaweeds *Peter Smyth* (Ireland)
11.35–11.40	Discussion
11.45–12.30	Lunch and Poster Vision

Iodine Nutrition Status in West Central Europe: An Update on Iodine Prophylaxis

Chairs: *Gregory Gerasimov* (Russia)
Aldo Pinchera (Italy)

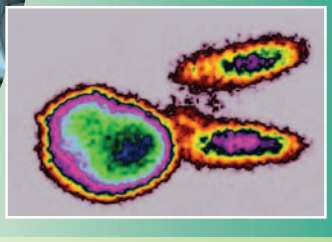
12.30–12.40	Introduction *Aldo Pinchera* (ICCIDD West Central Europe Regional Coordinator), *Gregory Gerasimov* (ICCIDD Eastern Europe Regional Coordinator)
12.40–14.10	Presentation of country data ICCIDD National Representatives
Section 1	Albania – *Argon Ylli* Belgium – *Rodrigo Moreno-Reyes* Bosnia Herzegovina – *Jasminka Mujkic* Bulgaria – *Roussanka Kovatcheva* Croatia – *Zvonko Kusic* Czech Republic – *Václav Zamrazil* Denmark – *Peter Laurberg* Estonia – *Toomas Podar* Finland – *Georg Alfthan* France – *Philippe Caron* Germany – *Henry Völzke* Greece – *Kostas B. Markou* Hungary – *Endre V. Nagy* Ireland – *Peter Smyth* Italy – *Fabrizio Aghini-Lombardi* Latvia – *Valdis Pirags*
14.10–15.40	Presentation of country data: continuation ICCIDD National Representatives
Section 2	Luxemburg – *Yolande Wageneer* Lithuania – *Albertas Barzda* Macedonia – *Karafilski Borislav* Netherlands – *Robin Peeters* N. Cyprus – *Hasan Sav* Poland – *Zbigniew Szybiński* Portugal – *Edward Limbert* Romania – *Mihaela Simescu* Serbia – *Tanja Knezevic* Slovakia – *Jan Podoba* Slovenia – *Sergej Hojker* Spain – *Lluis Vila* Sweden – *Mehari Gebre-Medhin* Switzerland – *Hans Bürgi* Turkey – *Murat Faik Erdoğan* United Kingdom – *John Lazarus*
15.40–16.00	Discussion and Conclusions
16.00	Closure

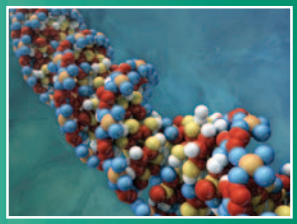
For further details contact: iccidd@endoc.med.unipi.it

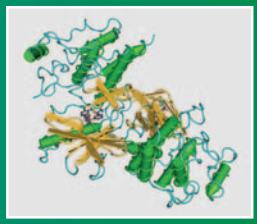
A satellite symposium held during the 36th Annual Meeting of the European Thyroid Association, Pisa, Italy

Recent Progress and Unmet Need in Differentiated Thyroid Cancer (DTC): Role of Targeted Therapies

Program Host and Moderator:
Rossella Elisei, MD







Saturday, 8 September 2012
16.00 – 18.00

Main Auditorium
(Plenary Hall)
Palazzo dei Congressi
Pisa, Italy

Snacks and refreshments will be provided at 15.45

Agenda

16.00 **Welcome and Introduction**
Rossella Elisei, MD
University of Pisa, Italy

16.10 **Advanced DTC and Unmet Medical Need**
Martin Schlumberger, MD
Institut Gustave Roussy
Villejuif, France

16.30 **Molecular Pathogenesis of Thyroid Cancer: A Rationale for Multikinase Inhibition**
Furio Pacini, MD
University of Siena, Italy

16.50 **Targeted Therapies in DTC: Clinical Development and Current Treatment Landscape**
Marcia Brose, MD, PhD
University of Pennsylvania
Philadelphia, United States

17.20 **Identifying the Patient Profile for Targeted Therapies in DTC: The RAI-Refractory Patient**
Rossella Elisei, MD (Moderator)
Marcia Brose, MD, PhD
Furio Pacini, MD
Martin Schlumberger, MD

17.55 **Summary and Conclusion**
Martin Schlumberger, MD

Bayer HealthCare

Supported by Bayer HealthCare

G.SM.ON.06.2012.0435

Saturday, 8th September 2012

Main Auditorium
16.00–18.00

Bayer HealthCare Satellite Symposium

Recent Progress and Unmet Need in Differentiated Thyroid Cancer (DTC): Role of Targeted Therapies

Program Host and Moderator: *Rossella Elisei*, Italy

16.00 Welcome and Introduction
Rossella Elisei

16.10 Advanced DTC and Unmet Medical Need
Martin Schlumberger, France

16.30 Molecular Pathogenesis of Thyroid Cancer: A Rationale for Multikinase Inhibition
Furio Pacini, Italy

16.50 Targeted Therapies in DTC: Clinical Development and Current Treatment Landscape
Marcia Brose, USA

17.20 Identifying the Patient Profile for Targeted Therapies in DTC: The RAI-Refractory Patient
Rossella Elisei, Marcia Brose, Furio Pacini, Martin Schlumberger

17.55 Summary and Conclusion
Martin Schlumberger

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Published by S. Karger AG, Basel

Accessible online at:
www.karger.com/etj

Main Auditorium
18.00–18.15

Opening Ceremony

Welcome by *Theo Visser* and *Paolo Vitti*

Main Auditorium
18.15–19.00

The European Thyroid Journal Lecture

Chair: *Wilmar M. Wiersinga,* The Netherlands
Editor-in-Chief of the European Thyroid Journal

The role of the iodothyronine deiodinases in thyroid physiology
P. Reed Larsen, USA

19.30

Welcome Reception at the Leopolda Station

Sunday, 9th September 2012

Main Auditorium and Fermi Hall
08.00–10.00

Oral Session 1: Topic Highlights (OP01–OP06)

Chairs: *Theo Visser* (The Netherlands)
Paolo Vitti (Italy)

08.00–08.20
OP1 **CLINICAL AND BIOCHEMICAL ACTIVITY IN THE EXAM TRIAL, A PHASE 3 STUDY OF CABOZANTINIB (XL184) IN PATIENTS WITH HEREDITARY AND NON-HEREDITARY MEDULLARY THYROID CARCINOMA (MTC)**

Elisei R[1], Mueller S[2], Schöffski P[3], Brose M[4], Shah M[5], Licitra L[6], Jarzab B[7], Medvedev V[8], Kreissl MC[9], Niederle B[10], Cohen E[11], Wirth L[12], Ali H[13], Clary D[14], Mangeshkar M[14], Ball D[15], Nelkin B[15], Sherman S[16], Schlumberger M[17]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy, [2]University Hospital of Essen, Essen, Germany, [3]UZ Leuven, Leuven, Belgium, [4]University of Pennsylvania Health System, Philadelphia, United States, [5]Ohio State University Medical Center, Columbus, United States, [6]Istituto Nazionale dei Tumori, Milano, Italy, [7]Centrum Onkology, Instytut im. M. Sklodowskiej-Curie oddzial w Gliwicach, Gliwicach, Poland, [8]Medical Radiology Research Center of RAMS, Obnisk, Russian Federation, [9]University Hospital of Wuerzburg, Wuerzburg, Germany, [10]Medical University of Vienna, Vienna, Austria, [11]University of Chicago Medical Center, Chicago, United States, [12]Massachusetts General Hospital, Boston, United States, [13]Henry Ford Health System, Detroit, United States, [14]Exelixis, South San Francisco, United States, [15]John Hopkins Hospital and Health System, Baltimore, United States, [16]MD Anderson Cancer Center, Houston, United States, [17]Institut Gustave Roussy, Paris, France

08.20–08.40
OP02 **EFFICACY AND SAFETY OF THREE DIFFERENT CUMULATIVE DOSES OF INTRAVENOUS METHYLPREDNISOLONE FOR MODERATE-TO-SEVERE AND ACTIVE GRAVES' ORBITOPATHY (GO): A MULTICENTER, RANDOMIZED, DOUBLE-BLIND CLINICAL STUDY OF 159 PATIENTS**

Bartalena L[1], Krassas G[2], Wiersinga WM[3], Marcocci C[4], Salvi M[5], Daumerie C[6], Bournaud C[7], Stahl M[8], Sassi L[1], Veronesi G[9], Azzolini C[10], Boboridis KG[11], Mourits MP[12], Soeters MR[3], Baldeschi L[12], Nardi M[13], Currò N[14], Boschi A[15], Bernard M[16], von Arx G[17], European Group on Graves' Orbitopathy (EUGOGO)
[1]University of Insubria, Clinical & Experimental Medicine, Varese, Italy, [2]Panagia General Hospital, Endocrinology, Diabetes & Metabolism, Thessaloniki, Greece, [3]Academic Medical Center, Endocrinology & Metabolism, Amsterdam, Netherlands, [4]University of Pisa, Endocrinology & Metabolism, Pisa, Italy, [5]University of Milan, Medical Sciences, Milan, Italy, [6]Université catholique de Louvain, Internal Medicine, Brussels, Belgium, [7]GHE-Hospices Civils de Lyon and Lyon 1 University, Endocrinology & Nuclear Medicine, Lyon, France, [8]Kantonsspital, Endocrinology & Metabolism, Olten, Switzerland, [9]University of Insubria, Clinical & Experimental Medicine, Epidemiology & Preventive Medicine, Varese, Italy, [10]University of Insubria, Surgical & Morphological Sciences, Section of Ophthalmology, Varese, Italy, [11]Ahepa Hospital, Ophthalmology, Thessaloniki, Greece, [12]Academic Medical Center, Amsterdam, Netherlands, [13]University of Pisa, Neuroscience, Section of Ophthalmology, Pisa, Italy, [14]Ospedale Maggiore Policlinico, Ophthalmology, Milan, Italy, [15]Université Catholique de Louvain, Ophthalmology, Brussels, Belgium, [16]GHE-Hospices Civils de Lyon and Lyon 1 University, Neuro-Ophthalmology Outpatient Clinics, Lyon, France, [17]Interdisziplinaires Zentrum fur Endokrine Orbitopathie, Ophthalmology, Olten, Switzerland

08.40–09.00
OP03 **DEFECTIVE VASCULAR DEVELOPMENT IS ASSOCIATED WITH ABNORMAL THYROID ORGANOGENESIS IN ZEBRAFISH**

Opitz R[1], Maquet E1, Antonica F[1], Costagliola S[1]
[1]IRIBHM, Université Libre de Bruxelles, Brussels, Belgium

09.00–09.20
OP04 **IMPACT OF THE THYROCYTE-SELECTIVE INACTIVATION OF THE MEN1 GENE ON THE BASAL AND TSH-STMULATED GROWTH OF THE THYROID GLAND**

Selmi-Ruby S[1], Du Payrat J[1], D'orazio T[1], Bonnavion R[1], Zhang CX[1], Rousset B[1], Borson-Chazot F[1]
[1]CRCL Inserm U1052, Université Lyon 1, Faculté de Médecine RTH-Laennec, Lyon, France

09.20–09.40
OP05 **MYOCARDIAL INFARCTION INDUCES AN UNEXPECTED CARDIAC MICRORNA SIGNATURE OF PLURIPOTENCY, ASSOCIATED WITH IMPAIRED THYROID-HORMONE SIGNALING**

Janssen R[1], *Zuidwijk M*[1], *Mulders J*[2], *Muller A*[1], *Oudejand C*[2], *Simonides W*[1]
[1]Institute for Cardiovascular Research / VU University Medical Center, Department of Physiology, Amsterdam, The Netherlands, [2]VU University Medical Center, Department of Clinical Chemistry, Amsterdam, The Netherlands

09.40–10.00
OP06 **PROTEOMICS DIFFERENTIATE BETWEEN GRAVES' ORBITOPATHY AND DRY EYE SYNDROME - A PROSPECTIVE AND CONTROLLED STUDY**

Matheis N[1], *Grus FH*[2], *Knych I*[1], *Breitenfeld M*[1], *Kahaly GJ*[1]
[1]Gutenberg University Medical Center, Department of Medicine I, Mainz, Germany, [2]Gutenberg University Medical Center, Experimental Ophthalmology, Mainz, Germany

Main Auditorium and Fermi Hall
10.00–10.10

Lissitzky Career Award

The 2012 award is sponsored exclusively by Quidel Corporation, San Diego, CA, USA

Chairs: *Theo Visser* (The Netherlands)
Luigi Bartalena (Italy)

10.10–10.30 **Coffee break**

Pacinotti Hall
10.30–12.00

Symposium 1: Genetic Causes of Congenital Hypothyroidism

Chairs: *Roberto Di Lauro* (Italy)
Massimo Tonacchera (Italy)

10.30–11.00 Defects in thyroid development
Juliane Leger (France)

11.00–11.30 DUOXa2
Samuel Refetoff (USA)

11.30–12.00 DEHAL
Jose Moreno (Spain)

Main Auditorium and Fermi Hall
10.30–12.00

Symposium 2: Thyroid and Mental Health

Chairs: *Ulla Feldt-Rasmussen* (Denmark)
Stefano Mariotti (Italy)

10.30–11.00 Iodine and developmental outcomes
Michael Zimmermann (Switzerland)

11.00–11.30 Hypothyroidism and mental health
Colin Dayan (UK)

11.30–12.00 Hyperthyroidism and mental health
Torquil Watt (Denmark)

Poster Area
12.00–13.00

Lunch and Poster Discussion 1 (Posters 1–121)

Poster Session 1: MTC Basic and translational
Chair: *M. Chiara Zatelli* (Italy)

Poster Session 2: Thyroid Cancer Diagnostics Clinical 1
Chair: *Jean Louis Wemeau* (France)

Poster Session 3: Thyroid Cancer Pathogenesis Basic
Chair: *Martin Schlumberger* (France)

Poster Session 4: Thyroid Cancer Therapeutics Clinical 1
Chair: *Camilla Schalin-Jantti* (Finland)

Poster Session 5: Clinical Thyroid Autoimmunity 1
Chair: *Patrice Rodien* (France)

Poster Session 6: Thyroid hormone and the Cardiovascular System
Chair: *Fabio Monzani* (Italy)

Poster Session 7: Graves' Orbitopathy Clinical 1
Chair: *Petros Perros* (UK)

Poster Session 8: Hypothyroidism Clinical 1
Chair: *Peter Taylor* (UK)

Poster Session 9: Subclinical Thyroid Disease
Chair: *Valentin Fadeyev* (Russia)

Poster Session 10: Goiter and Nodular Disease Clinical 1
Chair: *Roland Gärtner* (Germany)

Poster Session 11: Imaging in Thyroidology
Chair: *Murat Erdogan* (Turkey)

Poster Session 12: Case Reports 1
Chair: *Istvan Szabolcs* (Hungary)

Poster Session 13: Thyroid Hormone Action 1
Chair: *Maria Jesus Obregon* (Spain)

Main Auditorium
13.00–14.00

genzyme
A SANOFI COMPANY

Genzyme Symposium
(Lunch boxes will be provided for symposium attendees)
Differentiated Thyroid Carcinoma: From the Lump to the Long Term Follow Up

13.00–13.05	Opening, Welcome and Introduction Chairs: *Furio Pacini* (Italy) *Martin Schlumberger* (France)
13.05–13.20	Nodular thyroid disease. Diagnostic strategies *Laszlo Hegedus* (Denmark)
13.20–13.35	Ablation of thyroid remnants: when and how? *Markus Luster* (Germany)
13.35–13.50	Long-term follow up of the thyroid cancer patient *Rossella Elisei* (Italy)
13.50–13.55	Discussion
13.55–14.00	Closing Remarks *Furio Pacini* and *Martin Schlumberger*

14.00–14.45
Meet the Expert 1–4

Room 90A
14.00–14.45 **MTE 1:** Alternative splicing of thyroid hormone pathway genes in cancer
Agnieszka Piekielko-Witkowska (Poland)

Fermi Hall
14.00–14.45 **MTE 2:** Stimulated calcitonin cut-offs by different tests
Laura Fugazzola (Italy)

Main Auditorium
14.00–14.45 **MTE 3:** Amiodarone-induced thyroid dysfunction
Enio Martino (Italy)

Pacinotti Hall
14.00–14.45 **MTE 4:** The thyroid and metabolic syndrome
Georg Brabant (Germany)

14.45–15.00 **Coffee Break**

15.00–15.45
Meet the Expert 5–8

Pacinotti Hall
15.00–15.45 **MTE 5:** Deiodinase regulation during inflammation and infection (Basic)
Anita Boelen (The Netherlands)

Room 90 A
15.00–15.45 **MTE 6:** Genetic rearrangements in thyroid cancer (Basic)
Corinne Dupuy (France)

Main Auditorium
15.00–15.45 **MTE 7:** Clinical debate: this house believes that all pregnant women should be screened for thyroid dysfunction
For: *Brigitte Velkeniers* (Belgium)
Against: *Bijay Vaidya* (UK)
Chair: *John Lazarus* (UK)

Fermi Hall
15.00–15.45 **MTE 8:** Hashimoto's thyroiditis in children (Clinical)
Marek Niedziela (Poland)

Main Auditorium
16.00–18.00

Oral Session 2: Young Investigator Session (OP07–OP14)

Chairs: *Josef Köhrle* (Germany)
Peter Laurberg (Denmark)

16.00–16.15
OP07 **HYPOXIA-INDUCIBLE FACTOR 2α (HIF-2α) EXPRESSION CORRELATES WITH CLINICALLY AGGRESSIVE THYROID TUMOURS. IN VITRO, HYPOXIA-MODULATED TARGETS ARE REGULATED BY BOTH HIF-1/HIF-2 AND PROMOTE RADIO-RESISTANCE**
Burrows N[1,2], Resch J[2], Brabant G[2], Williams K[1]
[1]University of Manchester, Hypoxia and Therapeutics group, School of Pharmacy, Manchester, United Kingdom, [2]Med Clinic I - University of Lübeck, Experimental and Clinical Endocrinology, Lübeck, Germany

16.15–16.30
OP08 **THYROID HORMONE AND TRα1 FORM A NEUROGENIC SWITCH REPRESSING SOX2 IN THE ADULT NEURAL STEM CELL NICHE**
Remaud S[1], Lopez-Juarez A[1], Hassani Z[2], Morvan G[1], Demeneix B[1]
[1]Muséum National d'Histoire Naturelle, UMR CNRS 7221, Evolution des Régulations Endocriniennes, Département Régulations, Développement et Diversité Moléculaire, Paris, France, [2]King's College London, Centre for the Cellular Basis of Behaviour, The James Black Centre, London, United Kingdom

16.30–16.45
OP09 **FACILITATION OF MEMORY ACQUISITION AND RETENTION IN MOUSE BY 3-IODOTHYRONAMINE**
Musilli C[1], Manni ME[1], De Siena G[1], Saba A[2], Marchini M[2], Zucchi R[2], Raimondi L[1]
[1]Università di Firenze, Firenze, Italy, [2]Università di Pisa, Pisa, Italy

16.45–17.00
OP10 **MIR-218 IS A MARKER OF OXIDATIVE PHOSPHORYLATION PROCESS IN ONCOCYTIC THYROID TUMOURS**
Carat S[1], Guillotin D[2], Le Pennec S[2], Houlgatte R[1], Savagner F[2]
[1]Inserm U915, Nantes, France, [2]Inserm U694, Angers, France

17.00–17.15
OP11 **CLINICAL PHENOTYPE OF A NEW TYPE OF THYROID HORMONE RESISTANCE CAUSED BY MUTATION OF THE T3 RECEPTOR TRα1**
van Mullem A[1], van Heerebeek R[1], Chrysis D[2], Visser E[1], Medici M[1], Andrikoula M[3], Tsatsoulis A[3], Visser TJ[1], Peeters R[1]
[1]Erasmus MC, Internal Medicine, Rotterdam, Netherlands, [2]University of Patras, Department of Pediatrics, Division of Endocrinology, Patras, Greece, [3]Universiy of Ioannina, Department of Endocrinology, Ioannina, Greece

17.15–17.30
OP12 **TWO NOVEL CHIMERIC TSH RECEPTOR BIOASSAYS MEASURING THYROID-STIMULATING AND BLOCKING AUTOANTIBODIES DIFFERENTIATE THYROIDAL VERSUS ORBITAL INVOLVEMENT IN PEDIATRIC GRAVES' DISEASE - A MULTICENTER TRIAL**
Diana T[1], Bossowski A[2], Sawicka B[2], Borysewicz-Sanczyk H[2], Pietrewicz E[2], Ziora K[3], Bossowska A[4], Kanitz M[1], Kim J[5], Olivo PD[5], Kahaly GJ[1]
[1]Gutenberg University Medical Center, Department of Medicine I, Mainz, Germany, [2]Medical University in Bialystok, Department of Pediatrics, Endocrinology, Diabetology with the Cardiology Division, Bialystok, Poland, [3]Medical University of Silesia, Department of Pediatrics in Zabrze, Katowice, Poland, [4]Internal Affair and Administration Ministry Hospital, Department of Cardiology, Bialystok, Poland, [5]Diagnostic Hybrids, Inc, R & D, Athens, United States

17.30–17.45
OP13 **NEW SOMATIC MUTATIONS AND CLONAL EVOLUTION IN AGGRESSIVE PAPILLARY THYROID CARCINOMA REVEALED BY WHOLE-TRANSCRIPTOME DEEP SEQUENCING**
Le Pennec S[1], Gacquer D[1], Detours V[1], Maenhaut C[2]
[1]IRIBHM - ULB, Bruxelles, Belgium, [2]IRIBHM - ULB - Welbio, Bruxelles, Belgium

17.45–18.00
OP14 **IGSF1 GENE DELETION CAUSE CENTRAL HYPOTHYROIDISM AND MACROORCHIDISM WITH DECREASED OF TSH BIOACTIVITY**
Escudero A[1], Gorbenko D[2], Barrio R[3], Vallespín E[4], Nevado J[4], De Graaff L[2], Lapunzina P[4], Hokken-Koelega A[2], Moreno JC[1]
[1]Institute for Medical and Molecular Genetics (INGEMM). La Paz University Hospital, Thyroid Molecular Laboratory, Madrid, Spain, [2]Pediatric Endocrinology, Sophia Children's Hospital. Erasmus University Medical Center, Rotterdam, Netherlands, [3]Ramón y Cajal University Hospital, Pediatric Endocrinology, Madrid, Spain, [4]Institute for Medical and Molecular Genetics (INGEMM). La Paz University Hospital, Structural Genomic Laboratory, Madrid, Spain

Main Auditorium
18.05–18.50

Special Lecture in Honour of Prof. Aldo Pinchera

Chairs: *Theo Visser* (The Netherlands)
Luigi Bartalena (Italy)

Immunopathogenesis of chronic autoimmune thyroiditis one century after Hashimoto
Anthony P. Weetman (UK)

Main Auditorium
19.00–20.30

Merck Serono

Merck Serono Symposium

Thyroid Hormone Substitution of Hypothyroidism: Searching for the Optimum

Chair: *George J. Kahaly* (Germany)

19.00–19.05 Short introduction: *George J. Kahaly*

19.05–19.30 Impact of hypothyroidism on the cardiovascular system
Bernadette Biondi (Italy)

19.30–19.55 Targeting the T4 substitution in thyroid cancer
Jennifer Sipos (USA)

19.55–20.20 New European guidelines for a combined T3/T4 substitution
Birte Nygaard (Denmark)

20.20–20.30 General Discussion

20.30–21.30 Symposium participants are cordially invited to the cocktail reception (in foyer)

Monday, 10th September 2012

Main Auditorium
08.00–10.00

Oral Session 3: Clinical Thyroidology (OP15–OP22)

Chairs: *Birte Nygaard* (Denmark)
Claudio Marcocci (Italy)

08.00–08.15
OP15 **MENTAL VULNERABILITY IS HIGH IN PREVIOUSLY TREATED HYPER AND HYPOTHYROIDISM**

Perrild H[1], Knudsen N[1], Bjergved L[1,2], Carle A[3], Bulow I[3], Vejbjerg P[1], Laurberg P[3], Ovesen L[4], Rasmussen L[5], Jørgensen T[2]
[1]Bispebjerg University Hospital, Department of Endocrinology, Copenhagen, Denmark, [2]Research Centre for Prevention and Health, The Capital region of Denmark, Glostrup, Denmark, [3]Aalborg Hospital, Aarhus University Hospital, Department of Endocrinology, Aalborg, Denmark, [4]Slagelse Hospital, Department of Gastroenterology, Slagelse, Denmark, [5]National Food Institute, Department of Nutrition, Copenhagen, Denmark

08.15–08.30
OP16 **THE ASSOCIATION BETWEEN HYPERTHYROIDISM AND MORTALITY IS NOT EXPLAINED BY PRE-EXISTING CO-MORBIDITY, BUT INFLUENCED BY GENETIC CONFOUNDING. EVIDENCE FROM A DANISH NATION-WIDE REGISTER-BASED STUDY OF TWINS AND SINGLETONS**

Brandt F[1], Almind D[2], Christensen K[2, 3, 4], Green A[5], Hegedüs L[1], Brix TH[1]
[1]Odense University Hospital, Department of Endocrinology and Metabolism, Odense, Denmark, [2]University of Southern Denmark, The Danish Aging Research Center and The Danish Twin Registry, Odense, Denmark, [3]Odense University Hospital, Department of Clinical Genetics, Odense, Denmark, [4]Odense University Hospital, Department of Clinical Biochemistry and Pharmacology, Odense, Denmark, [5]University of Southern Denmark, Odense Patient data Exploratory Network, Institute of Clinical Research, Odense, Denmark

08.30–08.45
OP17 **AGE AND GENDER SUBSTANTIALLY INFLUENCE THE RELATIONSHIP BETWEEN THYROID STATUS AND LIPOPROTEIN PROFILE: RESULTS FROM A LARGE CROSS-SECTIONAL STUDY**

Tognini S[1], Polini A[1], Pasqualetti G[1], Ursino S[1], Ferdeghini M[2], Monzani F[1]
[1]University of Pisa, Internal Medicine, Pisa, Italy, [2]Universty of Verona, Morphological and Biomedical Sciences, Verona, Italy

08.45–09.00
OP18 **HYPOTHYROIDISM IS ASSOCIATED WITH CURRENT BUT NOT WITH INCIDENT HYPERTENSION**

Ittermann T[1], Tiller D[2], Meisinger C[3], Agger C[4], Nauck M[1], Rettig R[1], Hofman A[5], Jorgensen T[4], Linneberg A[4], Witteman JCM[5], Franco OH[5], Greiser KH[2], Werdan K[2], Döring A[3], Kluttig A[2], Stricker BHC[5], Völzke H[1]
[1]University of Greifswald, Greifswald, Germany, [2]Martin-Luther-University Halle-Wittenberg, Halle, Germany, [3]German Research Center for Environmental Health, München, Germany, [4]University of Copenhagen, Copenhagen, Denmark, [5]Erasmus Medical Center, Rotterdam, The Netherlands

09.00–09.15
OP19 **THE EFFECT OF HYPOTHYROIDISM ON COLOUR VISION: A PROSPECTIVE STUDY**

Cakir M[1], Ozturk B[2], Turan E[1], Gonulalan G[1], Polat I[3], Gunduz K[2]
[1]Konya University Meram School of Medicine, Division of Endocrinology and Metabolism, Konya, Turkey, [2]Konya University Meram School of Medicine, Department of Ophthalmology, Konya, Turkey, [3]Konya University Meram School of Medicine, Department of Internal Medicine, Konya, Turkey

09.15–09.30
OP20 **REDUCTION OF LEVOTHYROXINE (L-T4) REQUIREMENTS IN HYPOTHYROID OBESE PATIENTS AFTER BARIATRIC SURGERY**

Martinelli S[1], Pinchera A[1], Fierabracci P[1], Piaggi P[2], Tamberi A[1], Basolo A[1], Ceccarini G[1], Marsili A[1], Scartabelli G[1], Landi A[2], Vitti P[1], Santini F[1]
[1]University of Pisa, School of Medicine, Endocrinology Unit, Obesity Center, Pisa, Italy, [2]University of Pisa, Department of Electrical Systems and Automation, Pisa, Italy

09.30–09.45
OP21 **TAZ DOES NOT RESCUE THE LUNG PROMOTER ACTIVITY OF A NOVEL NKX2-1 MUTATION IN A BOY WITH SEVERE LUNG EMPHYSEMA**

Moya CM[1], Garzón L[2], Luna C[3], Simón R[4], Zaballos MA[5], Santisteban P[5], Gallego E[2], Moreno JC[1]
[1]INGEMM- Institute for Medical and Molecular Genetics. 'La Paz' University Hospital, Thyroid Molecular Laboratory, Madrid, Spain, [2]'12 de Octubre' University Hospital, Paediatric Endocrinology, Madrid, Spain, [3]'12 de Octubre' University Hospital, Paediatric Pneumology and Allergy, Madrid, Spain, [4]'12 de Octubre' University Hospital, Neuropediatric, Madrid, Spain, [5]Biomedical Research Institute, Endocrine Physiopathology and Nervous System, Madrid, Spain

09.45–10.00
OP22 **PERIPHERAL TISSUE BIOMARKERS IN RESISTANCE TO THYROID HORMONE**
Moran C[1], Schoenmakers N[1], Mitchell C[1], Talbot F[1], Watson L[1], Lyons G[1], Raymond-Barker P[1], Taylor K[2], Halsall D[2], Chatterjee K[1]
[1]University of Cambridge, Institute of Metabolic Science, Cambridge, United Kingdom, [2]University of Cambridge, Clinical Biochemistry, Cambridge, United Kingdom

Fermi Hall
08.00–10.00

Oral Session 4: Thyroid Cell Biology (OP23-OP30)

Chairs: *Sabine Costagliola* (Belgium)
Mariastella Zannini (Italy)

OP23 **PAX8 EXPRESSION IS REQUIRED FOR THE DIFFERENTIATION OF THYROID FOLLICULAR CELLS**
Marotta P[1], Amendola E[1], De Luca P[1], Zoppoli P[1], Di Lauro R[1,2], De Felice M[1,2]
[1]Biogem, Ariano Irpino (Av), Italy, [2]University Federico II, DBPCM, Napoli, Italy

08.15–08.30
OP24 **PAX8 IS A SURVIVAL FACTOR FOR THYROID CELLS AND IS INVOLVED IN THE CONTROL OF CELL PROLIFERATION**
Di Palma T[1], de Cristofaro T[1], Filippone MG[1,2], Pierantoni GM[2], Fusco A[1,2], Zannini M[1]
[1]Institute of Experimental Endocrinology and Oncology (IEOS)-CNR, Naples, Italy, [2]University of Naples 'Federico II', Dpt. of Cellular and Molecular Biology and Pathology, Naples, Italy

08.30–08.45
OP25 **DYNAMIC CHANGES OF LAMININ EXPRESSION AND BASEMENT MEMBRANE ORGANIZATION IN THE DEVELOPING THYROID**
Johansson E[1], Johansson BR[2], Nilsson M[1]
[1]Sahlgrenska Cancer Centre, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [2]Electron Microscopy Unit, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

08.45–09.00
OP26 **GLOBAL NOTCH PATHWAY PERTURBATIONS AS A NOVEL MODEL OF THYROID DYSGENESIS IN ZEBRAFISH**
Marelli F[1], Porazzi P[2], Benato F[3], Argenton F[3], Tiso N[3], Persani L[1,4]
[1]IRCCS Istituto Auxologico Italiano, Endocrinology and Metabolic Disorders, Cusano Milanino, Italy, [2]Childen's Hospital of Philadelphia, Philadelphia, United States, [3]University of Padua, Padua, Italy, [4]University of Milan, Milan, Italy

09.00–09.15
OP27 **MOLECULAR FUNCTIONS OF THE DNAJC17 PROTEIN, A CANDIDATE MODIFIER FOR CONGENITAL HYPOTHYROIDISM**
Ferrandino G[1], Spadaro O[1], Di Campli A[2], Luini A[2], de Franciscis V[3], De Felice M[1,4], Di Lauro R[1,4]
[1]IRGS, Biogem, Ariano Irpino (AV), Italy, [2]Istituto di Biochimica delle proteine del CNR, Napoli, Italy, [3]Istituto di Endocrinologia ed Oncologia Sperimentale del CNR, Napoli, Italy, [4]Università di Napoli Federico II, Dipartimento di Biologia e Patologia Cellulare e Molecolare, Napoli, Italy

09.15–09.30
OP28 **INVOLVEMENT OF NITRIC OXIDE IN IODINE DEFICIENCY-INDUCED ANGIOGENESIS: ROLE OF NOS3 AND OF RYANODINE RECEPTORS**
Craps J[1], Vanderstraeten J[1], Lobysheva I[2], Balligand J-L[2], Sonveaux P[2], Gilon P[3], Colin IM[1], Gerard A-C[1]
[1]UCL, Pôle de Morphologie, Bruxelles, Belgium, [2]UCL, Pôle de Pharmacologie Expérimentale, Bruxelles, Belgium, [3]UCL, Pôle d'endocrinologie, diabète et nutrition, Bruxelles, Belgium

09.30–09.45
OP29 **CA^{2+}-BINDING PROTEIN EXPRESSION IN PRIMARY HUMAN THYROCYTES**
Lorenz S[1,2], Krohn K[1]
[1]University of Leipzig, Medical Faculty, Interdisciplinary Center for Clinical Research, Leipzig, Germany, [2]University of Leipzig, Medical Faculty, Division of Endocrinology and Nephrology, Leipzig, Germany

09.45–10.00
OP30 **INTRATHYROID REARRANGEMENT IN SPACE ENVIRONMENT**
Albi E[1], Curcio F[2], Spelat R[2], Lazzarini A[2], Lazzarini R[1], Cataldi S[1], Loreti E[3], Ferri I[3], Ambesi-Impiombato FS[2]
[1]Sphingolipid Club - CRABioN Research Centre, Perugia, Italy, [2]University of Udine, Dipartimento di Scienze Mediche e Biologiche, Udine, Italy, [3]University of Perugia, Institute of Pathologic Anatomy and Histology, Perugia, Italy

10.00–10.30 **Coffee break**

36th Annual Meeting of the European Thyroid Association
Industry-sponsored symposium

Heralding a New Era in the Treatment of Advanced Medullary Thyroid Cancer

Monday 10th September 2012 1:00–2:00 pm

Main Auditorium (Plenary Hall) ground floor
Palazzo dei Congressi, Pisa, Italy

Programme

- **Welcome and Introduction**
  Martin Schlumberger — *Institut Gustave Roussy, Villejuif, France*
- **A 2012 perspective on the management of patients with advanced medullary thyroid cancer**
  Dagmar Führer — *University of Essen, Germany*
- **Treating patients with advanced medullary thyroid cancer – some practical considerations**
  Kate Newbold — *The Royal Marsden NHS Foundation Trust, London, UK*
- **Case study presentation and panel discussion**
  Rossella Elisei — *University of Pisa, Italy*
- **Closing remarks**
  Martin Schlumberger — *Institut Gustave Roussy, Villejuif, France*

Lunch will be provided

AstraZeneca
Health Connects Us All

AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK
www.astrazeneca.com
ID=090082f182179873 15/06/2012

Fermi Hall
10.30–12.00

Symposium 3: Thyroid Hormone Action: the Role of TRα Mutations

Chairs: *Graham Williams* (UK)
Paolo Beck-Peccoz (Italy)

10.30–1.00 TRα mutant mouse models: modeling a human disorder
Jens Mittag (Sweden)
11.00–11.30 TRα mediated resistance to thyroid hormone
Krishna Chatterjee (UK)
11.30–12.00 Clinical phenotype of TRα mutation
Theo Visser (The Netherlands)

Main Auditorium
10.30–12.00

Symposium 4: Anaplastic Thyroid Carcinoma: from Molecular Biology to Novel Therapeutic Options

Chairs: *Jacques Dumont* (Belgium)
Rossella Elisei (Italy)

10.30–11.00 Molecular biology
Carine Maenhaut (Belgium)
11.00–11.30 Epidemiological and diagnostic aspects
Laurence Leenhardt (France)
11.30–12.00 Therapeutic options
Barbara Jarzab (Poland)

Poster Area
12.00–13.00

Lunch and Poster Discussion 2 (Poster 122-245)

Poster Session 14: Medullary Thyroid Cancer Clinical
Chair: *Joao de Castro* (Portugal)
Poster Session 15: Thyroid Cancer Diagnostics Basic/ Translational
Chair: *Gabriella Pellegritti* (Italy)
Poster Session 16: Thyroid Cancer Diagnostics Clinical 2
Chair: *Jennifer Sipos* (USA)
Poster Session 17: Thyroid Cancer Therapeutics Clinical 2
Chair: *Ian Hay* (USA)
Poster Session 18: Thyroid Autoimmunity and Hypothyroidism Translational
Chair: *Matthias Schott* (Germany)
Poster Session 19: Thyroid Hormone Transport
Chair: *Edward Visser* (NL)
Poster Session 20: Goiter and Nodular Disease Clinical 2
Chair: *Francoise Borson-Chazot* (France)
Poster Session 21: Case Reports 2
Chair: *Kostas Markou* (Greece)
Poster Session 22: Thyroid Hormone Effects on Metabolism and Bone
Chair: *Duncan Bassett* (UK)
Poster Session 23: Thyroid Hormone Action 2
Chair: *Francesco Trimarchi* (Italy)
Poster Session 24: Thyroid Function Regulation Basic
Chair: *Denise Carvalho* (Brazil)
Poster Session 25: Clinical Thyroid Autoimmunity 2
Chair: *Chantal Daumerie* (Belgium)
Poster Session 26: Environmental Factors and Drugs affecting Thyroid Function 1
Chair: *Leonidas Duntas* (Greece)
Poster Session 27: Graves' Orbitopathy Clinical 2
Chair: *Jacques Orgiazzi* (France)

Main Auditorium
13.00–14.00

AstraZeneca

AstraZeneca Symposium

(Lunch boxes will be provided for symposium attendees)

Heralding a New Era in the Treatment of Advanced Medullary Thyroid Cancer

Welcome and Introduction
Martin Schlumberger (France)

A 2012 perspective on the management of patients with advanced medullary thyroid cancer
Dagmar Führer (Germany)
Treating patients with advanced medullary thyroid cancer – some practical considerations
Kate Newbold (UK)
Case study presentation and panel discussion
Rossella Elisei (Italy)
Closing remarks
Martin Schlumberger (France)

Merck Serono

Main Auditorium
14.00–14.45

ETA Merck Serono Prize Lecture

Chairs: *Theo Visser* (The Netherlands)
Luigi Bartalena (Italy)

Thyroid hormone actions in bone and cartilage

Graham Williams (UK)

14.45–15.00 **Coffee Break**

Main Auditorium
15.00–16.30

Oral Session 5: Autoimmunity (OP31–OP36)

Chairs: *Simon Pearce* (UK)
Marco Centanni (Italy)

15.00–15.15
OP31 **CORTICOSTEROIDS AND RAPAMYCIN INHIBIT TH1 AND TH2 CHEMOKINES SECRETION, INDUCED BY CYTOKINES, IN ORBITAL CELLS OF PATIENTS WITH GRAVES' OPHTHALMOPATHY**
Ferrari SM[1], *Fallahi P*[1], *Ruffilli I*[1], *Di Domenicantonio A*[1], *Sellari Franceschini S*[2], *Ferrannini E*[1], *Antonelli A*[1]
[1]University of Pisa, School of Medicine, Department of Internal Medicine, Pisa, Italy, [2]University of Pisa, School of Medicine, Otorhinolaryngology Unit, Pisa, Italy

15.15–15.30
OP32 **OXIDATIVE STRESS OF EYE MUSCULAR CELLS IN GRAVES' OPHTHALMOPATHY IS ASSOCIATED TO DOWN-REGULATION OF CAVEOLIN-1 AND UPREGULATION OF TYPE III-DEIODINASE**
Van Regemorter E[1], *Van Regemorter V*[1], *Marique L*[1], *Senou M*[1], *de Bournonville M*[1], *Delacourt V*[1], *Behets C*[1], *Lengelé B*[1], *Brichard S*[2], *Boschi A*[3], *Daumerie C*[2], *Many M-C*[1]
[1]UCL, MORF, Bruxelles, Belgium, [2]UCL, Endocrinologie, Bruxelles, Belgium, [3]UCL, Ophthalmology, Bruxelles, Belgium

15.30–15.45
OP33 **RELATIONSHIP BETWEEN USE OF IODIZED SALT AND THYROID AUTOIMMUNITY AFTER UNIVERSAL IODINE PROPHYLAXIS: THE 2010 PESCOPAGANO SURVEY**
Provenzale MA[1], *Frigeri M*[1], *Puleo L*[1], *Antonangeli L*[1], *Rago T*[1], *Fiore E*[1], *Tonacchera M*[1], *Grasso L*[1], *Pinchera A*[1], *Aghini-Lombardi F*[1], *Vitti P*[1]
[1]University of Pisa, Endocrinology, Pisa, Italy

15.45–16.00
OP34 **CHARACTERIZATION OF A NOVEL DETECTION BIOASSAY FOR THYROID BLOCKING ANTIBODY**
Li Y[1], *Kim J*[1], *Larrimer A*[1], *Klausen R*[1], *Yu L*[1], *Diana T*[2], *Kahaly GJ*[2], *Olivo PD*[1]
[1]Diagnostic Hybrids, Inc. (A Quidel Company), R&D, Athens, United States, [2]Gutenberg University Medical Center, Thyroid Research Laboratory, Mainz, Germany

16.00–16.15
OP35 **TGAB OF PATIENTS WITH SUBACUTE THYROIDITIS ARE RESTRICTED TO A MAJOR B CELL EPITOPE**
Ricci D[1], *Montanelli L*[1], *Altea MA*[1], *Pucci A*[1], *Pinchera A*[1], *Vitti P*[1], *Latrofa F*[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

16.15–16.30
OP36 **RISK FACTORS FOR POST-OPERATIVE DIPLOPIA IN PRIMARY GAZE AFTER REHABILITATIVE ORBITAL DECOMPRESSION FOR GRAVES' ORBITOPATHY**
Leo M[1], *Lenzi R*[2], *Marinò M*[1], *Latrofa F*[1], *Sisti E*[1], *Altea MA*[1], *Profilo MA*[1], *Megna L*[3], *Mazzi B*[1], *Pinchera A*[1], *Vitti P*[1], *Marcocci C*[1], *Sellari-Franceschini S*[2], *Rocchi R*[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Unit of Endocrinology, Pisa, Italy, [2]University of Pisa, Department of Neuroscience, Unit of Otolaryngology, Pisa, Italy, [3]University of Pisa, Department of Neuroscience, Unit of Ophthalmology, Pisa, Italy

Fermi Hall
15.00–16.30

Oral Session 6: Thyroid Cell Biology and Cancer (OP37–OP42)

Chairs: *Xavier de Deken* (Belgium)
Rosa Marina Melillo (Italy)

15.00–15.15
OP37 **THE THYROID OXIDATIVE CAPACITY IS ENHANCED BY THE TH2 CYTOKINES, IL-4 AND IL-13, THROUGH INCREASED EXPRESSION OF THE DUAL OXIDASE 2 AND ITS MATURATION FACTOR DUOXA2**
De Deken X[1], *Raad H*[1], *Eskalli Z*[1], *Hoste C*[1], *Corvilain B*[1], *Miot F*[1]
[1]Université Libre de Bruxelles, IRIBHM - DUOXLab, Brussels, Belgium

15.15–15.30
OP38 **DNA MICROARRAY AND MIRNA ANALYSES REINFORCE THE CLASSIFICATION OF FOLLICULAR THYROID TUMOURS**

Jacques C[1], Guillotin D[1], Franc B[2], Malthiery Y[1], Savagner F[1]
[1]Inserm U694, Angers, France, [2]Laboratoire d'Anatomopathologie, Hopital A PAré, Boulogne Billancourt, France

15.30–15.45
OP39 **CAMP MAY NOT ALWAYS BE A PROLIFERATION SIGNAL IN THYROID CANCER CELLS**

Grassi ES[1], Dicitore A[2], Borghi MO[3,4], Vitale G[1,2], Persani L[1,2]
[1]Università degli studi di Milano, Dipartimento di Scienze Mediche, Milan, Italy, [2]Istituto Auxologico Italiano, Laboratory of Endocrine and Metabolic Research, Milan, Italy, [3]Istituto Auxologico Italiano, Laboratory of Immunology, Milan, Italy, [4]Università degli studi di Milano, Dipartimento di Medicina Interna, Milan, Italy

15.45–16.00
OP40 **GENOME-WIDE LINKAGE ANALYSIS TO IDENTIFY GENES INVOLVED IN THYROID GROWTH AND NEOPLASIA**

Bakhsh ADQ[1,2], Hamshere M[3], Gregory J[4], Kirov G[3], Williams D[5], Ludgate M[1]
[1]Cardiff University, Institute of Molecular & Experimental Medicine, Cardiff, United Kingdom, [2]Institute of Molecular & Experimental Medicine, Endocrinology, Cardiff, United Kingdom, [3]Cardiff University, Psychological Medicine & Neurology, Cardiff, United Kingdom, [4]Institute of Molecular & Experimental Medicine, Department of Child Health, Cardiff, United Kingdom, [5]Cambridge University, Strangeways Laboratory, Cambridge, United Kingdom

16.00–16.15
OP41 **METABOLIC ENGINEERING OF IODINE CONTENT IN ARABIDOPSIS**

Landini M[1], Tonacchera M[2], Gonzali S[1], Agretti P[3], Dimida A[4], Vitti P[3], Alpi A[5], Pinchera A[4], Perata P[1]
[1]Scuola S Anna Pisa, Plant Lab, Pisa, Italy, [2]University of Pisa, School of Medicine, Dep of Endocrinology, Pisa, Italy, [3]University of Pisa, School of Medicine, Pisa, Italy, [4]University of Pisa, Pisa, Italy, [5]University of Pisa, Dep Crop Plant Biology, Pisa, Italy

16.15–16.30
OP42 **RNA-SEQ PROVIDES ISOFORM SPECIFIC MIRNA EXPRESSION DATA WHICH REQUIRE ISOFORM SPECIFIC QPCR VERIFICATION**

Stokowy T[1,2], Swierniak M[1], Wojtas B[1], Danch M[2], Krohn K[3], Fujarewicz K[2], Jarzab B[1], Paschke R[4], Eszlinger M[4]
[1]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Nuclear Medicine and Endocrine Oncology Department, Gliwice, Poland, [2]Silesian University of Technology, Institute of Automatic Control, Gliwice, Poland, [3]University of Leipzig, Interdisziplinares Zentrum fur Klinische Forschung, Leipzig, Germany, [4]University of Leipzig, Klinik fur Endokrinologie und Nephrologie, Leipzig, Germany

16.45 Departure for Excursion to Calci Charterhouse

Tuesday, 11th September 2012

Main Auditorium
08.00–10.00

Oral Session 7: Pregnancy and Iodine (OP43–OP50)

Chairs: *Bijay Vaidya* (UK)
Francesco Vermiglio (Italy)

08.00–08.15
OP43 **THYROGLOBULIN ANTIBODIES: AN ADDED VALUE IN THE DETECTION OF THYROID AUTOIMMUNITY IN FEMALE PATIENTS OF INFERTILE COUPLES?**

Unuane D[1], Haentjens P[1], Schiettecatte J[1], Tournaye H[1], Velkeniers B[1], Poppe K[1]
[1]University Hospital UZ-Brussel, Free University Brussels (VUB), Endocrinology, Centre for Reproductive Medicine and Centre for Outcomes Research and Laboratory for Experimental Surgery, Brussels, Belgium

08.15–08.30
OP44 **THYROID HORMONE LEVELS IN NORMAL PREGNANCY ARE ASSOCIATED WITH ALTERED METABOLIC PARAMETERS**

Knight B[1,2], Shields B[1], Hattersley A[1,2], Vaidya. B[3,4]
[1]PCMD (University of Exeter), Peninsula NIHR Clinical Research Facility, Exeter, United Kingdom, [2]RD&E NHS Foundation Trust, Exeter, United Kingdom, [3]RD&E NHS Foundation Trust, Dept of Diabetes and Endocrinology, Exeter, United Kingdom, [4]PCMD (University of Exeter), Exeter, United Kingdom

08.30–08.45
OP45 **THE TYPE 2 DEIODINASE THR92ALA POLYMORPHISM SEEMS TO BE A MARKER OF INCREASED INSULIN RESISTANCE DURING PREGNANCY: A GENETIC ASSOCIATION STUDY**

Dora JM[1], Wajner S[1], Costa JD[1], Pinto Ribeiro RV[1], Lopes MG[1], da Silva AV[1], Leiria L[1], Crispim D[1], Maia AL[1]
[1]Hospital de Clínicas de Porto Alegre, Endocrine Division, Porto Alegre, Brazil

08.45–09.00
OP46 **IODINE-CONTAINING MULTIVITAMINS FAIL TO CORRECT IODINE DEFICIENCY IN BELGIAN PREGNANT WOMEN**

Vandevijvere S[1], Amsalkhir S[2], Mourri Bensouda A[2], Van Oyen H[1], Moreno-Reyes R[2]
[1]Scientific Institute of Public Health, Department of Public Health and Surveillance, Brussels, Belgium, [2]Hôpital Erasme, Université Libre de Bruxelles, Department of Nuclear Medicine, Brussels, Belgium

09.00–09.15
OP47 **GLOBAL IODINE STATUS IN 2011 AND TRENDS OVER THE PAST DECADE**

Andersson M[1], Karumbunathan V[1], Zimmermann MB[1]
[1]Swiss Federal Institute of Technology (ETH) Zürich, Department of Health Sciences and Technology (D-HEST), Zurich, Switzerland

09.15–09.30
OP48 **TIROKID STUDY: STATUS OF IODINE NUTRITION OF SPANISH INFANTS**

Vila L[1], Donnay S[2], Arena J[3], Arrizabalaga JJ[4], Pîneda J[5], Guzmán A[6], Luengo LM[7], Villar A[8], Bandrés O[9], Muñoz Z[10], Guerrero E[11], Moll G[12], Vich F[12], Muñoz JA[13], Riestra M[14], Menéndez E[14], Beato P[7], Aguirre M[15], Santiago P[16], Aranda J[17], Torres Y[1], Gentil A[18], Serra-Prat M[19], Iodine Deficiency and Thyroid Dysfunction group (SEEN)
[1]Hospital Moisès Broggi, Endocrinology and Nutrition, Sant Joan Despí, Spain, [2]Fundation Hospital Alcorcón, Endocrinology and Nutrition, Alcorcón, Spain, [3]Hospital Universitario Donostia, Neonatology, San Sebastián, Spain, [4]Hospital Txagorritxu, Endocrinology and Nutrition, Vitoria, Spain, [5]Hospital Garcia Orcoyen, Endocrinology and Nutrition, Estella, Spain, [6]Complejo Asistencial de Ávila, Endocrinology and Nutrition, Ávila, Spain, [7]Hospital Universitario Infanta Cristina, Endocrinology and Nutrition, Badajoz, Spain, [8]Hospital Clínico, Endocrinology and Nutrition, Valladolid, Spain, [9]Hospital Royo Villanova, Endocrinology and Nutrition, Zaragoza, Spain, [10]Centro de Salud Arisa, Calatayud, Spain, [11]Hospital Río Carrión, Endocrinology and Nutrition, Palencia, Spain, [12]Hospital de Inca, Endocrinology and Nutrition, Inca, Spain, [13]ICS, ABS, Seu d'Urgell, Spain, [14]Hospital Central de Asturias, Endocrinology and Nutrition, Oviedo, Spain, [15]Hospital General, Valladolid, Spain, [16]Complejo Hospitalario, Endocrinology and Nutrition, Jaén, Spain, [17]Hospital Virgen de la Luz, Cuenca, Spain, [18]Hospital Universitario Virgen de la Macarena, Endocrinology and Nutrition, Sevilla, Spain, [19]Hopital de Mataró, Research Unit, Barcelona, Spain

09.30–09.45
OP49 **BREAD FORTIFICATION WITH IODISED SALT CORRECTS IODINE DEFICIENCY IN SCHOOL-AGED CHILDREN BUT NOT IN THEIR MOTHERS: A NATIONAL SURVEY IN BELGIUM**

Moreno-Reyes R[1], Mourri Bensouda A[1], Amsalkhir S[1], Avni F[2], Van Oyen H[3], Vandevijvere S[3]
[1]Hôpital Erasme, Université Libre de Bruxelles, Department of Nuclear Medicine, Brussels, Belgium, [2]Höpital Erasme, Université Libre de Bruxelles, Department of Radiology, Brussels, Belgium, [3]Scientific Institute of Public Health, Department of Public Health and Surveillance, Brussels, Belgium

09.45–10.00
OP50 **PREDICTORS OF CHANGE IN SERUM TSH AFTER IODINE FORTIFICATION: AN 11 YR FOLLOW-UP OF THE DANTHYR STUDY**

Bjergved L[1,2], Jørgensen T[2,3], Perrild H1, Laurberg P[4,5], Ovesen L[6], Rasmussen LB[7], Knudsen N[1]
[1]Bispebjerg University Hospital, Department of Endocrinology and Gastroenterology, Copenhagen, Denmark, [2]Research Centre for Prevention and Health, The Capital region of Denmark, Glostrup, Denmark, [3]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [4]Aalborg Hospital, Aarhus University Hospital, Department of Endocrinology and Medicine, Aalborg, Denmark, [5]Faculty of Medicine, Aalborg University, Aalborg, Denmark, [6]Slagelse Hospital, Department of Gastroenterology, Slagelse, Denmark, [7]National Food Institute, Technical University of Denmark, Department of Nutrition, Søborg, Denmark

Fermi Hall
08.00–10.00

Oral Session 8: Thyroid Cancer Basic (OP51–OP58)

Chairs: *Dillwyn Willliams* (UK)
Massimo Santoro (Italy)

08.00–08.15
OP51 **IDENTIFICATION OF NEW INHIBITORS OF RET RECEPTOR TYROSINE KINASE**

Moccia M[1], Guida T[1], Gray N[2], Liu Q[2], Carlomagno F[1], Santoro M[1]
[1]University of Naples, Federico II, Istituto di Endocrinologia ed Oncologia Sperimentale del CNR/Dipartimento di Biologia e Patologia Cellulare e Molecolare 'L.Califano', Facoltà di Medicina e Chirurgia, Naples, Italy, [2]Dana Farber Cancer Institute, Department of Cancer Biology, Harvard Medical School, Department of Biological Chemistry and Molecular Pharmacology, Boston Massachusetts, United States

08.15–08.30
OP52 **3D CULTURE OF RECONSTITUTED THYROID FOLLICLES FOR EX VIVO EVALUATION OF CANDIDATE DRUGS INTERFERING WITH CELL MIGRATION: A POTENTIAL TUMOR INVASION ASSAY**

Ingeson Carlsson C[1], Nilsson M[1]
[1]Sahlgrenska Cancer Center, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

08.30–08.45
OP53 **CLM3, A NOVEL MULTITARGET TYROSINE KINASE INHIBITOR WITH ANTIANGIOGENIC PROPERTIES, IS ACTIVE AGAINST PRIMARY ANAPLASTIC THYROID CANCER IN VITRO AND IN VIVO**

Fallahi P[1], Ferrari SM[1], Bocci G[2], La Motta C[3], Mancusi C[1], Corrado A[1], Materazzi G[4], Danesi R[2], Da Settimo F[3], Miccoli P[4], Antonelli A[1]
[1]University of Pisa, School of Medicine, Department of Internal Medicine, Pisa, Italy, [2]University of Pisa, School of Medicine, Division of Pharmacology, Pisa, Italy, [3]University of Pisa, School of Medicine, Department of Pharmaceutical Science, Pisa, Italy, [4]University of Pisa, Department of Surgery, Pisa, Italy

08.45–09.00
OP54 **MICRORNAS INFLUENCE THE TUMORIGENESIS OF COLD BENIGN THYROID NODULES BY ACTING ON CELL CYCLE AND APOPTOSIS**

Ferraz C[1], Lorenz S[1], Moll A[1], Paschke R[1], Eszlinger M[1]
[1]Universität Leipzig, Endocrinology and Nephrology, Leipzig, Germany

09.00–09.15
OP55 **TRAIL CAN EFFICIENTLY KILL ANAPLASTIC THYROID CANCER (ATC) CELLS IN VITRO AND IN VIVO**

Pilli T[1, 2], Ranganath R[2], Carr R[2], Qin J[2], Maker AV[2, 3], Li LC[2], Pacini F[1], Prabhakar BS[2]
[1]University of Siena, Department of Internal Medicine, Endocrinology&Metabolism and Biochemistry, Siena, Italy, [2]University of Illinois at Chicago, Department of Microbiology & Immunology, Chicago, United States, [3]University of Illinois at Chicago, Department of Surgery, Chicago, United States

09.15–09.30
OP56 **THERAPEUTIC STRATEGY TO TARGET THE RECEPTOR TYROSINE KINASE AXL IN THYROID CANCER**

Krishnamoorthy GP[1], Guida T[1], Visciano C[1], Liotti F[1], Carlomagno F[1], Melillo RM[1]
[1]University of Naples-Federico II, Dipartimento di Biologia e Patologia Cellulare e Molecolare/Istituto di Endocrinologia ed Oncologia Sperimentale del CNR 'G.Salvatore', Napoli, Italy

09.30–09.45
OP57 **HYPERMETHYLATION OF A NEW CPG ISLAND IS ASSOCIATED WITH REDUCED *NIS* GENE EXPRESSION IN THYROID TUMORS**

Galrao AL[1], Sodré AK[1], Camargo RY[1], Friguglietti CU[1], Kulcsar MA[1], Lima EU[1], Moraes LS[2], Cerutti JM[2], Medeiros-Neto G[1], Rubio IG[3]
[1]University of Sao Paulo Medical School, Endocrinology - Thyroid, Sao Paulo, Brazil, [2]UNIFESP EPM, Genetics, Sao Paulo, Brazil, [3]UNIFESP, Biological Sciences, São Paulo, Brazil

09.45–10.00
OP58 **IDENTIFICATION OF TARGETS OF TWIST1 TRANSCRIPTION FACTOR IN ANAPLASTIC THYROID CANCER**
Di Maro G[1], Orlandella FM[1], Salerno P[1], Bencivenga TC[1], Santoro M[1], Salvatore G[2]
[1]University of Naples, Federico II, Naples, Italy, [2]University of Naples Parthenope, Naples, Italy

10.00–10.30 **Coffee Break**

Fermi Hall
10.30–12.00

Symposium 5: Signaling in the Thyroid

Chairs: *Pilar Santisteban* (Spain)
Alfredo Fusco (Italy)

10.30–11.00 Requirements for normal thyroid differentiation
Sabine Costagliola (Belgium)
11.00–11.30 PI3K/PTEN signaling in the thyroid
Antonio De Cristofano (USA)
11.30–12.00 Ras and transformation of thyroid cells
Gabriella de Vita (Italy)

Main Auditorium
10.30–12.00

Symposium 6: TSH Receptor in Thyroid Autoimmunity

Chairs: *George J. Kahaly* (Germany)
Luca Chiovato (Italy)

10.30–11.00 Interaction of the TSH receptor with autoantibodies: structure and dynamics
Jane Sanders (UK)
11.00–11.30 Bioassays for TSH receptor autoantibodies
Giorgio Napolitano (Italy)
11.30–12.00 Thyroid blocking antibodies: methodology and clinical relevance
Paul Olivo (USA)

Poster Area
12.00–13.00

Lunch and Poster Discussion 3 (Poster 246–331)

Poster Session 28: Thyroid cancer diagnostics clinical 3
Chair: *Philippe Caron* (France)
Poster Session 29: Thyroid cancer therapeutics clinical 3
Chair: *Sophie Leboulleux* (France)
Poster Session 30:
Thyroid cancer pathogenesis translational/clinical
Chair: *Clara Alvarez* (Spain)
Poster Session 31:
Thyroid hormone and reproduction/fetal-maternal unit
Chair: *Kris Poppe* (Belgium)
Poster Session 32: Environmental factors and drugs affecting thyroid function 2
Chair: *Peter Smyth* (Ireland)
Poster Session 33: Hypothyroidism clinical 2
Chair: *Salvatore Benvenga* (Italy)
Poster Session 34: Hyperthyroidism clinical
Chair: *Fausto Bogazzi* (Italy)
Poster Session 35: Graves' disease and orbitopathy basic/translational
Chair: *Milos Zarkovic* (Serbia)
Poster Session 36: Thyroid gland development/thyroid hormone synthesis
Chair: *Mikael Nilsson* (Sweden)
Poster Session 37: Clinical thyroidology
Chair: *Roussanka Kovatcheva* (Bulgaria)

Main Auditorium
13.00–14.00

IBSA

IBSA Symposium

(Lunch boxes will be provided for symposium attendees)
Controversies on levothyroxine therapy
Chairs: *Aldo Pinchera* (Italy) and *P. Reed Larsen* (USA)

13.00 **Introduction**
P. Reed Larsen (USA)
13.05 **Levothyroxine therapy in nodular goiter**
Laszlo Hegedüs (Denmark)
Paolo Vitti (Italy)
13.25 **Q&A Session**
Moderation: *P. Reed Larsen* (USA)
13.30 **Replacement therapy in hypothyroidism**
Bernadette Biondi (Italy)
P. Reed Larsen (USA)
13.50 **Q&A Session**
Moderation: *Aldo Pinchera* (Italy)
13.55 **Conclusions**
Aldo Pinchera
14.00 **End of Session**

14.00–14.45
Meet the Expert 9–11

Main Auditorium
14.00–14.45 **MTE 9:** Genome Wide Association Analysis and thyroid function, recent outcomes and future challenges
Robin Peeters (The Netherlands)

Fermi Hall
14.00–14.45 **MTE 10:** Stress and thyroid autoimmunity
Agathocles Tsatsoulis (Greece)

Pacinotti Hall
14.00–14.45 **MTE 11:** Low-risk thyroid carcinoma
Maria Alevizaki (Greece)

Main Auditorium
15.00–17.00

Oral Session 9: Thyroid Nodules and Cancer (OP59–OP66)

Chairs: *Steen Bonnema* (Denmark)
Laura Fugazzola (Italy)

15.00–15.15
OP59 **TI-RADS SCORE: DIAGNOSTIC PERFORMANCE WITH AND WITHOUT ELASTOGRAPHY PROSPECTIVE STUDY ON 1305 THYROID NODULES**
Russ G[1,2], Rouxel A[1,2], Bienvenu-Perrard M[1,3], Royer B[1,4], Bigorgne C[1], Leenhardt L[2]
[1]Centre de Pathologie et d'Imagerie, Paris, France, [2]Hopital La Pitié Salpétrière, Service de Médecine Nucléaire du Pr Aurengo, Paris, France, [3]Hôpital Cochin, Service de Médecine Nucléaire du Pr Richard, Paris, France, [4]Hopital Cochin, Service d'Anatomopathologie du Pr Vacher-Lavenu, Paris, France

15.15–15.30
OP60 **INTERSTITIAL LASER PHOTOCOAGULATION (ILP) OF BENIGN CYSTIC THYROID NODULES- A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL**
Døssing H[1], Bennedbæk FN[2], Hegedüs L[3]
[1]Odense University Hospital, Oto-Rhino-Laryngology and Neck Surgery, Odense, Denmark, [2]Herlev Hospital, Endocrinology, Herlev, Denmark, [3]Odense University Hospital, Endocrinology, Odense, Denmark

15.30–15.45
OP61 **MULTICENTER RANDOMIZED PROSPECTIVE TRIAL OF PERCUTANEOUS LASER ABLATION VERSUS FOLLOW-UP FOR THE TREATMENT OF COLD THYROID NODULES-TWELVE-MONTH RESULTS**
Rago T[1], Papini E[2], Vitti P[1], De Feo P[3], Gambelunghe G[3], Valcavi R[4], Bizzarri G[5], Pacella CM[6]
[1]University of Pisa, Endocrinology Dept, Pisa, Italy, [2]Regina Apostolorum Hospital, Endocrinology Dept, Albano Laziale, Italy, [3]University of Perugia, Department of Internal Medicine and Endocrine and Metabolic Sciences, Perugia, Italy, [4]Arcispedale Santa Maria Nuova, Endocrine Unit &Thyroid Diseases Center, Reggio Emilia, Italy, [5]Regina Apostolorum Hospital, Radiology Dept, Albano Laziale, Italy, [6]Regina Apostolorum Hospital, Interventional Radiology, Albano Laziale, Italy

15.45–16.00
OP62 **ULTRASOUND-GUIDED PERCUTANEOUS ETHANOL ABLATION (UPEA) OF SELECTED NECK NODAL METASTASES (NNM) IN DIFFERENTIATED THYROID CARCINOMA (DTC): A 21-YEAR EXPERIENCE IN 161 PATIENTS**
Hay I[1], Lee R[1], Davidge-Pitts C[1], Geske J[1], Reading C[1], Charboneau W[1]
[1]Mayo Clinic, Rochester, United States

16.00–16.15
OP63 **LEPTIN AND SERUM THYROTROPIN CONCENTRATIONS IN A REPRESENTATIVE SAMPLE OF IODINE-SUFFICIENT, EUTHYROID MEDITERRANEAN POPULATION WITH DIFFERENT BODY MASS INDEX. RELATIONSHIP WITH THYROID AUTOIMMUNITY AND SMOKING HABIT**
Lucas A[1], Granada ML[2], Olaizola I[1], Castell C[3], Julian MT[1], Pellitero S[1], Puig-Domingo M[1]
[1]Germans Trias i Pujol, Hospital, Endocrinologia i Nutrició, Badalona, Spain, [2]Germans Trias i Pujol, Hospital, Hormone Laboratory, Badalona, Spain, [3]General Direction of Public Health, Health Department, Generalitat of Catalonia, Barcelona, Spain

16.15–16.30
OP64 **STAGE I PAPILLARY THYROID CARCINOMAS WITH HIGH PERCENTAGE OF BRAFV600E ALLELES HAVE A HIGH RISK OF RECURRENCE**
Guerra A[1], Fugazzola L[2], Rossi S[2], Ciriello V[2], Forno I[2], Marotta V[3], Cirillo M[1], Di Stasi V[1], Volpe A[1], Murino A[1], Izzo G[1], Vitale M[1]
[1]University of Salerno, Department of Medicine and Surgery, Baronissi, Italy, [2]University of Milan, Milan, Italy, [3]University of Naples "Federico II', Naples, Italy

16.30–16.45
OP65 **QUALITY OF LIFE AND DEPRESSION IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA**
Molinaro E[1], Lippi C[1], Piaggi P2, Agate L[1], Passannanti P[1], Valeria B[1], Biagini A[1], Santini F[1], Vitti P[1], Pinchera A[1], Elisei R[1]
[1]Department of Endocrinology, University of Pisa, Pisa, Italy, [2]Department of Energy and Systems Engineering, University of Pisa, Pisa, Italy

16.45–17.00
OP66 **OBESITY AND OVERWEIGHT ARE MAJOR RISK FACTORS OF RECURRENCE AFTER THYROIDECTOMY FOR MACROSCOPIC PAPILLARY CANCER**
Tresallet C[1], Noullet S[1], Godiris-Petit G[1], Hoang C[2], Leenhardt L[3], Menegaux F[1]
[1]APHP, Université Pierre et Marie Curie, Paris 6, Endocrine Surgery, Paris, France, [2]APHP, Université Pierre et Marie Curie, Paris 6, Pathology Departement, Paris, France, [3]APHP, Université Pierre et Marie Curie, Paris 6, Nuclear Medicine, Paris, France

Fermi Hall
15.00–17.00

Oral Session 10: Thyroid Basic 1 (OP67–OP74)

Chairs: *Ulrich Schweizer* (Germany)
Monica Dentice (Italy)

15.00–15.15
OP67 **THE THYROID HORMONE RECEPTOR-COACTIVATOR INTERFACE MEDIATES NEGATIVE FEEDBACK REGULATION OF THE HUMAN PITUITARY THYROID AXIS**
Agostini M[1], Moran C[1], Schoenmakers E[1], Mitchell C[1], Gregory J[2], Gurnell M[1], Chatterjee K[1]
[1]University of Cambridge, Institute of Metabolic Science, Cambridge, United Kingdom, [2]University Hospital Wales, Department of Child Health, Cardiff, United Kingdom

15.15–15.30
OP68 **ROLE OF CYSTEINE RESIDUES IN THE MCT8 THYROID HORMONE TRANSPORTER**
Lima de Souza EC[1], Groeneweg S[1], Visser EW[1], Peeters RP[1], Visser TJ[1]
[1]Eramus University Medical Center, Internal Medicine, Rotterdam, The Netherlands

15.30–15.45
OP69 **UNCOUPLING PROTEIN-3 (UCP3) IS INVOLVED IN METABOLIC ADAPTATION INDUCED BY TRIIODOTHYRONINE**
Lombardi A[1], Busiello RA[1], Senese R[2], Cioffi F[3], Goglia F[3]
[1]University of Naples 'Federico II', Biological Science, Napoli, Italy, [2]Second Univesity of Naples (SUN), Caserta, Italy, [3]Sannio University, Benevento, Italy

15.45–16.00
OP70 **ABSENCE OF TYPE 3 DEIODINASE LEADS TO RESTRICTIVE CARDIOMYOPATHY AND AGGRAVATES CARDIAC HYPERTROPHY IN MICE**
Olivares EL[1], Ueta CB[2], Oskouei BN[3], Pinto JR[4], Correa MM[2], Simovic G[2], Simonides WS[5], Hare JM[3], Bianco AC[2]
[1]Federal Rural University of Rio de Janeiro, Physiological Sciences, Seropedica, Brazil, [2]University of Miami Miller School of Medicine, Division of Endocrinology, Diabetes and Metabolism, Miami, United States, [3]University of Miami Miller School of Medicine, Interdisciplinary Stem Cell Institute, Miami, United States, [4]University of Miami Miller School of Medicine, Department of Molecular and Cellular Pharmacology, Miami, United States, [5]University Medical Center, Institute for Cardiovascular Research, Amsterdam, The Netherlands

16.00–16.15
OP71 **THE INTRACELLULAR INACTIVATION OF THYROID HORMONE SIGNALING IN MUSCLE STEM CELLS IS REQUIRED FOR SUCCESSFUL MUSCLE REGENERATION**
Dentice M[1], Ambrosio R[1], Sibilio A[1], Luongo C[1], Damiano V[1], Bonelli C[1], De Stefano A[1], Fenzi G[1], Larsen PR[2], Salvatore D[1]
[1]University of Naples 'Federico II', Department of Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]Brigham and Women's Hospital and Harvard Medical School, Thyroid Section, Division of Endocrinology, Diabetes and Hypertension, Boston, United States

16.15–16.30
OP72 **FUNCTIONAL ANALYSIS OF NEWLY DISCOVERED MUTATIONS IN THE SECIS ELEMENT OF THE THYROID HORMONE ACTIVATING TYPE 2 DEIODINASE**
Zevenbergen C[1], Visser WE[1], Visser TJ[1]
[1]Erasmus Medical Center, Internal Medicine, Rotterdam, The Netherlands

16.30–16.45
OP73 **ALTERNATIVE SPLICING OF TYPE 1 IODOTHYRONINE DEIODINASE IN PITUITARY ADENOMA IS REGULATED BY PROTO-ONCOGENIC SPLICING FACTOR SF2/ASF**
Kedzierska H[1], Poplawski P[1], Maksymowicz M[2], Grajkowska W[3,4], Matyja E[3,5], Bonicki W[5], Nauman P[6], Piekielko-Witkowska A[1]
[1]The Medical Centre of Postgraduate Education, Department of Biochemistry, Warsaw, Poland, [2]M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Department of Pathology, Warsaw, Poland, [3]M. Mossakowski Medical Research Centre, Polish Academy of Sciences, Department of Experimental and Clinical Neuropathology, Warsaw, Poland, [4]The Children's Memorial Health Institute, Department of Pathology, Warsaw, Poland, [5]M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Department of Neurosurgery, Warsaw, Poland, [6]Institut of Psychiatry and Neurology, Department of Neurosurgery, Warsaw, Poland

16.45–17.00
OP74 **A CONTRIBUTING ROLE FOR HEPATIC SIRTUINS IN THE PREVENTION OF DIET-INDUCED ADIPOSITY BY 3,5-DIIODO-L-THYRONINE (T2)**
de Lange P[1], Senese R[1], Cioffi F[2], de Matteis R[3], Ziello A[1], Goglia F[2], Lanni A[1]
[1]Second Univesity of Naples (SUN), Caserta, Italy, [2]University of Sannio, Benevento, Italy, [3]Università degli Studi di Urbino 'Carlo Bo', Urbino, Italy

Main Auditorium
17.15–18.45

ETA General Assembly

20.00 Gala Dinner at the National Museum of the San Matteo Cloister

Wednesday, 12th September 2012

Main Auditorium
07.45–08.45

Short call/late breaking presentations (15 min x 4)

08.45–09.00 **Coffee Break**

Main Auditorium
09.00–11.00

Oral Session 11: Thyroid Cancer (OP75–OP82)

Chairs: *Jan Smit* (The Netherlands)
Francesca Carlomagno (Italy)

09.00–09.15
OP75 **LONG TERM EFFICACY AND TOLERABILITY OF SORAFENIB IN DIFFERENTIATED THYROID CARCINOMA: FINAL RESULTS OF A PHASE II TRIAL**
Schneider T[1], Abdulrahman R[1], Kapiteijn E[1], Smit JW[1]
[1]Leiden University Medical Center, Leiden, The Netherlands

09.15–09.30
OP76 **CLINICOPATHOLOGIC CHARACTERISTICS OF PAPILLARY THYROID CARCINOMA BASED ON AGE GROUPS**
Park YS[1], Jung SP[1], Lee J[1], Kim J[1], Choi MY[1], Lee SK[1], Kil WH[1], Lee JE[1], Nam SJ[1], Choe JH[1], Kim JH[1], Kim JS[1]
[1]Sungkyunkwan Univ., School of Medicine, Department of Surgery, Seoul, Korea, Republic of

09.30–09.45
OP77 **PAPILLARY THYROID CANCER GENE PROFILE MODIFICATION OVER THE LAST 15 YEARS**
Romei C[1], Fugazzola L[2], Puxeddu E[3], Frasca F[4], Viola D[1], Muzza M[2], Moretti S[3], Nicolosi ML[4], Giani C[1], Cirello V[2], Avenia N[5], Rossi S[6], Vitti P[1], Pinchera A[1], Elisei R[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy, [2]University of Milano, Department of Medical Sciences, Milano, Italy, [3]University of Perugia, Department of Medicine, Perugia, Italy, [4]University of Catania, Department of Clinical and Molecula Biomedicine, Catania, Italy, [5]University of Perugia, Department of Surgical, Radiological and Odontostomatologic Sciences, Perugia, Italy, [6]AO San Paolo, Department of Anatomic Pathology, Milano, Italy

09.45–10.00
OP78 **THE MAJOR IMPORTANCE OF AGE AT EXPOSURE AND LATENCY ON THE NUMBER AND PROPORTION OF THYROID CARCINOMAS IN BELARUS DUE TO CHERNOBYL, A 25 YEAR STUDY**
Demidchik Y[1], Williams D[2]
[1]Belarussian State Medical University, Minsk, Belarus, [2]Cambridge University, Cambridge, United Kingdom

10.00–10.15
OP79 **IS THE GENETIC PREDISPOSITION TO PAPILLARY MICROCANCER THE SAME AS FOR CLINICALLY EVIDENT PTC?**
Kalemba M[1], Handkiewicz-Junak D[1], Kula D[1], Oczko-Wojciechowska M[1], Kowal M[1], Tyszkiewicz T[1], Zebracka-Gala J[1], Polańska J[2], Jarzab B[1]
[1]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Dept. of Nuclear Medicine and Endocrine Oncology, Gliwice, Poland, [2]Silesian University of Technology, Institute of Automatic Control, Gliwice, Poland

10.15–10.30
OP80
THE PREVALENCE OF RAS MUTATIONS IN AN ITALIAN MEDULLARY THYROID CANCER SERIES AND A META-ANALYSIS OF PUBLISHED STUDIES
Ciampi R[1], Mian C[2], Fugazzola L[3], Cosci B[1], Romei C[1], Barollo S[2], Cirello V[3], Bottici V[1], Marconcini G[1], Pelizzo MR[4], Borrello MG[5], Basolo F[6], Ugolini C[6], Materazzi G[6], Pinchera A[1], Elisei R[1]
[1]Università di Pisa, Department of Endocrinology and Metabolism, Pisa, Italy, [2]Università di Padova, Department of Medicine-DIMED, Padova, Italy, [3]Fondazione IRCCS Ca' Granda, Endocrine Unit, Milano, Italy, [4]Università di Padova, Department of Surgical, Oncological and Gastroenterological Sciences- DISCOG, Padova, Italy, [5]Fondazione IRCCS Istituto Nazionale dei Tumori, Experimental Oncology Department-U.O. Molecular Mechanisms, Milano, Italy, [6]Università di Pisa, Department of Surgery, Pisa, Italy

10.30–10.45
OP81 **DIAGNOSTIC IMPACT OF THE DETECTION OF POINT MUTATIONS AND REARRANGEMENTS IN 320 ROUTINE AIR DRIED FINE NEEDLE ASPIRATION (FNA) SMEARS**
Eszlinger M[1], Muenz S[1], Ferraz C[1], Rehfeld C[1], Krogdahl A[2], Jensen E[2], Boesenberg E[1], Hegedus L[3], Paschke R[1]
[1]University of Leipzig, Divisions of Endocrinology and Nephrology, Leipzig, Germany, [2]Odense University Hospital, Department of Pathology, Odense, Denmark, [3]Odense University Hospital, Department of Endocrinology and Metabolism, Odense, Denmark

10.45–11.00
OP82 **EXPRESSION PATTERNS IN PAPILLARY THYROID CARCINOMAS WITH BRAF V600E OR RET/PTC SUGGESTS ACTIVATION OF DIFFERENT PATHWAYS**
Bastos AU[1], Oler G[1], Cerutti JM[1]
[1]Genetic Bases of Thyroid Tumors Laboratory, Universidade Federal de São Paulo, Department of Morphology and Genetics, São Paulo, Brazil

Fermi Hall
09.00–11.00

Oral Session 12: Thyroid Basic 2 (OP83-OP90)

Chairs: *Lutz Schomburg* (Germany)
Luca Persani (Italy)

09.00–09.15
OP83 **DOSE DEPENDENT EFFECTS OF A BLOCKING TYPE MONOCLONAL AUTOANTIBODY (K1-70) IN HYPERTHYROID RATS**
Furmaniak J[1], Sanders J[1], Young S[1], Kabelis K[1], Sanders P[1], Evans M[1], Clark J[1], Wilmot J[1], Rees Smith B[1]
[1]FIRS Laboratories, RSR Ltd, Cardiff, United Kingdom

09.15–09.30
OP84 **MOLECULAR SAMPLING OF TSH RECEPTOR ALLOSTERIC BINDING POCKET: SWITCHING AGONISM TO ANTAGONISM AND REVERSE**
Hoyer I[1], Haas A-K[1], Furkert J[1], Rutz C[1], Schülein R[1], Krause G[1]
[1]Leibniz-Institut für Molekulare Pharmakologie (FMP), Berlin, Germany

09.30–09.45
OP85
THYROTROPIN RECEPTOR (TSHR) ACTIVATION ENHANCES SUBCUTANEOUS ADIPOGENESIS, FAVOURING BROWN ADIPOSE TISSUE (BAT) FORMATION, A ROLE FOR HYALURONAN?
Zhang L[1], Grennan-Jones F[1], Dayan CM[1], Rees DA[1], Ludgate M[1]
[1]Cardiff University, School of Medicine, Cardiff, United Kingdom

09.45–10.00
OP86 **EFFECTS OF IN VIVO 3-IODOTHYRONAMINE ADMINISTRATION ON GENE EXPRESSION IN ADIPOSE TISSUE, LIVER AND HEART**
Righi M[1], Iofrida C[1], Melissari E[1], Mariotti V[1], Di Russo M[1], Pellegrini S[1], Zucchi R[1]
[1]Università di Pisa, Pisa, Italy

10.00–10.15
OP87 **METABOLOME DYNAMICS OF T1AM, AN ENDOGENOUS THYROID HORMONE DERIVATIVE: EFFECTS ON LIPID METABOLISM, WEIGHT LOSS, AND APPETITE IN MICE**
Assadi-Porter F[1], Reiland H[1], Butz D[1], Tonelli M[1], Ghelardoni S[2], Scanlan T[3], Zucchi R[2], Chiellini G[2]
[1]UWMadison, Biochemistry, Madison, United States, [2]University of Pisa, Scienze dell'Uomo e dell'Ambiente, Pisa, Italy, [3]OHSU Portland, Oregon, Portland, United States

10.15–10.30
OP88 **3,5-DIIODOTHYRONINE ADMINISTRATION IMPROVES CHOLESTEROL METABOLISM IN LDL RECEPTOR KNOCK-OUT MICE (LDLR –/–) BY MODIFYING HEPATIC PROTEOMIC PROFILE**
Moreno M[1], Silvestri E[1], Glinni D[1], Goldberg IJ[2], Ehrenkranz J[3], Scanlan TS[4], Goglia F[1]
[1]University of Sannio, Benevento, Italy, [2]Columbia U. College of Physicians and Surgeons, New York, United States, [3]Intermountain Healthcare, Murray, United States, [4]Oregon Health Sciences University, Portland, United States

10.30–10.45
OP89 **THE ROLE OF CONSERVED CHARGED AMINO ACIDS IN TRANSMEMBRANE DOMAINS OF THE THYROID HORMONE TRANSPORTER MCT8**
Groeneweg S[1], Friesema ECH[1], Visser TJ[1]
[1]Erasmus MC, Internal Medicine, Rotterdam, The Netherlands

10.45–11.00
OP90 **MUTATIONS OF MCT8 IN PATIENTS WITH ALLAN-HERNDON-DUDLEY SYNDROME AFFECT ITS CELLULAR DISTRIBUTION**
Kersseboom S[1], Friesema ECH[1], Visser WE[1], Klootwijk W[1], Visser TJ[1]
[1]Eramus University Medical Center, Internal Medicine, Rotterdam, The Netherlands

11.00–11.15 **Coffee Break**

Fermi Hall
11.15–12.45

Symposium 7: The Importance of Transport and Deiodination in Brain

Chairs: *Josef Köhrle* (Germany)
Domenico Salvatore (Italy)

11.15–11.45	'Secondary' thyroid hormone transporters *Ulrich Schweizer* (Germany)
11.45–12.15	The role of deiodinases in the control of brain gene expression *Juan Bernal* (Spain)
12.15–12.45	The T4 transporter Oatp1c1 *Steffen Mayerl* (Germany)

Main Auditorium
11.15–12.45

Symposium 8: Thyroid Nodules: Update in the Management

Chairs: *Ralf Paschke* (Germany)
Furio Pacini (Italy)

11.15–11.45	Molecular evaluation of indeterminate nodules: is there any added value? *Frédérique Savagner* (France)
11.45–12.15	TSH levels and risk of cancer *Paolo Vitti* (Italy)
12.15–12.45	Non-surgical local intervention *Enrico Papini* (Italy)

Main Auditorium
12.45–13.15

Young Investigator Awards, Poster Prizes, Jack Robbins Prize and Closing Ceremony

You may never meet the patients, but you touch them every day.

It's why you come to work. And it's why we work harder than anyone else to help you serve the doctors and patients who depend on you. Ortho Clinical Diagnostics knows the pressures you face in the lab. We bring you the technology, world-class process consulting and responsive support you need to help doctors make better informed decisions. Every day lives change because of you.

The science of knowing shapes the art of living.

Ortho Clinical Diagnostics

PART OF THE Johnson & Johnson FAMILY OF COMPANIES

European
Thyroid Journal

Full posters are available online from September 7 to December 31 at www.karger.com/etj

Sunday, 9th September 2012

Poster Exhibition Area

12.00–13.00
Poster Session 1

PO1 Medullary Thyroid Cancer Basic/Translational

Chair: *M. Chiara Zatelli* (Italy)

P1 **SIGNIFICANT DIFFERENCES IN FREQUENCIES OF RET POLYMORPHISMS IN HIRSCHSPRUNG'S DISEASE PATIENTS AND ITS ASSOCIATION WITH MEDULLARY THYROID CARCINOMA**

Vaclavikova E[1,2], Dvorakova S[1], Sykorova V[1], Vcelak J[1], Halkova T[1], Skaba R[3], Vlcek P[4], Bendlova B[1]
[1]Institute of Endocrinology, Department of Molecular Endocrinology, Prague, Czech Republic, [2]Faculty of Science, Charles University, Department of Biochemistry, Prague, Czech Republic, [3]2nd Faculty of Medicine, Charles University and Hospital Motol, Department of Pediatric Surgery, Prague, Czech Republic, [4]2nd Faculty of Medicine, Charles University and Hospital Motol, Department of Nuclear Medicine and Endocrinology, Prague, Czech Republic

P2 **TPRAZOSIN INDUCES APOPTOSIS IN MEDULLARY THYROID CARCINOMA CELLS BY TARGETING MULTIPLE ORGANELLES**

Fuchs R[1], Schwach G[1], Rinner B[2], Stracke A[1], Allard N[1], Kueznik T[2], Froehlich E[2], Birner-Gruenberger R[2], Sadjak A[1], Roswitha P[1]
[1]Medical University of Graz, Institute of Pathophysiology and Immunology, Graz, Austria, [2]Medical University of Graz, Center for Medical Research, Graz, Austria

P3 **IDENTIFICATION OF NOVEL VARIANTS OF RET ONCOGENE POTENTIALLY LINKED TO THE PATHOGENESIS OF PHEOCHROMOCYTOMA AND MEDULLARY THYROID CARCINOMA**

Bim LV[1], Delcelo R[2], Lima Jr. JV[3,4], Dias da Silva MR[4], Maciel RM[4], Cerutti JM[1]
[1]Universidade Federal de São Paulo, Genetic Bases of Thyroid Tumor Laboratory, Department of Morfology and Genetics, São Paulo, Brazil, [2]Universidade Federal de São Paulo, Department of Pathology, São Paulo, Brazil, [3]Hospital Santa Casa de São Paulo, Department of Endocrinology, São Paulo, Brazil, [4]Universidade Federal de São Paulo, Department of Endocrinology, São Paulo, Brazil

P4 **ANGIOGENESIS-RELATED GENE EXPRESSION PROFILE ASSOCIATED WITH RET MUTATIONS IN MEDULLARY THYROID CANCER PATIENTS**

Durante C[1], Sponziello M[1], Checquolo S[2], Boichard A[3], Dima M[1], Verrienti A[1], Tamburrano G[1], Russo D[4], Schlumberger M[5], Bidart J-M[3], Filetti S[1]
[1]University of Rome Sapienza, Department of Internal Medicine and Medical Specialties, Rome, Italy, [2]University of Rome Sapienza, Department of Experimental Medicine, Rome, Italy, [3]Institut de Cancérologie Gustave Roussy, Laboratoire de Recherche Translationnelle, Villejuif, France, [4]University of Catanzaro Magna Graecia, Department of Pharmacobiological Sciences, Catanzaro, Italy, [5]Institut de Cancérologie Gustave Roussy, Départment de médecine nucléaire et de carcinologie endocrinienne, Villejuif, France

P5 **DIFFERENTIAL HES1 METHYLATION PROFILE IN FAMILIAL AND SPORADIC MEDULLARY THYROID CANCER**

Cardoso MG[1], Kizys MML[2], Harada MY[2], Ierardi DF[3], Molognoni F[3], Lindsey SC[2], Valente FOF[2], Delcelo R[4], Martins JRM[2], Maciel RMB[2], Jasiulionis MG[3], Dias da Silva MR[2]
[1]Universidade Federal de Sao Paulo, Biochemistry, Sao Paulo, Brazil, [2]Universidade Federal de Sao Paulo, Medicine, Sao Paulo, Brazil, [3]Universidade Federal de Sao Paulo, Pharmacology, Sao Paulo, Brazil, [4]Universidade Federal de Sao Paulo, Pathology, Sao Paulo, Brazil

P6 **EXPRESSION PATTERN OF MATRIX METALLOPROTEASES IN HUMAN MEDULLARY THYROID CARCINOMA CELL LINES**

Ghaffari Tabrizi N[1], Haas HS[1], Fuchs R[1], Schwach G[1,2], Allard N[1], Webersinke G[3], Sadjak A[1], Pfragner R[1]
[1]Medical University of Graz, Institute of Pathophysiology and Immunology, Graz, Austria, [2]Yale School of Surgery, Department of Surgery, New Haven, United States, [3]Hospital Barmherzige Schwestern, Department of Internal Medicine, Laboratory for Molecular Biology and Tumorcytogenetics, Linz, Austria

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/etj

P7 **MICRORNA PROFILES IN FAMILIAL AND SPORADIC MEDULLARY THYROID CARCINOMA: PRELIMINARY RELATIONSHIPS WITH RET STATUS AND OUTCOME**

Mian C[1], Pennelli G[1], Fassan M[1], Balistreri M[1], Barollo S[1], Cavedon E[1], Galuppini F[1], Pizzi M[1], Vianello F[2], Pelizzo MR[1], Girelli ME[1], Opocher G[2], Rugge M[1]
[1]University of Padua, Padua, Italy, [2]Veneto Institute of Oncology -IRCCS, Padua, Italy

P8 **SUNITIB REDUCES CELL VIABILITY IN PRIMARY CULTURES AND IN A CELL LINE OF MEDULLARY THYROID CARCINOMA**

Rossi M[1], Gentilin E[1,2], Minoia M[1], Tagliati F[1], degli Uberti E[1,2], Zatelli MC[1,2]
[1]University of Ferrara, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy, [2]LTTA, University of Ferrara, Ferrara, Italy

P9 **MTOR INHIBITORS HAMPERS CELL VIABILITY IN SELECTED HUMAN MEDULLARY THYROID CARCINOMA PRIMARY CULTURES**

Minoia M[1], Rossi M[1], Tagliati F[1], Rossi R[1], degli Uberti E[1,2], Zatelli MC[2,3]
[1]University of Ferrara, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy, [2]LTTA, University of Ferrara, Ferrara, Italy, [3]University of Ferrara, Section of Endocrinology, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy

P10 **HIGH PREVALENCE OF RAS MUTATIONS IN SPORADIC MEDULLARY THYROID CARCINOMA**

Sykorova V[1], Dvorakova S[1], Vaclavikova E[1,2], Halkova T[1,2], Ryska A[3], Kodet R[4], Kodetova D[4], Astl J[5], Betka J[5], Duskova J[6], Vlcek P[7], Novak Z[8], Bendlova B[1]
[1]Institute of Endocrinology, Department of Molecular Endocrinology, Prague, Czech Republic, [2]Charles University, Faculty of Science, Department of Biochemistry, Prague, Czech Republic, [3]Charles University Faculty of Medicine and University Hospital, The Fingerland Department of Pathology, Hradec Kralove, Czech Republic, [4]2nd Faculty of Medicine and Faculty Hospital Motol, Department of Pathology and Molecular Medicine, Prague, Czech Republic, [5]1st Faculty of Medicine and Faculty Hospital Motol, Charles University, Department of Otorhinolaryngology and Head and Neck Surgery, Prague, Czech Republic, [6]Institute of Pathology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [7]2nd Faculty of Medicine, Charles University and Hospital Motol, Department of Nuclear Medicine and Endocrinology, Prague, Czech Republic, [8]Institute of Endocrinology, Department of Clinical Endocrinology, Prague, Czech Republic

P11 **COMPARISON OF THE FREQUENCY OF VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS) IN RET ONCOGENE BETWEEN PATIENTS WITH MEDULLARY THYROID CANCER (MTC) AND AN UNAFFECTED CONTROL POPULATION**

Lindsey SC[1], Germano Neto F[1], Kunii IS[1], Sittoni MY[1], Camacho CP[1], Valente FOF[1], Yang JH[1], Signorini PS[1], Maciel RMB[1], Dias da Silva MR[1]
[1]Federal University of São Paulo, Medicine, São Paulo, Brazil

PO2 Thyroid Cancer Diagnostics Clinical 1

Chair: *Jean Louis Wemeau* (France)

P12 **THE COMBINATION OF AUTOIMMUNE TIREODIT AND MALIGNANT LESIONS OF THYROID TISSUE**

Ryabchenko E[1]
[1]Krasnodar Municipal Medicinal - Diagnostic Association, Department of Endocrinologycal Surgery, Krasnodar, Russian Federation

P13 **CONVENTIONAL PAPILLARY THYROID CARCINOMA IN CHILDREN AND ADOLESCENTS**

Frydman M[1], Mankovskaya S[1], Savva N[2], Krasko O[3], Schmid KW[4], Demidchik Y[5]
[1]Republic Centre of Thyroid Tumors, Pathology, Minsk, Belarus, [2]Republic Scientific and Practical Centre for Childhood Tumors and Hematology, Childhood Cancer SubRegistry of the Republic of Belarus, Minsk, Belarus, [3]United Institute of Informatics Problems, Biomedical Statistic, Minsk, Belarus, [4]University Hospital of Essen, University of Duisburg-Essen, Institute of Pathology and Neuropathology, Essen, Germany, [5]Republic Centre of Thyroid Tumors, Surgery, Minsk, Belarus

P14 **UNDETECTABLE PRE-ABLATION THYROGLOBULIN LEVELS IN PATIENTS WITH DIFFERENTIATED THYROID CANCER: NOT ALWAYS WHAT IT SEEMS**

Pitoia F[1], Bueno F[1], Abelleira E[1], Salvai ME[1], Niepomniszcze H[1]
[1]Hospital de Clinicas - University of Buenos Aires, Buenos Aires, Argentina

P15 **INTRINSIC FACTORS AFFECTING ADEQUACY IN THYROID NODULE FINE-NEEDLE ASPIRATION CYTOLOGY**

Grani G[1], Calvanese A[1], Carbotta G[1], D'Alessandri M[1], Nesca A[1], Bianchini M[1], Del Sordo M[1], Fumarola A[1]
[1]Sapienza University of Rome, Dept. of Experimental Medicine, Rome, Italy

P16 **DETECTION OF RESIDUAL THYROID TISSUE AFTER TOTAL THYROIDECTOMY FOR DIFFERENTIATED THYROID CARCINOMA**

Nabawi A[1], Al-Wagih H[1], Zakarya SED[1], El serfay M[2], Arafat W[3], Mansour F[1]
[1]Alexandria University, Faculty of Medicine, Surgery, Alexandria, Egypt, [2]Alexandria University, Faculty of Medicine, Radiology, Alexandria, Egypt, [3]Alexandria University, Faculty of Medicine, Clinical Oncology, Alexandria, Egypt

P17 **THE UTILITY OF BONE SCINTIGRAPHY AND THORAX CT BEFORE RAI TREATMENT FOR DETECT BONE AND LUNG METASTASES**

Ozkaya M[1], *Elboga U*[2], *Kalender E*[2], *Celen YZ*[2]
[1]University of Gaziantep, Endocrinology, Gaziantep, Turkey, [2]University of Gaziantep, Nuclear Medicine, Gaziantep, Turkey

P18 **UNDERUSE OF DIAGNOSTIC POSSIBILITIES IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMAS**

Lincke T[1], *Dörnfelder M*[2], *Paschke R*[3], *Sabri O*[1]
[1]Uniklinik für Nuklearmedizin, Leipzig, Germany, [2]Uniklinik, Leipzig, Germany, [3]Uniklinik für Endokrinologie, Leipzig, Germany

P19 **MULTIFOCAL PAPILLARY THYROID CARCINIOMA ASSESSMENT IN PATIENTS WITH HASHIMOTO THYROIDITIS AFTER POSSIBLE RADIATION EXPOSURE**

Zaplatnikov K[1], *Soukhov V*[2]
[1]Clinic for Nuclearmedicine Nuernberg, Nuclearmedicine, Nuernberg, Germany, [2]Militar Medical Academy St. Petersburg, Nuclermedicine, St. Petersburg, Russian Federation

P20 **POORLY DIFFERENTIATED FORMS OF THYROID CARCINOMA ARE OVER REPRESENTED IN CANCER DIAGNOSED AT AN ADVANCED STAGE. PRELIMINARY ANALYSIS OF A FRENCH PROSPECTIVE COHORT IN THE FRAME OF TUTHYREF NETWORK**

Bournaud C[1], *Decaussin M*[2], *Cimarelli S*[3], *de la Fouchardière C*[3], *Nejjari Z*[4], *Sassolas G*[4], *Bringuier PP*[2], *Mognetti T*[3], *Masson S*[1], *Borson Chazot F*[1,4], *Schlumberger M*[5], *TUTHYREF network*
[1]Groupement Hospitalier Lyon-Est, Federation d'Endocrinologie et CMN, Bron Cedex, France, [2]Groupement Hospitalier Lyon-Sud, Service de Chirurgie et Anapathologie, Lyon, France, [3]CLCC Léon Bérard, Lyon, France, [4]CRCL Inserm U1052, Université Lyon 1, Lyon, France, [5]Institut Gustave Roussy, Service de Médecine Nucléaire et Endocrinologie, Paris, France

P21 **ULTRASONOGRAPHIC FEATURES OF PAPILLARY CARCINOMA: FIVE-YEAR EXPERIENCE IN THYROID REFFERAL CENTER**

Sisko Markos I[1], *Franceschi M*[1], *Roncevic S*[1], *Gladic Nenadic V*[1], *Matesa N*[1], *Kusic Z*[1]
[1]University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia

P22 **FEASIBILITY OF REAL-TIME PCR TESTING FOR BRAF V600E MUTATIONS IN FINE-NEEDLE ASPIRATES OF THYROID TISSUE**

Lozano MD[1], *Labiano T*[1], *Montanana M*[1], *Echeveste JI*[1], *Lawrence HJ*[2], *Shieh F*[2], *Algarra SM*[1]
[1]Universidad de Navarra, Department of Oncology, Pamplona, Spain, [2]Roche Molecular Systems, Genomics and Oncology, Pleasanton, United States

P23 **FIRST UK THYROID CANCER AWARENESS CAMPAIGN**

Farnell K[1], *Perros P*[1], *Bliss R*[1], *Mallick UK*[1]
[1]Freeman Hospital, Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom

P24 **RATE, TIME AND RISK FACTORS FOR RECURRENCE IN PATIENTS AFFECTED WITH DIFFERENTIATED THYROID CANCER (DTC): A 10 YEAR PROSPECTIVE STUDY**

Pieruzzi L[1], *Molinaro E*[1], *Giani C*[1], *Marconcini G*[1], *Viola D*[1], *Valerio L*[1], *Biagini A*[1], *Bianchi F*[1], *Brozzi F*[1], *Taddei D*[1], *Nencetti C*[1], *Pinchera A*[1], *Vitti P*[1], *Elisei R*[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy

PO3 Thyroid Cancer Pathogenesis Basic

Chair: *Martin Schlumberger* (France)

P25 **FREQUENT INCIDENCE OF BRAF MUTATION IN POST-CHORNOBYL PAPILLARY THYROID CARCINOMA**

Dinets A[1,2], *Hulchiy M*[2], *Sofiadis A*[1], *Ghaderi M*[3], *Höög A*[3], *Larsson C*[1], *Zedenius J*[1]
[1]Karolinska Institutet, Molecular Medicine and Surgery, Stockholm, Sweden, [2]Kyiv City Teaching Endocrinlogical Center, Endocrine Surgery, Kyiv, Ukraine, [3]Karolinska University Hospital, Pathology-Cytology, Stockholm, Sweden

P26 **HIGHER EXPRESSION OF AMPK AND PHOSPHO-THR172-AMPK IN PAPILLARY THYROID CANCER**

Andrade B[1], *Vidal AP*[2], *Vaisman F*[3], *Cazarin J*[1], *Caroli-Bottino A*[2], *Corbo R*[4], *Vaisman M*[2], *Carvalho D*[1]
[1]Federal University of Rio de Janeiro, IBCCF, Rio de Janeiro, Brazil, [2]Federal University of Rio de Janeiro, Clementino Fraga Filho University Hospital-UFRJ, Rio de Janeiro, Brazil, [3]Federal University of Rio de Janeiro/ National Institute of Cancer, Endocrine Service - Clementino Fraga Filho University Hospital-UFRJ, Rio de Janeiro, Brazil, [4]National Institute of Cancer, Rio de Janeiro, Brazil

P27 **CHARACTERISTICS OF ADULT-ONSET PAPILLARY THYROID CANCER WITH REARRANGED ALK GENE IN ATOMIC BOMB SURVIVORS**

Hamatani K[1], *Mukai M*[1], *Takahashi K*[1], *Hayashi Y*[2], *Nakachi K*[1], *Kusunoki Y*[1]
[1]Radiation Effects Research Foundation, Radiobiology/ Molecular Epidemiology, Hiroshima, Japan, [2]Geriatric Health Service Facility Hidamari, Hiroshima, Japan

P28 **GENETIC PREDISPOSITION TO THE DIFFERENTIATED THYROID CANCER**

Köhler A[1,2], Chen B[1], Gemignani F[3], Elisei R[4], Romei C[4], Kalemba M[2], Kula D[2], Broderick P[5], Houlston R[5], Jarząb B[2], Hemminki K[1,6], Landi S[3], Försti A[1,6]
[1]German Cancer Research Center (DKFZ), Molecular Genetic Epidemiology, Heidelberg, Germany, [2]Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Department of Nuclear Medicine and Endocrine Oncology, Gliwice, Poland, [3]University of Pisa, Department of Biology, Pisa, Italy, [4]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy, [5]Institute of Cancer Research, Section of Cancer Genetics, Sutton, United Kingdom, [6]Lund University, Center for Primary Health Care Research, Clinical Research Center, Malmö, Sweden

P29 **EXPRESSION OF THE RING LIGASE PRAJA2 IN THYROID CANCER**

Cantara S[1], D'Angeli F[1], Toti P[2], Castagna MG[1], Capuano S[1], Feliciello A[3], Pacini F[1]
[1]University of Siena, Department of Internal Medicine, Endocrinology & Metabolism and Biochemistry, Siena, Italy, [2]University of Siena, Department of Human Pathology and Oncology, Siena, Italy, [3]University of Naples, Federico II, Department of Biology and Molecular and Cellular Pathology 'L. Califano', Naples, Italy

P30 **HUMAN MAST CELL-DERIVED MEDIATORS INDUCE EPITHELIAL-TO MESENCHYMAL TRANSITION IN THYROID CANCER CELLS**

Visciano C[1], Liotti F[1], Prevete N[2], Sabetta RL[1], de Paulis A[2], Marone G[2], Santoro M[1], Melillo RM[1]
[1]University of Naples, Federico II, Dipartimento di Biologia e Patologia Cellulare e Molecol, Naples, Italy, [2]University of Naples, Federico II, Divisione di Immunologia Clinica ed Allergologia e Centro Interdipartimentale di Ricerca in Scienze Immunologiche di Base e Cliniche, Naples, Italy

P31 **LOSS OF HETEROZYGOSITY OF TUMOR SUPRESSOR GENES(FHIT, P16, RB, E-CADHERIN, P53) IN THYROID TUMORS**

Kim JH[1], Rho YS[2], Lee DJ[1], Park IS[3], Jung EJ[2]
[1]Hallym University Kangnam Sacred Heart Hospital, Otorhinolaryngology-Head and Neck Surgery, Seoul, Korea, Republic of, [2]Hallym University Kangdong Sacred Heart Hospital, Otorhinolaryngology-Head and Neck Surgery, Seoul, Korea, Republic of, [3]Hallym University Hankang Sacred Heart Hospital, Otorhinolaryngology-Head and Neck Surgery, Seoul, Republic of Korea

P32 **THYROID CANCER AND ACROMEGALY: INCIDENTAL ASSOCIATION?**

Achir S[1], Hasbellaoui F[2], Ziani K[2], Khalifa A[2], Semrouni M[2]
[1]Medical University of Algiers, Endocrinology, Algiers, Algeria, [2]Medical University of Algiers, Algiers, Algeria

P33 **MAPPING OF GENE EXPRESSION PATTERNS OF EPH RECEPTORS AND EPHRIN LIGANDS IN HUMAN THYROID CANCERS**

Liang S[1], Javadi A[1], Hussein Z[1], Ingeson C[1], Nilsson M[1]
[1]Sahlgrenska Cancer Center, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

P34 **EXPRESSION OF PODOLANIN AND TRANSCRIPTION FACTOR PROX 1 IN THYROID CANCER CELLS**

Sikorska J[1], Rudzińska M[1], Strzyżewska-Jówko I[1], Czerwińska J[2], Kiedrowski M[3], Olszewski W[3], Górnicka B[4], Sowiński J[5], Czarnocka B[1]
[1]Medical Center of Postgraduate Education, Department of Biochemistry and Molecular Biology, Warsaw, Poland, [2]Medical Center of Postgraduate Education, Department of Pathology, Warsaw, Poland, [3]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Department of Pathology, Warsaw, Poland, [4]Medical University of Warsaw, Department of Pathology, Warsaw, Poland, [5]Poznan University of Medical Sciences, Department of Endocrynology, Poznań, Poland

P35 **XRCC1 POLYMORPHISMS AND THE RISK OF PAPILLARY THYROID CANCER IN THE CZECH COHORT**

Halkova T[1,2], Vaclavikova E[1], Sykorova V[1], Dvorakova S[1], Vcelak J[1], Kodetova D[3], Kodet R[3], Astl J[4], Betka J[4], Vlcek P[5], Bendlova B[1]
[1]Institute of Endocrinology, Department of Molecular Endocrinology, Prague, Czech Republic, [2]Charles University, Faculty of Science, Department of Biochemistry, Prague, Czech Republic, [3]2nd Faculty of Medicine and Faculty Hospital Motol, Department of Pathology and Molecular Medicine, Prague, Czech Republic, [4]1st Faculty of Medicine and Faculty Hospital Motol, Charles University, Department of Otorhinolaryngology and Head and Neck Surgery, Prague, Czech Republic, [5]2nd Faculty of Medicine, Charles University, Department of Nuclear Medicine and Endocrinology, Prague, Czech Republic

PO4 Thyroid Cancer Therapeutics Clinical 1

Chair: *Camilla Schalin-Jäntti* (Finland)

P36 **SALIVARY GLAND DYSFUNCTION AFTER RADIOIODINE ABLATION IN A MURINE MODEL**

Choi J-S[1], Lim J-Y[1], Kim S-K[2], Kim Y-M[1]
[1]Department of Otorhinolaryngology, Inha University College of Medicine, Incheon, Korea, Republic of, [2]Department of Nuclear Medicine, National Cancer Center, Goyang, Republic of Korea

P37 **POST-THYROIDECTOMY CHYLOUS FISTULA. PLEASE GIVE YOUR PATIENT A CHANCE**

Abdelrahman TEF[1], Hassanein KM[2], Amer I[2], Gaber MA[1]
[1]Sohag University, Head and Neck Surgery Unit, Department of Surgery, Sohag, Egypt, [2]Sohag University, Maxillofacial , Head and Neck Surgery, Sohag, Egypt

P38 **MULTIPLICITY AS A PROGNOSTIC FACTOR OF PAPILLARY THYROID CARCINOMA**

Kim JM[1], Won JC[1], Ko KS[1], Rhee BD[1]
[1]Sanggye Paik Hospital, Inje University College of Medicine, Department of Internal Medicine, Seoul, Republic of Korea

P39 **DOES HÜRTHLE CELL CARCINOMA OF THE THYROID HAVE A POORER PROGNOSIS THAN ORDINARY FOLLICULAR THYROID CARCINOMA?**

Sugino K[1], Kameyama K[2], Ito K[1], Nagahama M[1], Kitagawa W[1], Shibuya H[1], Okuwa K[1], Yano Y[1], Uruno T[1], Suzuki A[1], Masaki C[1], Ito K[1]
[1]Ito Hospital, Surgery, Tokyo, Japan, [2]Keio University Hospital, Pathology, Tokyo, Japan

P40 **RADIOIODINE REMNANT ABLATION IN LOW-RISK PAPILLARY THYROID CARCINOMA: COMPARISON OF POST-SURGICAL STIMULATED THYROGLOBULIN PROTOCOL VERSUS CONVENTIONAL CARE ON RADIOIDINE ADMINISTRATION RATES AND RECURRENCE**

Etarsky D[1], Orlov S[1], Freeman JL[2], Walfish PG[1,2]
[1]Mount Sinai Hospital/University of Toronto, Department of Medicine, Endocrine Division, Toronto, Canada, [2]Mount Sinai Hospital/University of Toronto, Department of Otolaryngology-Head and Neck Surgery, Toronto, Canada

P41 **COMPARISON OF SURGICAL OUTCOMES BETWEEN HARMONIC ACE® AND LIGASURE PRECISE™ HEMOSTASIS IN OPEN THYROIDECTOMY OF PAPILLARY THYROID CANCINOMA : A PROSPECTIVE RANDOMIZED STUDY (PRELIMINARY REPORT)**

Kwak HY[1], Bae JS[1], Chae BJ[1], Song BJ[1], Jung SS[1]
[1]Seoul Saint Mary's Hospital, The Catholic University of Korea, Department of Surgery, Seoul, Republic of Korea

P42 **PERCUTANEOUS LASER ABLATION OF NECK RECURRENCES OF THYROID CANCER. A FEASIBILITY AND CLINICAL STUDY**

Papini E[1], Bizzarri G[2], Misischi I[1], Bianchini A[2], Valle D[2], Guglielmi R[1], Crescenzi A[3], Pedrazzini L[4], Baroli A[4], Salvatori M[5], Solbiati L[6], Pacella CM[2]
[1]Regina Apostolorum Hospital, Department of Endocrinology, Albano Laziale, Rome, Italy, [2]Regina Apostolorum Hospital, Department of Radiology and Diagnostic Imaging, Albano Laziale, Rome, Italy, [3]Regina Apostolorum Hospital, Anatomic Pathology Unit, Albano Laziale, Rome, Italy, [4]Circolo Hospital, Nuclear Medicine Unit, Busto Arsizio, Varese, Italy, [5]Policlinico Universitario A.Gemelli, Catholic University, Nuclear Medicine Institute, Rome, Italy, [6]Circolo Hospital, Department of Radiology, Busto Arsizio (VA), Italy

P43 **PROGNOSTIC FACTORS OF REFRACTORY PULMONARY METASTATIC DIFFERENTIATED THYROID CARCINOMAS (DTC)**

Wassermann J[1], Bernier M-O[1], Spano J-P[2], Simon J-M[3], Ménégaux F[4], Lepoutre C[1], Aurengo A[1], Leenhard L[1]
[1]Pitié-Salpêtrière University Hospital, Nuclear Medicine, Paris, France, [2]Pitié-Salpêtrière University Hospital, Medical Oncology, Paris, France, [3]Pitié-Salpêtrière University Hospital, Radiotherapy, Paris, France, [4]Pitié-Salpêtrière University Hospital, Endocrine Surgery, Paris, France

P44 **IS THYROID CANCER RECURRENCE RISK INCREASED AFTER TRANSPLANTATION?**

Tisset H[1], Kamar N[2], Faugeron I[3], Pouteil-Noble C[4], Klein M[5], Mourad G[6], Frimat L[7], Drui D[8], Docao C[9], Vantyghem M-C[9], Noel C[10], Leenhardt L[11], Rodien P[12], Bonichon F[13], Morelon E[14], Leboulleux S[15], Bournaud C[1], Kelly A[16], Niccoli P[17], Schlumberger M[15], Borson Chazot F[1]
[1]Groupement Hospitalier Lyon-Est, Federation d'Endocrinologie et CMN, Bron cedex, France, [2]CHU Rangueil, Service de Néphrologie, HTA, Dialyse, et Transplantation d'Organes, Toulouse, France, [3]Hôpital de Saint Louis, Service de Médecine Nucléaire, Paris, France, [4]Hôpital Lyon Sud, Service de Néphrologie, Lyon, France, [5]CHU Nancy, Service d'Endocrinologie, Nancy, France, [6]Hôpital Lapeyronie, Service de Néphrologie, Transplantation, Montpellier, France, [7]CHU - Hôpital de Brabois, Service de Néphrologie, Nancy, France, [8]Hôpital G&R Laënnec Saint Herblain, Endocrinologie, Maladies Métaboliques et Nutrition, Saint-Herblain, France, [9]CHRU Lille, Service Endocrinologie, Lille, France, [10]CHRU Lille, Service Endocrinologie CHRU Lille, Lille, France, [11]Hôpital Pitié-Salpetrière, Service de médecine nucléaire, Paris, France, [12]CHU d'Angers, Service d'Endocrinologie, Angers, France, [13]Institut Bergonié Bordeaux, Service de Médecine Nucléaire, Bordeaux, France, [14]Hôpital Edouard Herriot, Service de Néphrologie, Lyon, France, [15]Institut Gustave Roussy, Service de Médecine Nucléaire et Cancérologie Endocrinienne, Paris, France, [16]Centre Jean Perrin, Service de Médécine Nucléaire, Clermont-Ferrand, France, [17]CHU La Timone, Service d'Oncologie Médicale, Marseille, France

P45 **OFF-LABEL USE OF SUNITINIB IN PATIENTS WITH ADVANCED, EPITHELIAL THYROID CANCER: A RETROSPECTIVE ANALYSIS**

Pasqualetti G[1], Ricci S[2], Boni G[3], Tognini S[1], Polini A[1], Mariani G[3], Ferdeghini M[4], Monzani F[1]
[1]University of Pisa, Geriatrics Unit, Internal Medicine, Pisa, Italy, [2]University Hospital of Pisa, Oncology Unit, Pisa, Italy, [3]University Hospital of Pisa, Nuclear Medicine Unit, Department of Oncology and Transplantation, Pisa, Italy, [4]University of Verona, Department of Morphological-Biomedical Sciences, Verona, Italy

P46 **WHAT THE BEST TIME TO PERFORM POST-THERAPEUTIC 131I WHOLE BODY SCAN? COMPARISON BETWEEN EARLY AND LATE IMAGES**

Perotti G[1], Mazza R[2], Ianni F[3], Maussier ML[1], Paragliola RM[3], Ricciato MP[3], Salvatori M[1], Pontecorvi A[3]
[1]Catholic University of Sacred Heart, Institute of Nuclear Medicine, Rome, Italy, [2]Azienda Ospedaliera Universitaria, Nuclear Medicine, Parma, Italy, [3]Catholic University of Sacred Heart, Unit of Endocrinology, Rome, Italy

P47 **CENTRAL PATHOLOGY CONFIRMATION OF ANAPLASTIC THYROID CANCER (ATC) DEMONSTRATES HIGH RATE OF CONCORDANCE WITH LOCAL PATHOLOGY REVIEW IN A RANDOMIZED TRIAL OF THE VASCULAR DISRUPTING AGENT (VDA) FOSBRETABULIN TROMETHAMINE (CA4P) IN COMBINATION WITH CARBOPLATIN (C) AND PACLITAXEL (P) (FACT STUDY)**

Balkissoon J[1], Sosa JA[2], Lu S-P[1], Langecker P[1], Jarzab B[3], Bal CS[4], Koussis H[5], Marur S[6], Gramza A[7], Gitlitz B[8], Haugen B[9], Ondrey F[10], Lu C[11], Karandikar SM[12], Licitra L[13], Elisei R[14]
[1]Oxigene, Oncology, South San Francisco, United States, [2]Yale University, School of Medicine, Surgery, New Haven, United States, [3]MSC Cancer Center, Endocrinology, Gliwice, Poland, [4]AIIMS, Nuclear Medicine, New Delhi, Delhi, India, [5]IOV, Policlinico Universitario, Oncology, Padova, Italy, [6]Johns Hopkins University School of Medicine, Sidney Kimmel Cancer Center, Baltimore, United States, [7]National Cancer Institute, NIH, Oncology, Bethesda, United States, [8]USC/Norris Cancer Center, Oncology, Los Angeles, United States, [9]University of Colorado Cancer Center, Endocrinology, Aurora, United States, [10]University of Minnesota, Otolaryngology, Head and Neck Surgery, Minneapolis, United States, [11]Universtiy of Texas, M.D. Anderson Cancer Center, Thoracic/Head and Neck Oncology, Houston, United States, [12]Ruby Hall Clinic, Oncology, Pune, India, [13]Instituto Nazionale Per Lo Studio E La Cura Dei Tumori, Oncology, Milano, Italy, [14]University of Pisa, School of Medicine, Endocrinology and Metabolism, Pisa, Italy

PO5 Clinical Thyroid Autoimmunity 1

Chair: *Patrice Rodien* (France)

P48 **SERUM PEPSINOGEN I AND GASTRIN-17 LEVELS ARE PREDICTABLE OF ATROPHIC GASTRITIS IN PATIENTS WITH AUTOIMMUNE THYROIDITIS AND ANTI-GASTRIC PARIETAL CELL AUTOANTIBODIES**

Russo S[1], Provenzale MA[2], De Bortoli N[1], Martinucci I[1], Fiore E[2], Marchi S[1], Vitti P[2]
[1]University of Pisa, UO of Gastroenterology -Department of Internal Medicine, Pisa, Italy, [2]University of Pisa, Endocrinology, Pisa, Italy

P49 **HUMAN RADOIMMUNE ASSAYS FOR DIAGNOSTICS AND PROGNOSIS OF MIXED FORMS OF IMMUNTHYROIDITIS**

Soukhov V[1], Zaplatnikov K[2]
[1]Militar Medical Academy St. Petersburg, Nuclermedicine, St. Petersburg, Russian Federation, [2]Clinic for Nuclearmedicine Nuernberg, Nuclearmedicine, Nuernberg, Germany

P50 **NUTRITIONAL FACTORS MAY BE INVOLVED IN THE DEVELOPMENT OF THYROID AUTOANTIBODIES IN WOMEN**

Giannakou M[1], Saltiki K[1], Loukari E[1], Philippou G[1], Terzidis K[1], Spina J[1], Lili K[1], Stavrianos C[1], Mantzou E[1], Alevizaki M[1]
[1]Athens University School of Medicine, Dept of Endocrinology and Metabolism "Evgenidion" Hospital, Athens, Greece

P51 **DECREASED SERUM 25-HYDROXY-VITAMIN D3 IS ASSOCIATED WITH THE PRESENCE OF THYROID PEROXIDASE ANTIBODY IN PATIENTS WITH AUTOIMMUNE THYROID DISEASE**

Shin DY[1], Lim JS[1], Park KH[1], Lee EJ[1]
[1]Yonsei University College of Medicine, Internal Medicine, Seoul, Republic of Korea

P52 **HASHIMOTO'S THYROIDITIS MAY HAVE SIMILAR AND DISSIMILAR CHARACTERISTICS IN NEIGHBORING GEOGRAPHIC AREAS. POSSIBLE IMPLICATIONS FOR THE EPIDEMIOLOGY OF THYROID CANCER**

Latina A[1], Gullo D[1], Trimarchi F[2], Benvenga S[2]
[1]Garibaldi-Nesima Hospital, University of Catania Medical School, Endocrinology, Catania, Italy, [2]University Hospital of Messina, Department of Clinical and Experimental Medicine, Section of Endocrinology, Messina, Italy

P53 **SERUM INTERLEUKIN-22 (IL-22) IS INCREASED IN HASHIMOTO'S THYROIDITIS (HT) COMPARED WITH NON AUTOIMMUNE THYROID DISEASES AND HEALTHY CONTROLS**

Ruggeri RM[1], Minciullo P[2], Saitta A[2], Giovinazzo S[1], Certo R[1], Gangemi S[2], Trimarchi F[1], Benvenga S[1,3]
[1]Endocrinology Unit, University of Messina, Clinical-experimental Department of Medicine and Pharmacology, Messina, Italy, [2]Unit of Allergy and Clinical Immunology, University of Messina, Department of Human Pathology, Messina, Italy, [3]Programma Interdipartimentale di Endocrinologia Molecolare Clinica e Salute Endocrina della Donna, AOU Policlinico "G. Martino", Messina, Italy

P54 **PREVALENCE OF HASHIMOTO'S THYROIDITIS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME**

Del Ghianda S[1], Benelli E1, Rinaldi E[1], Burelli A[1], Cionini R[1], Ricci D[1], Vitti P[1], Pucci E[1], Tonacchera M[1], Latrofa F[1]
[1]Pisa, Endocrinology and Metabolism, Pisa, Italy

P55 **THE PRESENCE OF CIRCULATING AUTOANTIBODIES AGAINST INSULINE, ISLET CELLS AND GLUTAMIC ACID DECARBOXYLASE IN THYROID CARCINOMA PATIENTS**

Mityukova T[1], Leonava T[1], Akulevich N[1], Platonova T[1], Drozd V[2]
[1]Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus, [2]International Fund 'Arnika', Minsk, Belarus

P56 **THYROID AUTOIMMUNITY AND SPONDYLOARTHROPATHIES: A PREVALENCE STUDY**

Lupoli GA[1], Peluso R[2], Granieri L[1], Panico A[1], Martinelli A[1], Lupoli R[1], Di Minno NM[2], Verde N[1], Papa F[1], Scarpa R[2], Lupoli G[1]
[1]University 'Federico II', Dpt of Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]University Federico II, Rheumatology Research Unit, Dpt of Clinical and Experimental Medicine, Naples, Italy

PO6 Thyroid Hormone and the Cardiovascular System Clinical

Chair: *Fabio Monzani* (Italy)

P57 **LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 IS ASSOCIATED WITH SUBCLINICAL AND OVERT HYPERTHYROIDISM**

Duntas LH[1], Boutsiadis A[1], Mantzou E[1], Pitsouni E[1]
[1]Evgenidion Hospital, University of Athens, Endocrine Unit, Athens, Greece

P58 **RELATIONSHIP OF APOLIPOPROTEIN A-1, APOLIPOPROTEIN B AND LP(A) LEVELS TO THYROID FUNCTION STATUS IN KOREANSV**

Kim CS[1], Song YD[2], Park SO[3], Lee EJ[4]
[1]Hallym University Sacred Heart Hospital, Endocrinology, Anyang, Korea, Republic of, [2]NHIC Ilsan Hospital, Endocrinology, Goyang, Korea, Republic of, [3]Gwangmyeong Sung-Ae Hospital, Endocrinology, Kwangmyeong, Korea, Republic of, [4]Severance Hospital, Yonsei University, College of Medicine, Endocrinology, Republic of Korea

P59 **RH-TSH ADMINISTRATION DOES NOT AFFECT PARAMETERS OF VASCULAR FUNCTION IN SUBJECTS UNDERGOING EVALUATION FOR DIFFERENTIATED THYROID CANCER (DTC)**

Rentziou G[1], Stamatelopoulos K[1], Saltiki K[1], Kazani M[1], Athanasiadou A[1], Kyratzoglou E[1], Papamichael C[1], Alevizaki M[1]
[1]Athens University School of Medicine, Endocrine Unit and Vascular laboratory, Department of Clinical Therapeutics, Alexandra Hospital, Athens, Greece

P60 **TOTAL THYROIDECTOMY IN PATIENTS WITH AMIODARONE-INDUCED THYROTOXICOSIS AND SEVERE LEFT VENTRICULAR SYSTOLIC DYSFUNCTION**

Tomisti L[1], Materazzi G[2], Marchello A[1], Bartalena L[3], Rossi G[4], Moretti M[2], De Napoli L[2], Mariotti R[5], Miccoli P[2], Martino E[1], Bogazzi F[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy, [2]University of Pisa, Department of Surgery, Pisa, Italy, [3]University of Insubria, Department of Clinical and Experimental Medicine, Pisa, Italy, [4]National Research Council, Unit of Epidemiology and Biostatistics, Institute of Clinical Physiology, Pisa, Italy, [5]University of Pisa, Cardio-Thoracic Department, Pisa, Italy

P61 **POSTOCCLUSIVE REACTIVE HYPERAEMIA OF SKIN MICROCIRCULATION IS ALTERED IN PATIENTS WITH HYPOTHYROIDISM**

Gergar M[1], Mihor A[1], Hojker S[2], Gaberscek S[2], Lenasi H[3]
[1]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, [2]University Medical Centre Ljubljana, Ljubljana, Slovenia, [3]Faculty of Medicine, University of Ljubljana, Institute of Physiology, Ljubljana, Slovenia

P62 **GRAVES' DISEASE, AUTOIMMUNE THYROIDITIS, INSULIN RESISTANCE AND CARDIOVASCULAR RISK FACTORS**

Neves C[1], Esteves C[1], Sokhatska O[2], Palmares C[2], Pereira M[1], Dias CC[3], Carvalho D[1], Delgado L[2], Medina JL[1]
[1]São João Hospital, Faculty of Medicine, University of Porto, Endocrinology Service, Porto, Portugal, [2]São João Hospital, Faculty of Medicine, University of Porto, Immunology Department, Porto, Portugal, [3]São João Hospital, Faculty of Medicine, University of Porto, Department of Biostatistics and Medical Informatics, Porto, Portugal

PO7 Graves' Orbitopathy Clinical 1

Chair: *Petros Perros* (UK)

P63 **THE IMPACT OF DRY EYE SYNDROME IN GRAVES' ORBITOPATHY - A PROSPECTIVE AND CONTROLLED TRIAL**

Breitenfeld M[1], Matheis N[1], Grus FH[2], Pitz S[2], Kahaly GJ[1]
[1]Gutenberg University Medical Center, Department of Medicine I, Mainz, Germany, [2]Gutenberg University Medical Center, Department of Ophthalmology, Mainz, Germany

P64 **PREVALENCE AND NATURAL HISTORY OF GRAVES' ORBITOPATHY (GO) IN A LARGE COHORT OF NEWLY DIAGNOSED GRAVES' PATIENTS SEEN AT A SINGLE CENTER**

Liparulo L[1], Veronesi G[1], Lai A[1], Lombardi V[1], Dalle Mule I[1], Sassi L[1], Pariani N[1], Ferrario M[1], Azzolini C[2], Piantanida E[1], Tanda ML[1], Bartalena L[1]
[1]University of Insubria, Clinical & Experimental Medicine, Varese, Italy, [2]University of Insubria, Surgical Sciences, Varese, Italy

P65 **THERMAL IMAGING AND CHARACTERISTICS IN GRAVES´ ORBITOPATHY**

Perros P[1], Di Maria C[2], Dickinson J[3], Allen J[2]
[1]Joint Thyroid Eye Clinic, Newcastle upon Tyne, United Kingdom, [2]Microvascular Diagnostics, Regional Medical Physics Department, Freeman Hospital, Newcastle upon Tyne, United Kingdom, [3]Joint Thyroid Eye Clinic, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom

P66 **MORBIDITY AND MORTALITY OF ACUTE LIVER DAMAGE DURING OR AFTER HIGH DOSE INTRAVENOUS GLUCOCORTICOID PULSE THERAPY FOR GRAVES` OPHTHALMOPATHY**

Sisti E[1], Pinchera A[1], Marcocci C[1], Rocchi R[1], Latrofa F[1], Leo M[1], Profilo MA[1], Altea MA[1], Mazzi B[1], Albano E[1], Marinò M[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy

P67 **PATIENTS RESPONDING TO INTRAVENOUS STEROID THERAPY FOR ACTIVE GO SHOW CLINICAL IMPROVEMENT AS EARLY AS 6 WEEKS AFTER TREATMENT**

Vannucchi GM[1], Campi I[1], Covelli D[1], Currò N[2], Cirello V[1], Dazzi D[3], Beck-Peccoz P[1], Salvi M[1]
[1]Endocrine Unit, Fondazione IRCCS Cà Granda, Milano, Milan, Italy, [2]Ophthalmology, Fondazione IRCCS Cà Granda, Milan, Italy, [3]Internal Medicine, Ospedale di Fidenza, Fidenza, Italy

P68 **THE EVALUATION OF TREATMENT METHODS OF ENDOCRINE OPHTHALMOPATHY**

Papava M[1], Javashvili L[2], Dundua T[2], Jojua N[2]
[1]Research Institute of Clinical Medicine, Tbilisi, Georgia, [2]Clinic Cortex, Tbilisi, Georgia

P69 **RESPONSE TO HIGH DOSE GLUCOCORTICOID THERAPY IN PATIENTS WITH DYSTHYROID OPTIC NEUROPATHY (DON)**

Covelli D[1], Vannucchi G[1], Currò N[2], Campi I[1], Guastella C[3], Pignataro L[3], Beck Peccoz P[1], Salvi M[1]
[1]Endocrine Unit, Fondazione IRCCS Cà Granda Policlinico, Milano, Italy, [2]Ophthalmology, Fondazione IRCCS Cà Granda Policlinico, Milano, Italy, [3]Otolaryngology, Fondazione IRCCS Cà Granda Policlinico, Milano, Italy

P70 **ADVERSE EFFECTS AND EFFICACY OF METHYLPREDNISOLONE PULSES IN GRAVES OPHTALMOPATHY: COMPARISON BETWEEN ITERATIVE AND WEEKLY REGIMEN**

Rabot A[1,2], Gilly O[2], Lagier J[1], Brucker-Davis F[2], Hiéronimus S[2], Fénichel P[2], Sadoul J-L[2]
[1]CHU de Nice, Ophtalmologie, Nice, France, [2]CHU de Nice, Endocrinologie, Nice, France

P71 **UNILATERAL GRAVES' ORBITOPATHY AND TOXIC MULTINODULAR GOITER**

Kermaj M[1], Ylli A[1], Resuli K[1]
[1]University of Tirana, Endocrinology, Tirana, Albania

PO8 Hypothyroidism Clinical 1

Chair: *Peter Taylor* (UK)

P72 **PREVALENCE OF SUBCLINICAL AND CLINICAL HYPOTHYROIDISM IN WOMEN ABOVE 50, LIVING IN DISTRICT OF MODERATE IODINE DEFICIENCY, WITH PREVIOUSLY UNEXAMINED THYROID FUNCTION**

Glonti S[1,2], Bolkvadze G[2], Rukhadze T[1]
[1]Republican Clinical Hospital, Batumi, Georgia, [2]Rustaveli State University, Clinical Therapy Department, Batumi, Georgia

P73 **IN PATIENTS WITH NO INTERFERENCE ON THE INTESTINAL ABSORPTION OF L-T4 CAUSED BY GASTROINTESTINAL DISORDERS OR DRUGS, A LIQUID FORMULATION OF L-T4 PERMITS TO REACH TARGET TSH LEVELS THAT WERE MISSED BY THE CONVENTIONAL TABLET FORMULATION**

Vita R[1], Saraceno G[1], Trimarchi F[1], Benvenga S[1,2,3]
[1]University of Messina, Section of Endocrinology, Department of Experimental and Clinical Medicine & Paharmacology, Messina, Italy, [2]University of Messina, Master on Childhood, Adolescent and Women's Endocrine Health, Messina, Italy, [3]University Hospital, Interdepartmental Program of Molecular and Clinical Endocrinology & Women's Endocrine Health, Messina, Italy

P74 **GENETIC ANTICIPATION AND PTPN-22 GENE POLYMORPHISM**

Mikitinskaya A[1], Rymar O[1], Maksimov V[1], Mustafina S[1]
[1]Institute of Internal Medicine SB RAMS, Novosibirsk, Russian Federation

P75 **PULMONARY FUNCTION INVOLVEMENT IN PATIENTS WITH CLINICAL HYPOTHYROIDISM**

Marinov BI[1], Nonchev BI[2], Sirakova M[1], Kumanova I[2], Orbetzova M[2], Kostianev S[1]
[1]Medical University, Patophysiology, Plovdiv, Bulgaria, [2]Medical University, Endocrinology, Plovdiv, Bulgaria

P76 **THE VALUE OF MEASUREMENT OF TSH CONCENTRATIONS AFTER TRH STIMULATION TEST IN PREDICTING DEVELOPMENT OF CENTRAL HYPOTHYROIDISM**

Lombardi M[1], Urbani C[1], Manetti L[1], Sardella C[1], Scattina I[1], Lupi I[1], Raffaelli V[1], Marchello A[1], Nuzzo A[1], Calevro A[1], Brogioni S[1], Campomori A[1], Martino E[1], Bogazzi F[1]
[1]University of Pisa, Endocrinology, Pisa, Italy

P77 **SERUM LEPTIN AND ADIPONECTIN CONCENTRATIONS AFTER EXOGENOUS THYROTROPIN ADMINISTRATION**

Sieminska L[1], Jarzab B[2]
[1]Medical University of Silesia, Department of Pathophysiology and Endocrinology, Zabrze, Poland, [2]Cancer Center and Institute of Oncology, Nuclear Medicine and Endocrine Oncology Department, Gliwice, Poland

P78 **PRIMARY HYPOTHYROIDISM IN PATIENTS WITH PITUITARY INCIDENTALOMAS - A STUDY IN 158 PATIENTS**

Poiana C[1,2], Carsote M[1], Ene C[2], Popescu M[2], Trifanescu R[1,2], Samoila R[2], Hortopan D[2], Paun D[1,2]
[1]UMPh Carol Davila, Bucharest, Romania, 2I.Parhon, Bucharest, Romania

P79 **IDENTIFICATION OF A NOVEL MUTATION IN PAX8 IN A PATIENT WITH THYROID DYSGENESIS**

Nettore IC[1], Ferrara AM[1], Cacace V[1], Di Mase R[2], Salerno MC[2], Fenzi G[1], Macchia PE[1]
[1]University of Naples Federico II, Department of Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]University of Naples 'Federico II', Department of Pediatric, Naples, Italy

PO9 Subclinical Thyroid Diseases

Chair: *Valentin Fadeyev* (Russia)

P80 **DYSLIPIDEMIA AND ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH THE MILDEST HYPOTHYROIDISM: RELATIONSHIP TO TSH VALUES AND LEVOTHYROXINE TREATMENT**

Strongin LG[1], Nekrasova TA[1], Kazakova LV[2], Lukushkina AY[1], Ledentsova OV[3]
[1]Nizhny Novgorod State Medical Academy, Endocrinology, Nizhny Novgorod, Russian Federation, [2]Regional Volga Medical Center of MBA, Internal Medicine, Nizhny Novgorod, Russian Federation, [3]Nizhny Novgorod Regional Clinical Diagnostic Center, Endocrinology, Nizhny Novgorod, Russian Federation

P81 **SUBCLINICAL HYPOTHYROIDISM AND TOTAL SERUM CHOLESTEROL LEVEL IN THE ELDERLY**

Jukić T[1], Lukinac L[1], Kusić Z[1]
[1]University of Zagreb, School of Medicine, 'Sisters of Charity' University Hospital Center, University Department of Oncology and Nuclear Medicine, Zagreb, Croatia

P82 **DECREASED LEVEL OF SERUM THYROXINE IN SUBCLINICAL HYPOTHYROIDISM**

Feldthusen A-D[1], Toft Kristensen T[2], Larsen J[3], Pedersen PL[4], Kvetny J[5]
[1]University of Copenhagen, Dept. of Obstetrics and Gynecology, Næstved Hospital, Region Zealand, Næstved, Denmark, [2]University of Copenhagen, Dept. of Otorhinolaryngology, Slagelse Hospital, Denmark, [3]Dept. of Clinical Pathology, Næstved Hospital, Denmark, [4]Dept. of Clinical Biochemistry, Næstved Hospital, Denmark, [5]University of Copenhagen, Dept. of Internal Medicine, Næstved Hospital, Region Zealand, Denmark

P83 **NOVEL TECHNIQUE FOR THE RESECTION OF LINGUAL THYROID: TRANSORAL ROBOTIC SURGERY**

Kim S-H[1], Park YM[1]
[1]Yonsei University College of Medicine, Otorhinolaryngology, Seoul, Republic of Korea

P84 **THYROID FUNCTION AND ULTRASOUND IN THE OFF-SPRINGS OF THE CHERNOBYL-RELATED THYROID CARCINOMA SURVIVORS**

Akulevich N[1,2], Leonava T[1], Drozd V[3], Mityukova T[1], Platonova T[1], Korytko S[2]
[1]Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus, [2]State Center of Medical Rehabilitation, Minsk, Belarus, [3]International Fund 'Arnika', Minsk, Belarus

PO10 Goiter and Nodular Disease Clinical 1

Chair: *Roland Gärtner* (Germany)

P85 **EFFECTS OF 0.1 MG RECOMBINANT TSH RADIOIODINE THERAPY IN THYROIDECTOMIZED PATIENTS WITH RECURRENT MULTINODULAR GOITER**

Angelopoulos NG[1], Iakovou J[1], Boniakos A[1]
[1]Thessaloniki University, Nuclear Medicine, Thessaloniki, Greece

P86 **MINIMALLY INVASIVE OPEN APPROACH IN THE SURGICAL TREATMENT OF THE NODULAR THYROID DISEASE**

Nenkov RN[1], Radev RS[1]
[1]Medical University-Varna, Thoracic Surgery, Varna, Bulgaria

P87 **EFFICACY OF PERCUTANEOUS ETHANOL INJECTION IN BENIGN THYROID NODULES CLASSIFIED AS PURE CYSTS, COMPLEX CYSTS, AND SOLID NODULES**

Choi SH[1], Jeong JP[1], Kim GW[1], Park CW[1], Lee JH[1], Jung SW[1], Kim YA[1], Kim SH[1], Lim JK[1], Kim TH[1]
[1]Kwangju Christian Hospital, Internal Medicine, Gwang Ju, Republic of Korea

P88 **HIGH PREVALENCE OF GOITER IN GUINEA-BISSAU SCHOOLCHILDREN - A CROSS-SECTIONAL SURVEY**

Carvalho AC[1], Machado A[2], Bordalo AA[2]
[1]St. Antonio Hospital - Centro Hospitalar Porto, Endocrinology, Porto, Portugal, [2]Institute of Biomedical Sciences (ICBAS) - University of Porto, Laboratory of Hydrobiology, Porto, Portugal

P89 **PERCUTANEUS LASER ABLATION IN BENIGN THYROID NODULES: FIRST BRAZILIAN EXPERIENCE**

Andreoni DM[1], Garcia RG[2], Janovsky CC[1], Pitman WJ[2], Hidal JT[1], Francisco Neto MJ[2], Maciel RMB[1]
[1]UNIFESP EPM, Sao Paulo, Brazil, [2]HIAE, Sao Paulo, Brazil

P90 **THYROID DISORDERS IN ACROMEGALY: A SINGLE CENTER EXPERIENCE**

Urbani C[1], Nuzzo A[1], Sardella C[1], Lombardi M[1], Scattina I[1], Calevro A[1], Marchello A[1], Dell'Unto E[1], Lupi I[1], Manetti L[1], Martino E[1], Bogazzi F[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

PO11 Imaging in Thyroidology

Chair: *Murat Erdogan* (Turkey)

P91 **RISK OF MALIGNANCY IN THYROID INCIDENTALOMAS DETECTED BY 18F-FDG-PET IS RELATED TO FOCAL UPTAKE BUT INDEPENDENT OF CONTINENTAL DIFFERENCES IN ABSOLUTE THYROID CANCER INCIDENCES**

Soelberg KK[1], Bonnema SJ[1], Brix TH[1], Hegedüs L[1]
[1]Odense University Hospital, Department of Endocrinology, Odense, Denmark

P92 **REAL-TIME ELASTOGRAPHY IN ADDITION TO TRADITIONAL ULTRASOUND FINDINGS PROVIDES A BETTER SELECTION OF THYROID NODULES TO BE BIOPSIED. RESULTS OF A PROSPECTIVE MULTICENTER TRIAL**

Trimboli P[1], Misischi I[2], Monti S[3], Valabrega S[4], Graziano FM[2], Nasrollah N[1], Amendola S[1], Morgante SN[3], Deiana MG[3], Pascucci C[3], Guglielmi R[2], Toscano V[3], Papini E[2]
[1]Section of Endocrinology and Diabetology, Ospedale Israelitico, Rome, Italy, Rome, Italy, [2]Regina Apostolorum Hospital, Department of Endocrinology, Albano Laziale, Rome, Italy, [3]S. Andrea Hospital, 'Sapienza' University, Department of Endocrinology, Rome, Italy, [4]S. Andrea Hospital, 'Sapienza' University, Department of Surgery, Rome, Italy

P93 **ULTRASOUND (US) GUIDED RADIOFREQUENCY THERMOABLATION OF THYROID BENIGN AND MALIGNANT NEOPLASMS: A PRELIMINARY EXPERIENCE**

Mazzeo S[1], Battaglia V[1], Cappelli C[1], Pontillo Contillo B[1], Elisei R[2], Vitti P[2], Bartolozzi C[1]
[1]University of Pisa, Department of Oncology, Transplants and New Technologies in Medicine, Pisa, Italy, [2]University of Pisa, Department of Endocrinology and Metabolic Diseases, Pisa, Italy

P94 **FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA: DISTINCT BIOLOGIC BEHAVIOR ACCORDING TO US FEATURES**

Rhee S[1], Shin JH[1], Han B-K[1], Ko EY[1], Ko ES[1], Hahn SY[1]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Radiology, Seoul, Republic of Korea

P95 **FAILED BRAFV600E MUTATION ANALYSIS WITH FINE NEEDLE ASPIRATES OF THYROID NODULES: INCIDENCE AND PREDICTIVE FACTORS OF INADEQUATE SPECIMENS**

Kim HS[1], Shin JH[1], Lee KH[1], Ki C-S[2], Han B-K[1], Ko EY[1]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Radiology, Seoul, Korea, Republic of, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Laboratory Medicine and Genetics, Seoul, Republic of Korea

P96 **THYROID INCIDENTALOMAS DETECTED ON 18F-FDG PET/CT IN NONTHYROIDAL CANCER PATIENTS: CLINICAL IMPLICATION AND VALUE OF US**

Lee KH[1], Shin JH[1], Han B-K[1], Hahn SY[1], Ko EY[1], Choi JY[2]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Radiology, Seoul, Korea, Republic of, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Nuclear Medicine, Seoul, Republic of Korea

P97 **USEFULNESS OF SALIVARY SCINTIGRAPHY FOR EVALUATION OF DYSFUNCTION OF SALIVARY GLANDS AFTER RADIOACTIVE IODINE THERAPY**

Choi J-S[1], Lim J-Y[1], Kim Y-M[1]
[1]Department of Otorhinolaryngology, Inha University College of Medicine, Incheon, Republic of Korea

P98 **ULTRASONOGRAPHIC AND CLINICAL FINDINGS IN PATIENTS WITH METASTASES TO THE THYROID**

Kim HK[1], Yoon TM[2], Kang H-C[1]
[1]Chonnam National University Medical School, Internal Medicine, Gwangju, Korea, Republic of, [2]Chonnam National University Medical School, Otolaryngology, Gwangju, Republic of Korea

P99 **ANALYSIS OF ULTRASOUND ELASTOGRAPHY, POWER DOPPLER, AND B-MODE ULTRASOUND FEATURES IN DIFFERENTIAL DIAGNOSIS OF MALIGNANT LYMPH NODES IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA**

Erdoğan MF[1], Unluturk U[1], Güllü S[1], Aydoğan İB[1], Uysal AR[2]
[1]Ankara University School of Medicine, Endocrinology and Metabolism, Ankara, Turkey, [2]Ankara University School of Medicine, Ankara, Turkey

P100 **THE CORRELATION BETWEEN SONOGRAPHIC AND HISTOPATHOLOGICAL FINDINGS IN THYROID NODULES**

Dural AC[1], Gonenc M[1], Buyukasik S[1], Bozkurt MA[1], Kalayci MU[1], Gulseven Ciftci S[2], Sever N[3], Alis H[1]
[1]Bakirkoy Doctor Sadi Konuk Education and Research Hospital, General Surgery, Istanbul, Turkey, [2]Bakirkoy Doctor Sadi Konuk Education and Research Hospital, Radiology, Istanbul, Turkey, [3]Bakirkoy Doctor Sadi Konuk Education and Research Hospital, Pathology, Istanbul, Turkey

PO12 Case Reports 1

Chair: *Istvan Szabolcs* (Hungary)

P101 **CLINICAL CASE OF CONCURRENT GRAVES DISEASE AND PRIMARY HYPERPARATHYROIDISM**

Volkova N[1], *Beltsevich D*[2], *Antonenko M*[1]
[1]Rostov State Medical University, Rostov on Don, Russian Federation, [2]National Research Centre for Endocrinology, Moscow, Russian Federation

P102 **UNMARKED CASE OF AMIODARONE-INDUCED THYROTOXICOSIS**

Davidenko I[1], *Volkova N*[1], *Rudakova J*[2]
[1]Rostov State Medical University, Rostov on Don, Russian Federation, [2]Municipal Centre of Endocrinology, Rostov on Don, Russian Federation

P103 **CLINICAL, BIOCHEMICAL CHARACTERISTICS AND TREATMENTS OF PATIENTS WITH TSH-SECRETING PITUITARY ADENOMAS**

Song YD[1], *Kim CS*[2], *Park SO*[3], *Shin DY*[4], *Lee EJ*[4]
[1]NHIC Ilsan Hospital, Endocrinology, Goyangsi, Republic of Korea, [2]Hallym University Sacred Heart Hospital, Endocrinology, Anyangsi, Republic of Korea, [3]Gwangmyeong Sung-Ae Hospital, Endocrinology, Kwangmyeongsi, Republic of Korea, [4]Yonsei University College of Medicine, Endocrinology, Seoul, Republic of Korea

P104 **CALCITONIN-NEGATIVE NEUROENDOCRINE TUMOR OF THE THYROID**

Jung ED[1], *Jun EJ*[1], *Shon HS*[1], *Kim MK*[2]
[1]Catholic University of Daegu, Internal Medicine, School of Medicine, Daegu, Korea, Republic of, [2]Keimyung University, Internal Medicine, School of Medicine, Daegu, Republic of Korea

P105 **MYALGIA: A PRESENTING SYMPTOM OF GRAVES´ DISEASE**

Papanikolaou N[1], *Perros P*[1]
[1]Royal Victoria Infirmary, Endocrinology, Newcastle upon Tyne, United Kingdom

P106 **CASE REPORT: PRIMARY SQUAMOUS CELL CARCINOMA OF THYROID - CLINICAL MANIFESTATION MIMICKED ACUTE THYROIDITIS**

Kriksciuniene R[1], *Knispelis R*[1], *Makstiene J*[2], *Sarauskas V*[2]
[1]Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Endocrinology, Kaunas, Lithuania, [2]Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Pathological Anatomy, Kaunas, Lithuania

P107 **WHEN THE THYROID REVEALED LANGERHANS' CELL HISTIOCYTOSIS**

Gilly O[1], *Hofman V*[2], *Mahdyoun P*[3], *Marquette C-H*[4], *Fénichel P*[1], *Castillo L*[3], *Sadoul J-L*[1]
[1]CHU de Nice, Endocrinologie, Nice, France, [2]CHU de Nice, Laboratoire de Pathologie Clinique et Expérimentale, Nice, France, [3]CHU de Nice, IUFC, ORL, Nice, France, [4]CHU de Nice, Pneumologie, Nice, France

P108 **THE ROLE OF OCTREOTIDE THERAPY IN THE TREATMENT OF HYPERTHYROIDISM ASSOCIATED WITH A THYROTROPIN SECRETING ADENOMA**

Esteves C[1,2], *Alves M*[3], *Neves C*[1,2], *Sande AV*[1,2], *Pereira J*[4], *Castro L*[5], *Carvalho D*[1,2]
[1]Centro Hospitalar São João, Department of Endocrinology, Diabetes and Metabolism, Porto, Portugal, [2]Faculty of Medicine of the University of Porto, Porto, Portugal, [3]Hospital de Braga, Braga, Portugal, [4]Centro Hospitalar São João, Department of Neurosurgery, Porto, Portugal, [5]Centro Hospitalar São João, Department of Pathology, Porto, Portugal

P109 **THYROID PLASMACYTOMA - A VERY UNCOMMON DISEASE WITH AN UNUSUAL MANAGEMENT AND OUTCOME**

Janovsky CPS[1], *Hidal JT*[1], *Dias da Silva MR*[1], *Chiamolera MI*[1], *Maciel RMDB*[1], *Martins JRM*[1]
[1]Federal University of Sao Paulo, Endocrinology, São Paulo, Brazil

P110 **AN ACCESSORY THYROID GLAND OF THE LATERAL NECK IN A 34-YEAR-OLD TURKISH WOMAN**

Sengul I[1], *Sengul D*[2]
[1]Giresun University Faculty of Medicine, General Surgery, Giresun, Turkey, [2]Giresun University Faculty of Medicine, Pathology, Giresun, Turkey

P111 **A RARE CASE OF DYSHORMONOGENIC FETAL GOITER: RESPONSE TO INTRAAMNIOTIC THYROXINE INJECTIONS**

Khamisi S[1], *Lindgren P*[2], *Karlsson A*[1]
[1]Uppsala University Hospital, Institute of Medical Science, Endocrinology and Diabetes, Uppsala, Sweden, [2]Uppsala University Hospital, Women's and Children's Health, Uppsala, Sweden

P112 **TOTAL THYROIDECTOMY AS AN ALTERNATIVE TREATMENT OF LIFE-THREATENING AMIODARONE INDUCED THYROTOXICOSIS.**

Fedorowicz A[1], *Hubalewska-Dydejczyk A*[1], *Matyja A*[2], *Cieniawa T*[2], *Kostecka-Matyja M*[1]
[1]Jagiellonian University Medical College, Department of Endocrinology, Krakow, Poland, [2]Jagiellonian University Medical College, Department of General and Gastrointestinal Surgery, Krakow, Poland

P113 **PRIMARY THYROID LYMPHOMAS - A CLINICAL STUDY OF FOUR CASES**

Trifanescu RA[1,2], Ghemigian AM[1,2], Neamtu C[2], Popescu I[1], Carsote M[1], Tupea C[2], Ioachim D[2], Ghemigian MV[2], Stanescu B[1,2], Poiana C[1,2]
[1']Carol Davila' University of Medicine and Pharmacy, Endocrinology, Bucharest, Romania, [2']C.I. Parhon' National Institute of Endocrinology, Bucharest, Romania

PO13 Thyroid Hormone Action 1

Chair: *Maria Jesus Obregon* (Spain)

P114 **DEIODINASES IN HUMAN ADIPOSE TISSUE FROM OBESE PATIENTS**

Calvo RM[1], Vesperinas G[2], Obregon M-J[1]
[1]Inst. Investigaciones Biomedicas, Endocrine and nervous system Physiopathology, Madrid, Spain, [2]Hospital La Paz, Dpt. Surgery, Madrid, Spain

P115 **TR-β SELECTIVE THYROMIMETICS (KB-141) STIMULATES THE PROLIFERATION OF INSULIN SECRETING β CELLS**

Kim T[1], Han N[1], Kim SM[1], Lee EJ[1], Kim TN[1], Kwon MJ[1], Lee SH[1], Kim MK[1], Rhee BD[1], Grover GJ[2], Park JH[1]
[1]College of Medicine, Inje University, Department of Internal Medicine, Busan, Korea, Republic of, [2]Eurofins-Drug Safety Laboratories, Department of Pharmacology, Dayton, NJ, United States

P116 **DETECTION OF IODOTHYRONINES (T4, T3, RT3 AND 3,5-T2) IN HUMAN BLOOD USING LC-MS/MS**

Hoefig CS[1], Wohlgemuth F[1], Rijntjes E[1], Daniel H[2], Köhrle J[1]
[1]Charité Universitätsmedizin Berlin, Institut für Experimentelle Endokrinologie, Berlin, Germany, [2]Technische Universiät München, Lehrstuhl für Ernährungsphysiologie, München, Germany

P117 **THE NEED OF PATHWAY TO MODULATE LEPTIN MRNA VIA TRIIODOTIRONINE (T3) IN ADIPOCYTES CELL CULTURE**

Oliveira M[1], de Sibio MT[2], Olimpio RMC[1], Silva CBR[3], Luvizotto RDAM[1], Ferreira T[1], Moretto FCF[1], Nogueira CR[1]
[1]Universidade Estadual Paulista, Clínica Médica, Botucatu, Brazil, [2]Universidade Estadual Paulista, Departamento de Clínica Médica, Botucatu, Brazil, [3]UNIFESP, Clínica Médica, São Paulo, Brazil

P118 **THE IMPERMEANT SULFO-NHS-LC-BIOTIN PROBE BLOCKS TYPE 3, BUT NOT TYPE 1, DEIODINASE ACTIVITY IN INTACT HUMAN CELLS**

Wajner SM[1,2], Larsen PR[3], Maia AL[1,2]
[1]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [2]Hospital de Clínicas de Porto Alegre, Endocrinology, Thyroid Section, Porto Alegre, Brazil, [3]Division of Endocrinology, Diabetes and Hypertension, Brigham and Women´s Hospital and Harvard Medical School, Boston, United States

P119 **DIFFERENTIAL ACTIONS OF 3-T1AM ON TRACE AMINE-ASSOCIATED RECEPTORS**

Pratzka J[1], Kleinau G[1], Krude H[1], Grüters-Kieslich A[1], Köhrle J[2], Biebermann H[1]
[1]Charité Universitätsmedizin Berlin- Campus Virchow, Institute for Experimental Pediatric Endocrinology, Berlin, Germany, [2]Charité Universitätsmedizin Berlin- Campus Virchow, Institute for Experimental Endocrinology, Berlin, Germany

P120 **CLINICALLY ASYMPTOMATIC HYPOTHYROIDISM SECONDARY TO HYPERCORTISOLISM**

Carvalho RR[1], Fonseca FV[2], Melo RL[2], Mecawi AS[3], Silveira AB[2], Império GE[2], Silva ACM[2], Reis LC[2]
[1]UFRRJ, Veterinary Medicine Post Graduation Program, Institute of Veterinary, Seropédica, Brazil, [2]UFRRJ, Physiological Sciences, Institute of Biology, Seropédica, Brazil, [3]University of São Paulo, Department of Physiology, Faculty of Medicine of Ribeirão Preto, Ribeirão Preto, Brazil

P121 **IMAGING TH AVAILABILITY AND ACTION IN THE NERVOUS SYSTEM**

Morvan-Dubois G[1], Préau L[1], Le Blay K[1], Gothié JD[1], Demeneix B[1]
[1]Evolution des Régulations Endocriniennes, UMR 7221 CNRS MNHN, Paris Cedex, France

Poster Exhibition Area
12.00–13.00
Poster Session 2

PO14 Medullary Thyroid Cancer Clinical

Chair: *Joao de Castro* (Portugal)

P122 **FINE NEEDLE ASPIRATION AND MEDULLARY THYROID CARCINOMA: THE RISK OF UNDERTREATMENT USING FNA ALONE IN PREOPERATIVE EVALUATION**

Walz PC[1], Porter K[2], Schneider D[3], Debora A[4], Lindsey S[5], Busonero G[6], Fineberg D[7], Fruci B[8], Boelaert K[9], Smit JW[10], Meijer JA[11], Duntas L[12], Sharma N[13], Costante G[8], Filletti S[14], Sippel RS[3], Biondi B[4], Topliss D[7], Pacini F[6], Maciel RM[5], Essig, Jr GF[1], Kloos RT[15]
[1]Wexner Medical Center at The Ohio State University, Otolaryngology- Head and Neck Surgery, Columbus, United States, [2]The Ohio State University, Center for Biostatistics, Columbus, United States, [3]University of Wisconsin, Department of Surgery, Madison, United States, [4]University of Naples, Federico II, Department of Clinical and Molecular Endocrinology and Oncology, Naples, Italy, [5]Federal University of Sao Paulo, Department of Medicine, Sao Paolo, Brazil, [6]University of Siena, Section of Endocrinology, Siena, Italy, [7]Alfred Hospital, Department of Endocrinology, Melbourne, Australia, [8]University of Catanzaro Magna Graecia, Dipartimento di Scienze della Salute, Catanzaro, Italy, [9]University of Birmingham, Centre for Endocrinology, Diabetes & Metabolism, Birmingham, United Kingdom, [10]Leiden University Medical Center, Internal Medicine and Endocrinology, Leiden, Netherlands, [11]Albert Schweitzer Hospital, Department of Internal Medicine, Dordrecht, Netherlands, [12]University of Athens, Department of Endocrinology and Internal Medicine, Athens, Greece, [13]University of Birmingham, Otolaryngology-Head and Neck Surgery, Birmingham, United Kingdom, [14]University of Rome Sapienza, Department of Medicine, Rome, Italy, [15]Wexner Medical Center at The Ohio State University, Endocrinology and Nuclear Medicine, Columbus, United States

P123 **SERUM CALCITONIN INCREASE-GUIDED EVALUATION OF MTC IN PATIENTS WITH MULTINODAL GOITER**

Wiedemann W[1], Soukhov V[2], Zaplatnikov K[1]
[1]Clinic for Nuclearmedicine Nuernberg, Nuclearmedicine, Nuernberg, Germany, [2]Militar Medical Academy St. Petersburg, Nuclermedicine, St. Petersburg, Russian Federation

P124 **SURGICAL OUTCOMES IN MEDULLARY THYROID CARCINOMA: SHORT-TERM RESULTS**

Chun KW[1], Jun HH[1], Kim B-W[1], Lee YS[1], Chang H-S[1], Park CS[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Republic of Korea

P125 **PROGNOSTIC FACTORS OF MEDULLARY THYROID CARCINOMA**

Bae SY[1], Jung S[1], Cho DH[2], Nam SJ[1], Kim JS[1]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Seoul Medical Center, Seoul, Republic of Korea

P126 **CLINICAL SIDE EFFECTS OF CALCITONIN STIMULATION WITH PENTAGASTRIN VERSUS CALCIUM IN PATIENTS WITH THYROID DISORDERS**

Ubl P[1], Ringhofer L[1], Dolliner P[1], Niederle B[2], Dudczak R[1], Li S[1]
[1]Medical University of Vienna, Department of Nuclear Medicine, Vienna, Austria, [2]Medical University of Vienna, Department of Surgery, Vienna, Austria

P127 **THE ROLE OF 68GA-DOTATATE PET/CT IN PATIENTS WITH MEDULLARY THYROID CARCINOMA WITH PERSISTENT OR RELAPSING DISEASE AFTER SURGERY**

Marciello F[1], Carratù AC[1], De Luca C[1], Esposito R[1], Aloj L[2], Colao A[1], Lastoria S[2], Faggiano A[1,3]
[1]'Federico II' University of Naples, Department of Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]National Cancer Institute, 'Fondazione G. Pascale', Nuclear Medicine, Naples, Italy, [3]National Cancer Institute, 'Fondazione G. Pascale', Endocrinology, Naples, Italy

P128 **OUTCOME OF MICROMEDULLARY THYROID CANCER**

Marconcini G[1], Romei C[1], Bottici V[1], Valerio L[1], Cappagli V[1], Luchetti F[1], Grasso L[1], Pinchera A[1], Vitti P[1], Elisei R[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

P129 **CARBOHYDRATE ANTIGEN 19.9 (CA 19.9): A NEW POOR PROGNOSTIC FACTOR FOR THE OUTCOME OF MEDULLARY THYROID CANCER (MTC) PATIENTS?**

Lorusso L[1], Romei C[1], Bottici V[1], Agate L[1], Molinaro E[1], Cappagli V[1], Viola D[1], Luchetti F[1], Grasso L[1], Pinchera A[1], Vitti P[1], Elisei R[1]
[1]University of Pisa, Endocrinology and Metabolism, Pisa, Italy

P130 **PROGNOSTIC FACTORS FOR RECURRENCE, METASTASIS AND DEATH FROM MEDULLARY THYROID CANCER**

Mandanas S[1], Chrisoulidou A[1], Doumala E[1], Boudina M[1], Mathiopoulou L[1], Pazaitou- Panayiotou K[1]
[1]Theagenio Cancer Hospital, Endocrinology and Endocrine Oncology, Thessaloniki, Greece

P131 **GLUCAGONLIKE PEPTIDE-1 RECEPTOR IMAGING IN THE DIAGNOSIS OF MEDULLARY THYROID CARCINOMA (MTC) - FIRST EXPERIENCES**

Hubalewska-Dydejczyk A[1], Sowa-Staszczak A[1], Pach D[1], Jabrocka-Hybel A[1], Tomaszuk M[1], Przybylik-Mazurek E[1], Mikolajczak R[2], Janota B[2]
[1]Jagiellonian University Medical College, Department of Endocrinology, Krakow, Poland, [2]Institute of Atomic Energy, Radioisotope Center POLATOM, Otwock Swierk, Poland

PO15 Thyroid Cancer Diagnostics Basic/ Translational

Chair: *Gabriella Pellegriti* (Italy)

P132 **ROLE OF SERUM T1799A BRAF MUTATION IN PREDICTION OF DISEASE STATUS IN PAPILLARY THYROID CARCINOMAS**

Bae MJ[1], Kim BH[1], Lee BJ[2], Lee JC[2], Kim IS[3], Kim S-J[4], Jeon YK[1], Kim SS[1], Kim IJ[1]
[1]Pusan National University Hospital, Internal Medicine, Busan, Korea, Republic of, [2]Pusan National University Hospital, Otolaryngology, Busan, Korea, Republic of, [3]Pusan National University Hospital, Diagnostic Medicine, Busan, Republic of Korea, [4]Busan National University Hospital, Nuclear Medicine, Busan, Republic of Korea

P133 **DIFFERENT EXPRESSION OF MIRNA IN THE SERA OF PATIENTS AFFECTED BY THYROID CANCER OR BENIGN THYROID PATHOLOGIES**

Cantara S[1], Capuano S[1], D'Angeli F[1], Busonero G[1], Cardinale S[1], Pilli T[1], Pacini F[1]
[1]University of Siena, Department of Internal Medicine, Endocrinology & Metabolism and Biochemistry, Siena, Italy

P134 **CAVEOLIN-1 IN DIAGNOSIS AND PROGNOSIS OF PAPILLARY THYROID CANCER: COMPARISON OF TWO COMERCIAL ANTIBODIES**

Paskaš S[1], Janković J[1], Marečko I[1], Božić V[2], Cvejić D[1], Savin S[1]
[1]Institute for Application of Nuclear Energy - INEP, Department for Endocrinology and Immunoradiology, Belgrade, Serbia, [2]Clinical Center of Serbia, Department of Endocrine and Cardiovascular Pathology, Belgrade, Serbia

P135 **ASSESSMENT OF SPAG9 TRANSCRIPT IN FINE NEEDLE ASPIRATES OF THYROID NODULES**

Volard B[1], Krieger S[1], Planchard G[1], Hardouin A[1], Vaur D[1], Rame J-P[2], Bardet S[3]
[1]Centre Francois Baclesse, Department of Biopathology, Caen, France, [2]Centre Francois Baclesse, Department of Head and Neck Surgery, Caen, France, [3]Centre Francois Baclesse, Nuclear Medicine and Thyroid Unit, Caen, France

P136 **A RAPID AND ACCURATE REAL-TIME PCR ASSAY FOR THE DETECTION OF BRAF V600E MUTATION IN FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUE (FFPET) SPECIMENS OF PAPILLARY THYROID CARCINOMA (PTC)**

DeMartin K[1], Walter S[1], Shah S[1], Soviero S[1], Halait H[1]
[1]Roche Molecular Systems, Pleasanton, United States

P137 **POTENTIAL CLINICAL APPLICATION OF ONCOFETAL FIBRONECTIN MRNA MEASUREMENT IN TUMOR TISSUES AND BLOOD OF PATIENTS WITH DIFFERENTIATED THYROID TUMORS**

Vivaldi A[1], Molinaro E[1], Agate L[1], Ciampi R[1], Valerio L[1], Viola D[1], Pinchera A[1], Vitti P[1], Elisei R[1]
[1]University of Pisa, Endocrinology, Pisa, Italy

P138 **STUDY OF PREVALENCE AND FUNCTIONAL SIGNIFICANCE OF RARE VARIATIONS IN THE BRAF GENE IN PAPILLARY THYROID CARCINOMA**

Barollo S[1], Pezzani R[1], Cristiani A[2], Pelizzo MR[1], Mantero F[1], Moro S[1], Mian C[1]
[1]University of Padua, Padua, Italy, [2]Center for Advanced Studies, Research and Development in Sardinia -CRS4, Pula, Italy

P139 **MIRNA EXPRESSION SIGNATURE AS PRE-OPERATIVE DIAGNOSTIC BIOMARKERS FOR THYROID CANCER**

Ducena K[1], Abols A[2], Pirags V[2], Line A[3], Andrejeva D[3], Vilmanis J[4], Narbuts Z[4], Tars J[5]
[1]University of Latvia, Endocrinology, Riga, Latvia, [2]University of Latvia, Riga, Latvia, [3]Latvian Biomedical Research and Study Centre, Riga, Latvia, [4]Pauls Stradins Clinical University Hospital, Riga, Latvia, [5]Riga Eastern Clinical University Hospital, Latvian Oncology Center, Riga, Latvia

PO16 Thyroid Cancer Diagnostics Clinical 2

Chair: *Jennifer Sipos* (USA)

P140 **SITES OF METASTASES IN ANAPLASTIC THYROID CARCINOMA - AN AUTOPSY STUDY OF 45 CASES**

Pirnat E[1], Gazic B[2], Besic N[3]
[1]University Medical Centre Ljubljana, Department of Nuclear Medicine, Ljubljana, Slovenia, [2]Institute of Oncology, Department of Pathology, Ljubljana, Slovenia, [3]Institute of Oncology, Department of Surgical Oncology, Ljubljana, Slovenia

P141 **IMPLICATION OF BRAF V600E GENE MUTATION IN PREOPERATIVE DIAGNOCTIC OF THYROID GLAND CANCER**

Boriskova ME[1], Semyonov DY[1], Zaraisky MI[2], Pankova PA[1], Farafonova UV[1], Bikov MA[1]
[1]Pavlovs State Medical Univarsity, General Surgery, St. Petersburg, Russian Federation, [2]Pavlovs State Medical Univarsity, Laboratory Diagnostic Department with course of Molecular Medicine, St. Petersburg, Russian Federation

P142 **OVERCOMING THE LIMITATION OF FINE NEEDLE ASPIRATION CYTOLOGY**

Jun HH[1], Chun KW[1], Kim BW[1], Lee YS[1], Chang H-S[1], Park CS[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Surgery, Thyroid Cancer Center, Seoul, Republic of Korea

P143 **PREABLATIVE STIMULATED THYROGLOBULIN LEVEL IS STRONGLY CORRELATED WITH PREOPERATIVE THYROGLOBULIN LEVEL**

Shin DY[1], Park KH[1], Lim JS[1], Lee EJ[1]
[1]Yonsei University College of Medicine, Internal Medicine, Seoul, Republic of Korea

P144 **IS THERE A DIFFERENCE IN TUMOR SIZE AND NUMBER OF FOCI IN HASHIMOTO'S ASSOCIATED THYROID CANCER?**

Hristozov KH[1], Siderova MV[1], Krasnaliev IJ[2], Nenkov R[3], Radev R[3]
[1]University Hospital 'St. Marina', Clinic of Endocrinology, Varna, Bulgaria, [2]University Hospital 'St. Marina', Department of Pathology, Varna, Bulgaria, [3]University Hospital 'St. Marina', Clinic of Thoracic Surgery, Varna, Bulgaria

P145 **POORLY DIFFERENTIATED THYROID CARCINOMA: CLINICAL AND THERAPEUTIC OUTCOMES**

Hasbellaoui F[1], Meziani N[1], Ziani K[2], Khalifa A[1], Benserai FZ[3], Amokrane L[2], Semrouni M[1]
[1]Medical University of Algiers, Endocrinology, Algiers, Algeria, [2]Medical University of Algiers, Nuclear Medicine, Algiers, Algeria, [3]Medical University of Algiers, Pathology, Algiers, Algeria

P146 **THYROID CARCINOMA IN YOUNG POPULATION**

Meziani N[1], Hasbellaoui F[2], Ziani K[2], Khalifa A[2], Amokrane L[2], Semrouni M[2]
[1]Medical University of Algiers, Endocrinology, Algiers, Algeria, [2]Medical University of Algiers, Algiers, Algeria

P147 **F-18 FDG PET/CT IMAGING IN THE DIAGNOSTIC WORK-UP OF THYROID CANCER PATIENTS WITH HIGH SERUM THYROGLOBULIN, NEGATIVE I-131 WHOLE BODY SCAN AND SUPPRESSED THYROTROPIN : 6-YEAR SINGLE INSTITUTION EXPERIENCE**

Elboga U[1], Ozkaya M[2], Celen YZ[1], Araz M[2], Akarsu E[2]
[1]University of Gaziantep, Nuclear Medicine, Gaziantep, Turkey, [2]University of Gaziantep, Endocrinology, Gaziantep, Turkey

P148 **ASSOCIATION BETWEEN EXPRESSION OF X-LINKED INHIBITOR OF APOPTOSIS PROTEIN AND THE CLINICAL OUTCOME IN BRAFV600E PREVALENT PAPILLARY THYROID CANCER POPULATION**

Kim TY[1], Yim JH[1], Kim WB[1], Hong SJ[2], Gong G[3], Shong YK[1]
[1]Asan Medical Center, Ulsan University, College of Medicine, Dept of Internal Medicine, Seoul, Republic of Korea, [2]Asan Medical Center, Ulsan University, College of Medicine, Dept of Surgery, Seoul, Republic of Korea, [3]Asan Medical Center, Ulsan University, College of Medicine, Dept of Pathology, Seoul, Republic of Korea

P149 **PROGNOSTIC FACTORS FOR PERSISTENT DISEASE IN DIFFERENTIATED THYROID CANCER (DTC)-PATIENTS**

Giani C[1], Molinaro E[1], Piaggi P[2], Pieruzzi L[1], Agate L[1], Biagini A[1], Lorusso L[1], Grasso L[1], Bianchi F[1], Brozzi F[1], Taddei D[1], Nencetti C[1], Pinchera A[1], Vitti P[1], Elisei R[1]
[1]Department of Endocrinology, University of Pisa, Pisa, Italy, [2]Department of Energy and Systems Engineering, University of Pisa, Pisa, Italy

P150 **CHALLENGES IN INTERPRETING LABORATORIAL, ULTRASSONOGRAPHIC AND CYTOLOGICAL TESTS IN THE FOLLOW UP OF PATIENTS WITH NECK LYMPH NODES SUSPICIOUS OF PAPILLARY THYROID CARCINOMA METASTASES**

Martins-Costa MC[1], Kazamatsu TS[1], Nakabashi CCD[1], Crispim F[1], Ikejiri E[1], Mamone MCOC[1], Andreoni DM[1], Camacho CP[1], Hidal JT[1], Vieira JGH[1], Maciel RMB[1], Biscolla RPM[1]
[1]Federal University of São Paulo, Endocrinology, São Paulo, Brazil

P151 **SCREENING DOPPLER US OF THE CAROTID ARTERIES IS NOT MANDATORY BEFORE LATERAL NECK DISSECTION**

Lombardi CP[1], Raffaelli M[1], Revelli L[1], De Crea C[1], Kateta Tshibamba P[1], Tondi P[2], Santoliquido A[2], Bellantone R[1]
[1]Catholic University of Sacred Heart, Surgery, Rome, Italy, [2]Catholic University of Sacred Heart, Angiology, Rome, Italy

PO17 Thyroid Cancer Therapeutics Clinical 2

Chair: *Ian Hay* (USA)

P152 **BURDEN OF THYROID CANCER: THE PATIENT PERSPECTIVE**

Perros P[1], *Farnell K*[1], *Bliss R*[1], *Mallick UK*[1]
[1]Freeman Hospital, Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom

P153 **HIGH MAD2 EXPRESSION AS A PREDICTOR OF RESPONSIVENESS OF ANAPLASTIC THYROID CANCER TO PACLITAXEL**

Suganuma N[1], *Ito K*[1], *Sugino K*[1], *Nagahama M*[1], *Kitagawa W*[1], *Shibuya H*[1], *Okuwa K*[1], *Yano Y*[1], *Uruno T*[1], *Suzuki A*[1], *Magoshi S*[1], *Hames K*[1], *Akaishi J*[1], *Masaki C*[1], *Masuda M*[2], *Yoshida A*[3]
[1]Ito Hopsital, Surgery, Shibuya, Japan, [2]Yokohama City University, Surgery, Yokohama, Japan, [3]Kanagawa Cancer Center, Breast and Endocrine Surgery, Yokohama, Japan

P154 **SOLITARY LATERAL NECK NODE METASTASIS IN PAPILLARY THYROID CARCINOMA**

Lee YS[1], *Kim SM*[1], *Jun HH*[1], *Chun KW*[1], *Chang HJ*[1], *Kim B-W*[1], *Chang H-S*[1], *Park CS*[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Republic of Korea

P155 **FDG-PET TO PREDICT RESPONSE TO SORAFENIB IN PATIENTS WITH IODINE-REFRACTORY DIFFERENTIATED THYROID CANCER**

Marotta V[1], *Ramundo V*[1], *Del Prete M*[1], *Marciello F*[1], *Esposito R*[1], *Carratù AC*[1], *De Luca C*[1], *Fonti R*[2], *Camera L*[2], *Salvatore M*[2], *Colao A*[1], *Faggiano A*[1,3]
[1]University Federico II, Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]University Federico II, Biomorphological and Functional Sciences, Naples, Italy, [3]Endocrinology, National Cancer Institute, 'Fondazione G. Pascale', Naples, Italy

P156 **EFFICACY OF SUBFASCIAL APPROACH IN THYROIDECTOMY TO QUALITY OF LIFE IN THYROID DISEASE PATIENTS: PROSPECTIVE RANDOMIZED STUDY**

Jung S[1], *Lee SK*[1], *Kim S*[1], *Choi M-Y*[1], *Bae SY*[1], *Kim J*[1], *Park YS*[1], *Kil WH*[1], *Kang B*[1], *Choe J-H*[1], *Kim J-H*[1], *Lee JE*[1], *Nam SJ*[1], *Kim JS*[1]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Division of Breast and Endocrine Surgery, Department of Surgery, Seoul, Republic of Korea

P157 **MANAGEMENT OF PROGRESSIVE PAPILLARY THYROID CARCINOMA (PTC) WITH UNRESECTABLE LOCAL INVASION OR GROSS LYMPH NODE INVOLVEMENT**

Tomemori T[1], *Mitsuhashi T*[1], *Watanabe R*[1], *Hiruma K*[1], *Sakitani E*[1], *Sugisaki H*[1], *Yanagi Y*[1]
[1]Tokyo Metropolitan Cancer and Infectious Diseases Center KOMAGOME Hospital, Otorhinolaryngology, Head and Neck Oncology, Tokyo, Japan

P158 **MANAGEMENT OF MEDIASTINAL METASTASIS FROM THYROID CANCERS**

Park CS[1], *Lee YS*[1], *Kim B-W*[1], *Chang H-S*[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Republic of Korea

P159 **IMPACT OF CLINICAL AND PATHOLOGICAL LYMPH NODE METASTASIS ON CLINICAL OUTCOMES IN PAPILLARY THYROID CANCER PATIENTS**

Matsuzu K[1,2], *Sugino K*[1], *Ito K*[1], *Masaki C*[1], *Akaishi J*[1], *Suzuki A*[1], *Uruno T*[1], *Yano Y*[1], *Ohkuwa K*[1], *Shibuya H*[1], *Kitagawa W*[1], *Nagahama M*[1], *Masudo K*[3], *Yoshida A*[2], *Masuda M*[3], *Ito K*[1]
[1]Ito Hospital, Tokyo, Japan, [2]Kanagawa Cancer Center, Yokohama, Japan, [3]Yokohama City University, Yokohama, Japan

P160 **COMPARISON OF LOW AND HIGH DOSES OF IODINE-131 FOR THE POSTOPERATIVE ABLATION OF REMNANT THYROID IN LOW-RISK DIFFERENTIATED THYROID CANCER PATIENTS**

Kim D-Y[1], *Hong I-K*[1]
[1]Kyung Hee University Hospital, Nuclear Medicine, Seoul, Republic of Korea

P161 **TUBERCULOSIS CERVICAL LYMPHADENOPATHY MIMICKING LATERAL NECK NODE METASTASIS FROM PAPILLARY THYROID CARCINOMA**

Kim SM[1], *Lee YS*[1], *Chang H-S*[1], *Park CS*[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Republic of Korea

P162 **TREATMENT OF DISTANT METASTASIS FROM DIFFERENTIATED THYROID CARCINOMA (DTC) IN OUR HOSPITAL**

Watanabe R[1], *Mitsuhashi T*[1], *Tomemori T*[1], *Hiruma K*[1], *Sakitani E*[1], *Sugisaki H*[1], *Yanagi Y*[1]
[1]Tokyo Metropolitan Cancer and Infectious Diseases Center KOMAGOME Hospital, Otorhinolaryngology, Head and Neck Oncology, Tokyo, Japan

P163 **PROGNOSIS OF THE EXTRATHYROIDAL EXTENSION IN PAPILLARY THYROID CARCINOMA**

Bae JS[1], *Kwak HY*[1], *Chae BJ*[1], *Song BJ*[1], *Jung SS*[1]
[1]Seoul Saint Mary's Hospital, The Catholic University of Korea, Department of Surgery, Seoul, Republic of Korea

PO18 Thyroid Autoimmunity and Hypothyroidism Basic

Chair: *Matthias Schott* (Germany)

P164 **CTLA-4 GENE POLYMORPHISMS AND AUTOIMMUNE THYROID DISEASES IN THAI PATIENTS**

Mayurasakorn N[1], Puttipokin S[1], Houngngam N[1], Sunthornyothin S[1], Chusrichun W[1], Snabboon T[1]
[1]Chulalongkorn, Medicine, Bangkok, Thailand

P165 **SERIAL DILUTION ANALYSIS IMPROVES THE CLINICAL UTILITY OF A CHIMERIC TSH RECEPTOR BIOASSAY FOR THYROID STIMULATING AUTOANTIBODIES**

Leschik JC[1], Diana T[1], Olivo PD[2], König J[3], Krahn U[3], Li Y[2], Kanitz M[1], Kahaly GJ[1]
[1]Gutenberg University Medical Center, Department of Medicine I, Mainz, Germany, [2]Diagnostic Hybrids, Inc, R & D, Athens, United States, [3]Gutenberg University Medical Center, Institute of Medical Biostatistics, Epidemiology and Informatics, Mainz, Germany

P166 **PTPN-22 GENE POLYMORPHISM AND FAMILIAL AUTOIMMUNE THYROID DISEASE**

Rymar O[1], Mikitinskaya A[1], Maksimov V[1], Mustafina S[1]
[1]Institute of Internal Medicine SB RAMS, Novosibirsk, Russian Federation

P167 **PHYSIOGICAL IODINE SUPPLEMENTATION DOES NOT INDUCE CLINICALLY RELEVANT CELLULAR IMMUNITY IN A TRANSGENIC AUTOIMMUNE THYROIDITIS MODEL**

Thiel A[1], Ehlers M[1], Papewalis C[2], Domröse A[3], Stenzel W[1], Bernecker C[1], Schinner S[1], Willenberg H[1], Schott M[1]
[1]Heinreich-Heine-University Duesseldorf, Division of Endocrinology, Düsseldorf, Germany, [2]University Hospital Bonn, Department for Pediatrics, Bonn, Germany, [3]Heinreich-Heine-University, Düsseldorf, Germany

P168 **HUMAN THYROCYTES IN PRIMARY CULTURES SECRETE CXC CHEMOKINES CXCL8 AND CXCL10 BY DISTINCT PRO-INFLAMMATORY PATHWAYS: A FIRST STEP TOWARD A DIFFERENTIATION BETWEEN AUTOIMMUNE AND TUMOR-RELATED INFLAMMATION?**

Coperchini F[1], Rotondi M[1], Pignatti P[1], Sideri R[1], Groppelli G[1], Leporati P[1], de Martinis L[1], La Manna L[1], Magri F[1], Mariotti S[2], Chiovato L[1]
[1]FSM, Pavia, Pavia, Italy, [2]Università di Cagliari, Cagliari, Italy

P169 **CYTOPHILIC ANTIBODIES AND MONOCYTE-MEDIATED CYTOTOXICITY IN HASHIMOTO'S THYROIDITIS**

Milicevic Z[1]
[1]Laboratory for Molecular Biology and Endocrinology, Vinca Institute of Nuclear Science, University of Belgrade, Belgrade, Serbia

P170 **DETERMINATION OF BIOLOGICAL ACTIVITIES OF TSH RECEPTOR (TSHR) AUTOANTIBODIES (TRABS) IN SERUM SAMPLES CONTAINING A MIXTURE OF STIMULATING AND BLOCKING ANTIBODIES**

Young S[1], Betterle C[2], Zanchetta R[2], Sanders J[1], Kabelis K[1], Sanders P[1], Evans M[1], Furmaniak J[1], Rees Smith B[1]
[1]FIRS Laboratories, RSR Ltd, Cardiff, United Kingdom, [2]University of Padua School of Medicine, Department of Medicine, Padua, Italy

P171 **PREVALENCE OF DIO2T92A POLYMORPHISM AND ITS ASSOCIATION WITH THYROID AUTOIMMUNITY**

Guerra A[1], Sapio MR[1], Di Stasi V[1], Volpe A[1], Murino A[1], Izzo G[1], Vitale M[1]
[1]University of Salerno, Department of Medicine and Surgery, Baronissi, Italy

P172 **ENHANCED EXPRESSION OF THE B CELL ACTIVATION FACTOR (BAFF) AND BAFF-RECEPTOR (BAFF-R) IN THYROID AND ORBITAL ADIPOSE TISSUE (OAT) FROM PATIENTS WITH AUTOIMMUNE THYROID DISEASES (AITD) AND ASSOCIATED ORBITOPATHY (GO)**

Campi I[1], Vannucchi G[1], Covelli D[1], Rossi S[2], Doi P[2], Vicentini L[3], Currò N[4], Pignataro L[5], Guastella C[5], Beck-Peccoz P[1], Salvi M[1]
[1]University of Milan- Fondazione IRCCS Cà Granda, Department of Medical Science, Endocrine Unit, Milan, Italy, [2]S. Paolo Hospital, Milan, Department of Pathology, Milan, Italy, [3]Fondazione IRCCS Cà Granda, Department of Endocrine Surgery, Milan, Italy, [4]Fondazione IRCCS Cà Granda, Department of Ophthalmology, Milan, Italy, [5]Fondazione IRCCS Cà Granda, Department of Otolaryngology, Milan, Italy

P173 **EXPRESSION OF DIFFERENT THYROPEROXIDASE (TPO) ISOFORMS IN THYROID (THY), BREAST CANCER (BC) AND OTHER TISSUES**

Muller I[1,2], Giani C[1], Fiore E[1], Belardi V[1], Rosellini V[1], Funel N[3], Campani D[3], Grennan-Jones F[2], Zhang L[2], Lewis M[2], Bakhsh A[2], Roncella M[4], Ghilli M[4], Pinchera A[1], Vitti P[1], Dayan C[2], Ludgate M[2]
[1]University of Pisa, School of Medicine, Endocrinology, Pisa, Italy, [2]Cardiff University, School of Medicine, Institute of Molecular & Experimental Medicine, Cardiff, United Kingdom, [3]University of Pisa, School of Medicine, Patology, Pisa, Italy, [4]University of Pisa, School of Medicine, Senology, Pisa, Italy

P174 **THYROID HORMONES ARE REQUIRED FOR NORMAL RESPIRATORY FUNCTION IN WISTAR RATS**

Pereira VS[1], Cagido VR[1], Machado MN[1], Taveira da Silva R[1], Einicker-Lamas M[1], Zin WA[1], Corrêa da Costa VM[1]
[1]Universidade Federal do Rio de Janeiro, IBCCF - Instituto de Biofísica Carlos Chagas Filho, Rio de Janeiro, Brazil

PO19 Thyroid Hormone Transport

Chair: *Edward Visser* (The Netherlands)

P175 **STRUCTURE-FUNCTION RELATIONS IN MCT8**

Braun D[1], *Köhrle J*[1], *Schweizer U*[1]
[1]Charité Universitätsmedizin Berlin, Institut für Experimentelle Endokrinologie, Berlin, Germany

P176 **THYROID HORMONE TRANSPORTER FAMILIES: DIFFERENCES IN SEQUENCES AND TRAFFICKING SUGGEST DIFFERENT MOLECULAR RECOGNITION MECHANISMS FOR TRANSPORT**

Kinne A[1], *Schuelein R*[1], *Krause G*[1]
[1]Leibniz-Institut für Molekulare Pharmakologie, Berlin, Germany

P177 **UPTAKE OF IODOTHYRONINES AND 3-IODOTHYRONAMINE BY LIVER CELLS**

Ghelardoni S[1], *Chiellini G*[1], *Frascarelli S*[1], *Marchini M*[1], *Saba A*[1], *Zucchi R*[1]
[1]Università di Pisa, Pisa, Italy

P178 **THYROXINE-BINDING GLOBULIN (TTR), TRANSTHYRETIN (TTR), ALBUMIN (HSA), APOLIPOPROTEINS (APOS) AND OTHER PLASMA CARRIERS OF THYROID HORMONES (TH) SHARE LOCAL AMINO ACID SEQUENCE HOMOLOGY (AASH) THROUGHOUT THE PHYLUM**

Benvenga S[1], *Guarneri F*[2]
[1]Università degli Studi di Messina, Dip. Clinico Sperimentale di Medicina e Farmacologia (sez. di Endocrinologia), Messina, Italy, [2]Università degli Studi di Messina, Dip. di Medicina Sociale del Territorio, Messina, Italy

P179 **THE ROLE OF MCT10 IN T3 UPTAKE IN LIVER CELLS**

Noort S[1], *van Heerebeek REA*[1], *Kersseboom S*[1], *Mol-van Mullem AAA*[1], *Peeters RP*[1], *Visser TJ*[1]
[1]Erasmus MC, Rotterdam, The Netherlands

P180 **THYROID HORMONE TRANSPORTERS (MCT8 AND MCT10) ARE REGULATED BY THYROID HORMONES IN LIVER AND PITUITARY IN A RAPID AND TISSUE SPECIFIC MANNER**

Pereira GF[1], *Ramos RG*[1], *Império GE*[1], *Faustino LC*[1], *Santiago LA*[1], *Ortiga TM*[1]
[1]Universidade Federal do Rio de Janeiro, Instituto de Biofísica Carlos Chagas Filho, Rio de Janeiro, Brazil

PO20 Goiter and Nodular Disease Clinical 2

Chair: *Francoise Borson-Chazot* (France)

P181 **IMPAIRED THYROID FUNCTION AND WEIGHT GAIN TWO YEARS AFTER HEMITHYROIDECTOMY FOR BENIGN EUTHYROID GOITER**

Toft Kristensen T[1], *Feldthusen A-D*[2], *Jacob L*[3], *Pedersen PL*[4], *Jelstrup S*[5], *Kvetny J*[6]
[1]University of Copenhagen, Department of Otorhinolaryngology, Region Zealand, Slagelse, Denmark, [2]University of Copenhagen, Department of Obstetrics and Gynaecology, Region Zealand, Næstved, Denmark, [3]Department of Clinical Pathology, Region Zealand, Næstved, Denmark, [4]Department of Clinical Biochemistry, Region Zealand, Næstved, Denmark, [5]Department of Otorhinolaryngology, Region Zealand, Slagelse, Denmark, [6]University of Copenhagen, Department of Internal Medicine, Region Zealand, Næstved, Denmark

P182 **CHANGES IN THYROID VOLUME AND STRUCTURE AFTER THE DANISH IODINE FORTIFICATION PROGRAM ARE DEPENDENT ON AGE AND REGION**

Krejbjerg A[1], *Bjergved L*[2,3], *Jørgensen T*[2], *Perrild H*[3], *Pedersen I*[1], *Rasmussen L*[4], *Knudsen N*[3], *Laurberg P*[1]
[1]Aalborg Hospital, Endocrinology, Aalborg, Denmark, [2]Research Centre for Prevention and Health, The Capital Region of Denmark, Glostrup, Denmark, [3]Department of Endocrinology and Gastroenterology, Bispebjerg University Hospital, Copenhagen, Denmark, [4]Department of Nutrition, National Food Institute, Technical University of Denmark, Søborg, Denmark

P183 **USEFULNESS OF ULTRASOUND ELASTOSONOGRAPHY IN PRIMARY HYPERPARATHYROIDISM**

Saponaro F[1], *Loiacono V*[1], *Di Rosa G*[1], *Scutari M*[1], *Chiavistelli S*[1], *Cianferotti L*[1], *Marcocci C*[1], *Vitti P*[1], *Cetani F*[1], *Rago T*[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

P184 **MICRORNA EXPRESSION PROFILE HELPS TO DISTINGUISH BENIGN NODULES FROM PAPILLARY THYROID CARCINOMAS STARTING FROM CELLS OF FINE NEEDLE ASPIRATION**

Ferrarini E[1], *Patrizia A*[1], *Rago T*[1], *De Marco G*[1], *Dimida A*[1], *Molinaro A*[1], *Niccolai F*[1], *Di Coscio G*[1], *Pinchera A*[1], *Vitti P*[1], *Tonacchera M*[1]
[1]Università di Pisa, Pisa, Italy

P185 **FREQUENCY OF POLYMORPHISMS IN THE VEGF, VEGFR AND HIF GENES IN NORMAL SUBJECTS AND PATIENTS WITH NODULAR GOITER FROM AN AREA WITH MILD IODINE DEFICIENCY**

Niccolai F[1], *Molinaro A*[1], *De Marco G*[1], *Agretti P*[1], *Di Cosmo C*[1], *Piaggi P*[2], *Pinchera A*[1], *Vitti P*[1], *Bocci G*[3], *Tonacchera M*[1]
[1]University of Pisa, School of Medicine, Endocrinology and Metabolism, Pisa, Italy, [2]University of Pisa, Energy and Systems Engineering, Pisa, Italy, [3]University of Pisa, Internal Medicine - Division of Pharmacology, Pisa, Italy

P186 **CERVICAL HEMATOMA AFTER THYROID SURGERY: IS AMBULATORY SURGERY SAFE?**

Ioan ME[1], Gaillat C[1], Royer C[1], Tresallet C[2], Menegaux F[2]
[1]Pitié Salpetrière University Hospital, Department of Anesthesia and Intensive Care, Paris, France, [2]Pitié Salpetrière University Hospital, Department of General, Digestive and Endocrine Surgery, Paris, France

PO21 Case Reports 2

Chair: *Kostas Markou* (Greece)

P187 **DE QUERVAIN'S THYROIDITIS: CLINICS PLUS MINDS THERE ARE RESULTS**

Antonenko M[1], Volkova N[1]
[1]Rostov State Medical University, Rostov on Don, Russian Federation

P188 **SURGICAL TREATMENT OF HUGE STERNAL METASTASES FROM PAPILLARY THYROID CARCINOMA: REPORT OF A CASES**

Abdelrahman TEF[1], Afifi TM[2], Hassanein KM[3]
[1]Sohag University, Head and Neck Surgery Unit, Department of Surgery, Sohag, Egypt, [2]Sohag University, Cardiothoracic Surgery Department, Sohag, Egypt, [3]Sohag University, Maxillofacial , Head and Neck Surgery, Sohag, Egypt

P189 **A CASE OF HYPERTHYROIDISM DUE TO FUNCTIONING BONE METASTASIS OF FOLLICULAR THYROID CARCINOMA**

Synak R[1], Panholzer PJ[1], Jordan S[1], Pirich C[2]
[1]LKH Voecklabruck, Voecklabruck, Austria, [2]Paracelsus University, Salzburg, Austria

P190 **A RARE CASE OF AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 3 INCLUDING DIABETES TYPE 1, GRAVES´ DISEASE AND SCLERODERMA BUSCHKE**

Lozanov BS[1], Lozanov LB[2], Gortcheva D[3], Kadurina M[4], Tzankov N[5]
[1]Clinical Centre of Endocrinology, Tokuda Hospital, Sofia, Bulgaria, [2]Tokuda Hospital, Dept.Endocrinol, Sofia, Bulgaria, [3]Tokuda Hospital, Sofia, Bulgaria, [4]Military Medical Academy, Dept. Dermatology, Sofia, Bulgaria, [5]Bulgarian Academy of Sciences, Sofia, Bulgaria

P191 **UNUSUAL SHORT-TERM COMPLETE RESPONSE TO TWO REGIMENS OF CYTOTOXIC CHEMOTHERAPY IN A PATIENT WITH POORLY DIFFERENTIATED THYROID CARCINOMA**

Crouzeix G[1,2], Michels J-J[3], Sevin E[4], Aide N[1], Bardet S[1], for the Tuthyref Network
[1]Centre Francois Baclesse, Nuclear Medicine and Thyroid Unit, CAEN, France, [2]Centre Hospitalo-Universitaire, Department of Endocrinology, Caen, France, [3]Centre Francois Baclesse, Department of Pathology, CAEN, France, [4]Centre Francois Baclesse, Department of Oncology, CAEN, France

P192 **PAPILLARY THYROID CARCINOMA IN IDENTICAL TWINS**

Chang H-S[1], Lee YS[1], Kim B-W[1], Park CS[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Republic of Korea

P193 **ONCE AGAIN - AMIODARONE-INDUCED THYROTOXICOSIS**

Luchina EI[1], Lukashova ME[1], Meleshkevich TA[1]
[1]'Central Clinical Hospital' 2 n.a. N.A. Semashko Public Corporation 'Russian Railways', Endocrinology, Moscow, Russian Federation

P194 **PREOPERATIVE SERUM THYROGLOBULIN AND OTHER SUGGESTED CRITERIA MAY NOT BE VALID INDEPENDENT PREDICTORS OF MALIGNANCY IN THYROID FOLLICULAR NEOPLASMS**

Bellabarba D[1], Langlois M-F[1]
[1]Faculté de Médecine, Université de Sherbrooke, Endocrinologie, Sherbrooke, Canada

P195 **RADIOIODINE UPTAKE IN ABDOMINAL DERMOID CYST IN A PATIENT WITH DIFFERENTIATED THYROID CANCER (DTC)**

Ruggeri RM[1], Giovinazzo S[1], Cucinotta M[2], Quartuccio N[2], Sindoni A[2], Baldari S[2], Campennì A[2]
[1]Endocrinology Unit, University of Messina, Clinical-experimental Department of Medicine and Pharmacology,, Messina, Italy, [2]Unit of Nuclear Medicine, University of Messina, Department of Radiological Sciences, Messina, Italy

P196 **NEW ONSET GRAVES' DISEASE DEVELOPED AFTER ABOUT 25 YEARS IN A PATIENT WITH SHEEHAN'S SYNDROME**

Ko SH[1], Kim MH[1], Cha BY[1]
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea

P197 **THYREOGLOBULIN AND CALCITONIN POSITIVITY AT FNA OF HURTHLE CELL CARCINOMA: A CASE REPORT**

Altieri B[1], Capozzi A[1], Di Pizio L[1], Schirò T[1], Sun VA[1], Sorice GP[1], Fabiano MC[1], Salomone E[1], Pontecorvi A[1], Della Casa S[1]
[1]Università Cattolica del Sacro Cuore, UOC di Endocrinologia e Malattie del Metabolismo, Roma, Italy

P198 **LONG-TERM FOLLOW-UP OF A SIMULTANEOUS MEDULLARY AND PAPILLARY THYROID MICROCARCINOMA: CASE REPORT**

Nogueira C[1,2], Souto SB[1,2], Vinha E[1], Carvalho DM[1,2]
[1]Centro Hospitalar São João, Endocrinology, Diabetes and Metabolism, Porto, Portugal, [2]Faculty of Medicine of the University of Porto, Porto, Portugal

P199 ***Withdrawn***

PO22 Thyroid Hormone Effects on Metabolism and Bone

Chair: *Duncan Bassett* (UK)

P200 **EFFECT OF TSH-SUPPRESSION THERAPY ON VOLUMETRIC BONE MINERAL DENSITY AND BONE GEOMETRY AT THE RADIUS AND TIBIA ASSESSED BY PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY IN WOMEN WITH DIFFERENTIATED THYROID CANCER**

Antoniou J[1], Tournis S[1], Liakou C[1], Christodoulou J[1], Galanos A[1], Nikopoulou S[2], Tzavara I[3], Papaioannou N[1], Lyritis GP[1], Alevizaki M[4]
[1]Laboratory of Research of Musculoskeletal System 'Th. Garofalidis', Athens University Medical School, KAT Hospital, Athens, Greece, [2]Department of Endocrinology, Elena Venizelou Hospital, Athens, Greece, [3]Department of Endocrinology, Diabetes and Metabolism, Amalia Fleming General Hospital, Athens, Greece, [4]Endocrine Unit, Department of Clinical Therapeutics, Athens University Medical School, Alexandra Hospital, Athens, Greece

P201 **LXR AND TR SIGNALING CROSSTALK: IMPLICATIONS IN THE CENTRAL CONTROL OF METABOLISM**

Clerget-Froidevaux M-S[1], Ghaddab-Zroud R[1], Seugnet I[1], Demeneix BA[1]
[1]Muséum National d'Histoire naturelle/CNRS UMR7221, RDDM, Paris cedex, France

P202 **PRIMARY HYPOTHYROIDISM IN 143 PATIENTS WITH OSTEOPENIA AND OSTEOPOROSIS: THE BONE PROFILE ANALYZE**

Carsote M[1], Ene C[2], Popescu M[2], Samoila R[2], Radoi V[1], Voicu G[2], Poiana C[1,2]
[1]UMPh Carol Davila, Bucharest, Romania, [2]I.Parhon, Bucharest, Romania

P203 **TIME-DEPENDENT UP-REGULATION OF TYPE 2 DEIODINASE AFTER MYOCARDIAL INFARCTION**

Araujo IG[1], Marassi MP[1], Silva AC[1], McElligott A[2], Paul J[2], Império GE[1], Carvalho DP[3], Henderson KK[2], Olivares EL[1]
[1]Federal Rural University of Rio de Janeiro, Physiological Science, Seropedica, Brazil, [2]Loyola University, Chicago, United States, [3]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

P204 **TRα1-MUTANT MICE MAINTAIN NORMAL BODY TEMPERATURE DESPITE DEFECTIVE VASCULAR CONTROL**

Warner A[1], Reheman A[2], Gottschling K[1], Davis B[2], Vennström B[1], Arner A[2], Mittag J[1]
[1]Karolinska Institutet, Department of Cell and Molecular Biology, Stockholm, Sweden, [2]Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden

P205 **CONCENTRATION-DEPENDENT STIMULATION OF MITOCHONDRIAL AND CELLULAR ENERGY METABOLISM BY 3,5-T2 IN HUMAN HEPG2 HEPATOCARCINOMA CELLS**

Lehmphul I[1], Vogel H[2], Kanzleiter T[2], Hoefig CS[1], Schürmann A[2], Köhrle J[1]
[1]Charité-Universitätsmedizin Berlin, Institut für Experimentelle Endokrinologie, Berlin, Germany, [2]German Institute of Human Nutrition, Experimental Diabetology, Potsdam-Rehbrücke, Germany

PO23 Thyroid Hormone Action 2

Chair: *Francesco Trimarchi* (Italy)

P206 **T3 ENHANCES GROWTH, GENE EXPRESSION, AND HORMONAL PRODUCTION IN RAT OVARIAN GRANULOSA CELL AND FOLLICLES**

Misiti S[1], Verga Falzacappa C[2], Santaguida MG[2], Alfei F[1], Furno A[1], Centanni M[2]
[1]Sapienza University of Rome, Department of Experimental Medicine, Roma, Italy, [2]Sapienza University of Rome, Department of Science and Medico-Surgical Biotechnologies, Latina, Italy

P207 **TYPE 2 DEIODINASE GENE GENOTYPE (D2 THR92ALA) INFLUENSE ON RISK OF DEVELOPMENT OF THYROID DISEASE?**

Babenko AY[1], Grineva EN[1], Kostareva AA[1], Popkova DA[1], Freylichman OA[2], Solncev VN[3]
[1]Almazov Federal Heart, Blood and Endocrinology Centre, Institute of Endocrinology, Saint- Petersburg, Russian Federation, [2]Almazov Federal Heart, Blood and Endocrinology Centre, Institute of Molecular Biology and Genetics, Saint- Petersburg, Russian Federation, [3]Almazov Federal Heart, Blood and Endocrinology Centre, Group of Medical Statistic, Saint- Petersburg, Russian Federation

P208 **THYROID HORMONE TRANSPORTERS DURING TESTICULAR DEVELOPMENT IN RODENTS**

Rijntjes E[1], Teerds KJ[2], Wirth EK[1], Hoefig CS[1], Köhrle J[1]
[1]Charité Universitätsmedizin Berlin, CVK, Institute for Experimental Endocrinology, Berlin, Germany, [2]Wageningen University, Dept. of Animal Sciences, Human and Animal Physiology Group, Wageningen, Netherlands

P209 **ASSOCIATION BETWEEN POST PARTUM THYROIDITIS AND THYROID HORMONE RESISTANCE IN AN ITALIAN PATIENT SHOWING A NOVEL P.V283A THRB (THYROID HORMONE RECEPTOR BETA) MUTATION**

Paragliola RM[1], Concolino P[2], De Rosa A[1], Mello E[2], Zuppi C[2], Pontecorvi A[1], Capoluongo E[2], Corsello SM[1]
[1]Catholic University School of Medicine, Endocrinology, Rome, Italy, [2]Catholic University School of Medicine, Biochemistry and Clinical Biochemistry, Rome, Italy

P210 **CENTRAL HYPOTHYROIDISM AND ITS REPLACEMENT CORRELATE TO A VARIETY OF CARDIOVASCULAR RISK FACTORS IN ADULT HYPOPITUITARY PATIENTS**

Hartoft-Nielsen M-L[1], Klose M[1], Klefter O[1], Marina D[1], Gavin V[1], Rasmussen AK[1], Feldt-Rasmussen U[1]
[1]Rigshospitalet, Medical Endocrinology PE 2132, Copenhagen, Denmark

P211 **PREVENTION OF POSTOPERATIVE HYPOCALCAEMIA AFTER TOTAL THYROIDECTOMY BY ALFACALCIDOL: A PROSPECTIVE RANDOMIZED CONTROL STUDY**

Genser L[1], Trésallet C[1], Li Sun Fui S[1], Salepcioglu H[1], Hoang C[2], Leenhardt L[3], Menegaux F[1]
[1]APHP, Université Pierre et Marie Curie, Paris 6, Endocrine Surgery, Paris, France, [2]APHP, Université Pierre et Marie Curie, Paris 6, Pathology Departement, Paris, France, [3]APHP, Université Pierre et Marie Curie, Paris 6, Nuclear Medicine, Paris, France

P212 **EXPRESSION OF TYPE 3 DEIODINASE (D3) IN THE HIPPOCAMPUS OF EPILEPTIC RATS**

Nassif R[1,2], Cysneiros R[1], Scorza F[2], Bianco A[3], Ribeiro M[1]
[1]Universidade Presbiteriana Mackenzie - Ciências Biológicas, Sao Paulo, Brazil, [2]UNIFESP, Neuroscience Department, Sao Paulo, Brazil, [3]University of Miami Miller School of Medicine, Division of Endocrinology, Diabetes and Metabolism, Miami, United States

PO24 Thyroid Function Regulation Basic

Chair: *Denise Carvalho* (Brazil)

P213 **DEIODINASE TYPE 2 ACTIVITY AND SERUM THYROID HORMONE LEVELS AFTER SLEEP LOSS IN RATS**

Rodrigues NC[1], Cruz NS[1], Nascimento CP[1], Conceição RR[1], Olivares EL[1], Silva AC[1], Carvalho DP[2], Andersen ML[3], Marassi MP[1]
[1]Federal Rural University of Rio de Janeiro, Physiological Sciences, Seropedica, Brazil, [2]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, 3UNIFESP, Psychobiology, Sao Paulo, Brazil

P214 **REGULATION OF THE NIS PROMOTER BY AMPK MODULATION**

Abdulrahman RM[1], Sips HCM[1], Smit JWA[1], Hovens GCJ[1]
[1]Leiden University Medical Center, Endocrinology, Leiden, Netherlands

P215 **THYROID PHENOTYPE IN SORTILIN KO MICE**

Profilo MA[1], Lisi S[1], Botta R[1], Chiarini R[1], Altea MA[1], Leo M[1], Sisti E[1], *Rocchi R[1], Latrofa F[1], Marinò M[1], Pinchera A[1]*
[1]University of Pisa, Department of Endocrinology, Pisa, Italy

P216 **PHENOTYPIC ANALYSIS OF THYROID-SPECIFIC NF-KB KNOCKOUT MICE**

Reale C[1,2], Guerrera D[1,2], Scudiero I[1,2], Zotti T[1,2], Vito P[1,2], Stilo R[1,2]
[1]Biogem, Ariano Irpino, Italy, [2]Università del Sannio, Benevento, Italy

P217 **AUDIT OF PATIENT INFORMATION FOR AGRANULOCYTOSIS DUE TO ANTI THYROID DRUG (ATD) THERAPY**

Richardson MN[1], Perros P[2]
[1]University of Newcastle upon Tyne, Medical School, Newcastle upon Tyne, United Kingdom, [2]Royal Victoria Infirmary, Endocrinology, Newcastle upon Tyne, United Kingdom

P218 **EFFECTS OF METFORMIN ON THYROID FUNCTION**

Hovens GCJ[1], Abdulrahman R[1], Sips H[1], Smit JWA[1]
[1]Leiden University Medical Center(LUMC), Dept. of Endocrinology and Metabolic Diseases, Leiden, Netherlands

P219 **FLAVONOID RUTIN INCREASES THYROID RADIOIODIDE UPTAKE**

Gonçalves CFL[1], Santos MCS[1], Carvalho DPD[1], Ferreira ACF[1]
[1]Federal University of Rio de Janeiro, IBCCF - Laboratory of Endocrine Physiology, Rio de Janeiro, Brazil

P220 **PAX8 CONTRIBUTES TO TSH REGULATION OF DIO1 GENE TRANSCRIPTION BY A NOVEL MECHANISM INVOLVING ITS BINDING TO THE 3'UTR REGION**

Leoni SG[1], Ruiz-Llorente S[2], Santisteban P[1]
[1]Inst. Investigaciones Biomedicas de Madrid, Departamento de Fisiopatología Endocrina y del Sistema Nervioso, Madrid, Spain, [2]Memorial Sloan-Kettering Cancer Center, New York, United States

P221 **TRANSCRIPTION FACTOR NKX2.5 REGULATES H2O2 GENERATION AND IODIDE UPTAKE IN PCCL3 CELLS**

Cardoso LC[1], Penha RCC[2], Carvalho DP[2], Ferreira ACF[2]
[1]UFF, Departamento de Patologia, Niterói, Brazil, [2]UFRJ, Instituto de Biofísica Carlos Chagas Filho, Rio de Janeiro, Brazil

P222 **THE FOLLICLE THYROID CELL LINE PCCL3 DIFFERENTIALLY RESPONDS TO LAMININ AND TO POLY-LAMININ, A POLYMERIC FORM OF LAMININ ASSEMBLED AT ACIDIC PH**

Palmero CY[1], Carvalho DPD[1], Merlmestein CS[1], Coelho-Sampaio T[1], Miranda-Alves L[1], Nasciutti LE[1]
[1]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

PO25 Clinical Thyroid Autoimmunity 2

Chair: *Chantal Daumerie* (Belgium)

P223 **AGE-RELATED FEATURES OF ASSOCIATIVE BONDS BETWEEN IMMUNOGLOBULINS TO LYMPHOTROPIC VIRUS AND IMMUNE RESPONSE COMPONENTS IN WOMEN WITH AUTOIMMUNE THYROIDITIS**

Karachentcev Y[1,2], Goncharova O[2], Kravchun N[1], Iliyna I[1]
[1]PI 'V. Danilevsky Institute of Endocrine Pathology Problems at AMS of Ukraine', AMS of Ukraine, Kharkov, Ukraine, [2]Kharkov Medical Academy of Postgraduate Education, of Endocrinology and Pediatric Endocrinology, Kharkov, Ukraine

P224 **EVALUATION OF CD4+CD161+CD196+ AND CD4+IL-17+ TH17 CELLS IN THE PERIPHERAL BLOOD OF YOUNG PATIENTS WITH GRAVES' DISEASE AND HASHIMOTO'S THYROIDITIS**

Bossowski A[1], Moniuszko M[2], Dąbrowska M[3], Jeznach M[2], Rusak M[3], Bossowska A[4], Sawicka B[1], Borysewicz-Sańczyk H[1], Bodzenta-Łukaszyk A[2]
[1]Medical University in Bialystok, Dep. of Pediatrics, Endocrinology,Diabetology with Cardiology Subdivision, Bialystok, Poland, [2]Medical University in Bialystok, Department of Allergology and Internal Medicine, Bialystok, Poland, [3]Medical University in Bialystok, Dep. of Hematology Diagnostic, Bialystok, Poland, [4]Internal Affairs and Administration Ministry Hospital in Białystok, Department of Cardiology, Bialystok, Poland

P225 **CHARACTERISTICS OF THE AUTOIMMUNE THYROIDITIS IN PATIENTS WITH DIABETES MELLITUS OF THE 1, 2 TYPE**

Kravchun NA[1], Chernjavskay IV[1]
[1]Institute of Problems of Endocrine Pathology n.a. V.Y. Danylevskogo of AMS of Ukraine, Department of Pharmacotherapy of Endocrine Diseases, Kharkov, Ukraine

P226 **AUTOIMMUNE THYROIDITIS IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS IN ARMENIA: ASSOCIATION WITH GENDER, AGE, DIABETES DURATION AND PUBERTY**

Navasardyan LV[1], Aghajanova YM[1], Arakelyan LM[1], Bayburdyan GM[1], Hakobyan SV[1], Kalantaryan LG[1]
[1]Yerevan State Medical University, Endocrinology, Yerevan, Armenia

P227 **DOES FAMILY AND PERSONAL HYSTORY OF AUTOIMMUNE AND THYROID DISEASES INFLUENCE GRAVES DISEASE PRESENTATION AND EVOLUTION?**

Martin CS[1,2], Predescu A[1], Fica S[1,2]
[1]Elias Hospital, Endocrinology, Bucharest, Romania, [2]'Carol Davila' University of Medicine and Pharmacy, Endocrinology, Bucharest, Romania

P228 **ANAEMIA IN INDIAN SUBJECTS WITH AUTOIMMUNE THYROID DISEASE: COULD IT BE A SURROGATE MARKER FOR AUTO IMMUNE GASTRITIS?**

Varthakavi PK[1], Lathia TB[1], Joshi AS[1], Nishtala S[2], Bhagwat NM[1], Chadha MD[1], Dholye JP[1], Rathi P[2], Kamat SM[1]
[1]T.N.Medical College & BYL Nair Ch.Hospital, Endocrinology, Mumbai, India, [2]T.N.Medical College & BYL Nair Ch.Hospital, Gastroenterology, Mumbai, India

P229 **THYROID DISORDERS IN CUSHING'S SYNDROME**

Manetti L[1], Raffaelli V[1], Scattina I[1], Lupi I[1], Cosci C[1], Gasperi M[2], Cosottini M[3], Iannelli A[3], Bogazzi F[1], Martino E[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy, [2]University of Molise, Chair of Endocrinology, Campobasso, Italy, [3]University of Pisa, Department of Neurosciences, Pisa, Italy

P230 **THYROID FUNCTION IN EUTHYROID PATIENTS WITH HASHIMOTO´S THYROIDITIS IS DIFFERENT THAN IN HEALTHY SUBJECTS**

Zaletel K[1], Žitko-Krhin M[1], Gaberšček S[1], Grabnar I[2], Hojker S[1]
[1]University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

PO26 Environmental Factors and Drugs Affecting Thyroid Function 1

Chair: *Leonidas Duntas* (Greece)

P231 **THYROID DISORDERS IN ADULT POPULATION OF UKRAINE AFTER THE CHERNOBYL NPP ACCIDENT**

Kaminskyi OV[1], Afanasyev DY[1], Kovalenko OM[1]
[1]National Research Center for Radiation Medicine of NAMS of Ukraine, Department of Radio-Induced General and Endocrine Disease, Kiew, Ukraine

P232 **SURVEY OF THE MANAGEMENT OF AMIODARONE INDUCED THYROTOXICOSIS**

Taylor P[1], Raghavan R[2], Bhake R[3], Vaidya B[4], Martino E[5], Bartelena L[6], Dayan C[1], Bradley K[2]
[1]Cardiff University, Centre for Endocrine and Diabetes Sciences, Cardiff, United Kingdom, [2]Bristol Royal Infirmary, Department of Endocrinology, Bristol, United Kingdom, [3]University of Bristol, HWLINE, Bristol, United Kingdom, [4]Peninsula Medical School, Department of Endocrinology, Royal Devon and Exeter Hospital, Exeter, United Kingdom, [5]University of Pisa, Department of Endocrinology, Pisa, Italy, [6]University of Insubria, Department of Cilnical Medicine, Varese, Italy

P233 **HOW IS IODINE SUPPLY MAINTAINED DESPITE LOW DIETARY IODINE INTAKE?**

Smyth PPA[1,2], Burns R[1], Huang R-J[2], Hoffman T[3], O'Dowd C[2]
[1]University College Dublin, School of Medicine, Dublin, Ireland, [2]National University of Ireland (Galway), School of Physics, Galway, Ireland, [3]Johannes Gutenberg Univ of Mainz, Inst. of Inorganic and Analytical Chemistry, Mainz, Germany

P234 **THYROID DISORDERS IN PATIENTS HEMATOLOGICAL MALIGNANCIES**

Nonchev BI[1], Goranova-Marinova V[2], Pavlov P[3], Orbetzova M[1], Goranov S[2]
[1]Medical University, Endocrinology, Plovdiv, Bulgaria, [2]Medical University, Hematology, Plovdiv, Bulgaria, [3]Medical University, Central Clinical Laboratory, Plovdiv, Bulgaria

P235 **IODINE DEFICIENCY IN EASTERN UKRAINE**

Mamenko M[1], Belykh N[1], Shleyenkova G[1], Sherbakova M[1]
[1]Luhansk State Medical University, Department of Postgraduate Education in Pediatrics, Luhansk, Ukraine

P236 **DRUG-INDUCED THYROIDITIS BY NEW TREATMENTS SUCH AS ANTI-TUMOR NECROSIS FACTOR (TNF)**

Favre L[1], Ducry J[1], Portmann L[1]
[1]University Hospital CHUV, Service d'endocrinologie, diabétologie et métabolisme, Lausanne, Switzerland

P237 **IODINE STATUS AND THYROID FUNCTION IN HIMALAYAN MOUNTAIN POPULATIONS**

Chandola-Saklani A[1], Kathait A[1,2], Farswan A[3], Yadav N[1], Kumar D[1]
[1]Apeejay Stya University, Biosciences & Clinical Research, Gurgaon, India, [2]HNBG Central University, Dept of Biotechnology, Srinagar Garhwal, India, [3]Govt PG College, Dept of Zoology, Agastya Muni, Rudraprayag, India

P238 **MULTIPLE PESTICIDES EXPOSURE OF GREENHOUSES WORKERS AND THYROID PARAMETERS**

Simescu MM[1], Podia Igna CC[2], Nicolaescu E[3], Caragheorgheopol A[4], Ion I[5], Ion AC[5], Neagu C[6], Negru M[6], Pribu M[6], Kochanska Dziurowicz A[7], Stanjek-Cichoracka A[7]
[1]National Institute of Endocrinology, Endocrinology, Bucharest, Romania, [2]Astra Clinic, Endocrinology, Sibiu, Romania, [3]SC SIMEDIS CONSULT SRL, Bucharest, Romania, [4]National Institute of Endocrinology, Bucharest, Romania, [5]Politechnic University, Bucharest, Romania, [6]National Institute of Public Health, Bucharest, Romania, [7]Department of Isotopic Diagnostics, Sosnowiec, Poland

PO27 Graves' Orbitopathy Clinical 2

Chair: *Jacques Orgiazzi* (France)

P239 **IS RECOMBINANT HUMAN TSH A TRIGGER FOR GRAVES´ ORBITOPATHY?**

Daumerie C[1], Boschi A[2], Perros P[3]
[1]Université catholique de Louvain, Clin. Univ. St-Luc, Endocrinology, Brussels, Belgium, [2]Université catholique de Louvain, Clin. Univ. St-Luc, Ophthalmology, Brussels, Belgium, [3]Royal Victoria Infirmary, Endocrinology, Newcastle Upon Tyne, United Kingdom

P240 **HIGH PREVALENCE OF SUBCLINICAL EXTRAOCULAR MUSCLES ALTERATIONS IN GRAVES' DISEASE PATIENTS WITHOUT CLINICALLY EVIDENT GRAVES'ORBITOPATHY**

Boi F[1], Vacca R[1], Zucca I[2], Cuccu A[2], Fossarello M[2], Marini S[3], Mariotti S[1]
[1]Endocrinology Unit, University of Cagliari, Department of Medical Sciences, Monserrato - Cagliari, Italy, [2]Ophthalmology Unit, University of Cagliari, Department of Surgical Sciences, Cagliari, Italy, [3]Radiology Unit, University of Cagliari, Department of Medical Sciences, Monserrato - Cagliari, Italy

P241 **METHYLPREDNISOLONE-INDUCED HEPATITIS DURING THYROID ORBITOPATHY TREATMENT CONDUCTED IN ACCORDANCE WITH EUGOGO RECOMMENDATIONS**

Poullot A-G[1], Fisch A-L[2,3], Speux A[4], Fénichel P[2], Sadoul J-L[5]
[1]CHU de Nice, Endocrinology, Nice, France, [2]CHU de Nice, Endocrinologie, Nice, France, [3]CHU de Nice, Ophtalmologie, Nice, France, [4]CHU de Nice, Pharmacovigilance, Nice, France, [5]CHU de Nice, Endocrinology, Nice Cedex, France

P242 **COMPARISON OF COURSE OF CHANGES IN LEVELS OF TSH-RECEPTOR ANTIBODIES (TRAB) AND COURSE OF GRAVES´ORBITOPATHY (GO) IN 160 PATIENTS WITH GRAVES´DISEASE AFTER TWO DIFFERENT ABLATIVE REGIMENS: (SUB)TOTAL THYROIDECTOMY VERSUS RADIOIODINE**

Grussendorf M[1], Bacher K[1], Cordes A[1], Feldmann B[1]
[1]Endokrinologie im Zentrum, Stuttgart, Germany

P243 **COMPARISON OF EARLY TOTAL THYROIDECTOMY WITH ANTITHYROID TREATMENT IN PATIENTS WITH MODERATE TO SEVERELY ACTIVE GRAVES' ORBITOPATHY, A RANDOMIZED PROSPECTIVE TRIAL**

Erdoğan MF[1], Demir Ö[1], Ersoy RÜ[2], Gül K[2], Ünlütürk U[1], Aydoğan Bİ[1], Üç ZA[3], Mete T[4], Ertek S[5], Çakır B[2], Aral Y[3], Güler S[4], Erdoğan G[5], Ankara Thyroid Study Group
[1]Ankara University, Endocrinology and Metabolic Diseases, Ankara, Turkey, [2]Ankara Atatürk Training and Research Hospital, Endocrinology and Metabolic Diseases, Ankara, Turkey, [3]Ankara Training and Research Hospital, Endocrinology and Metabolic Diseases, Ankara, Turkey, [4]Ankara Numune Training and Research Hospital, Endocrinology and Metabolic Diseases, Ankara, Turkey, [5]Ufuk University, Endocrinology and Metabolic Diseases, Ankara, Turkey

P244 **FEATURES OF GRAVES' OPHTHALMOPATHY IN TYPE 2 DIABETIC PATIENTS**

Le Moli R[1], Muscia V[1], Castoro C[1], Squatrito S[1], Vigneri R[1]
[1]University of Catania, Biomedicine, Clinical and Molecular, Catania, Italy

P245 **OPHTHALMOPATHY INDUCED BY BILATERAL CAROTID CAVERNOUS FISTULA IN A PATIENT WITH GRAVES' DISEASE**

Suk J[1]
[1]Maryknoll Hospital, Department of Internal Medicine, Busan, Republic of Korea

Poster Exhibition Area
12.00–13.00
Poster Session 3

PO28 Thyroid Cancer Diagnostics Clinical 3

Chair: *Philippe Caron* (France)

P246 **ULTRASONOGRAPHIC FEATURES PREDICTING RECURRENT LARYNGEAL NERVE INVOLVEMENT IN THYROID CANCER**

Kim B-W[1], Chang H-S[1], Park CS[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Departments of Surgery, Seoul, Korea, Republic of

P247 **DIFFERENTIATED CARCINOMA IN DYSEMBRIOGENETIC THYROID LESIONS**

Sturniolo G[1], Violi MA[1], Presti S[1], Moleti M[1], Di Bella B[1], Di Mauro F[1], Trimarchi F[1], Vermiglio F[1]
[1]Università degli Studi di Messina, Clinico-Sperimentale di Medicina e Farmacologia, Messina, Italy

P248 **REGULATION OF TIGHT JUNCTION PROTEINS DURING THE EPITHELIAL-MESENCHYMAL TRANSITION IN THYROID CANCER: THE ROLE OF THE SLUG TRANSCRIPTION FACTOR**

Colato C[1], Monzani F[2], Brazzarola P[3], Martignoni G[1], Chilosi M[1], Ferdeghini M[1]
[1]University of Verona, Pathology and Diagnostics, Verona, Italy, [2]University of Pisa, Internal Medicine, Pisa, Italy, [3]University of Verona, Surgery and Oncology, Verona, Italy

P249 **PREOPERATIVE MALIGNANCY RISK PREDICTION IN THYROID NODULES WITH "FOLLICULAR NEOPLASM" CYTOLOGY**

Lanshchakov K[1], Belousov P[2], Vanushko V[3], Beltsevich D[3], Fadeev V[3], Rumyantsev P[3], Abdulkhabirova F[3], Platonova N[3], Troshina E[3]
[1]Endocrinology Research Center, Endocrine Surgery, Moscow, Russian Federation, [2]Moscow State University, Moscow, Russian Federation, [3]Endocrinology Research Center, Moscow, Russian Federation

P250 **USEFULNESS OF ELASTOSONOGRAPHY AS AN ADDITIONAL DIAGNOSTIC TOOL FOR THYROID NODULES**

Filieri C[1], Rossi M[1], Trasforini G[1], Beccati MD[2], Rossi R[1], Zatelli MC[1,3], degli Uberti E[1,3]
[1]University of Ferrara, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy, [2]S.Anna Hospital, Ferrara, Cytopathology, Ferrara, Italy, [3]LTTA, University of Ferrara, Ferrara, Italy

P251 **FDG-PET/CT IN HIGH RISK DIFFERENTIATED THYROID CANCER**

Yang JH[1], Nakabashi CCD[1,2], Camacho CP[1,2], Andreoni DM[1,2], Padovani RP[1,2], Malouf EZ[1,2], Ikejiri ES[1,2], Mamone MCC[1,2], Abrahão M[3], Hojaij FC[3], Hidal JT[1,2], Osawa A[4], Yamaga LYI[4], Wagner J[4], Maciel RMB[1,2], Biscolla RPM[1,2]
[1]Federal University of São Paulo, Endocrinology, São Paulo, Brazil, [2]Thyroid Diseases Center, Instituto Israelita de Ensino e Pesquisa Albert Einstein and Federal University of São Paulo, São Paulo, Brazil, [3]Federal University of Sao Paulo, Otorhinolaryngology, Head and Neck Surgery, São Paulo, Brazil, [4]Hospital Israelita Albert Einstein, Imaging Department, São Paulo, Brazil

P252 **ROLE OF ULTRASONOGRAPHY, CLINICAL PROFILE, CYTOLOGY AND BRAF V600E MUTATION EVALUATION IN DETECTING MALIGNANT THYROID NODULES**

Zatelli MC[1,2], Rossi M[1], Buratto M[1], Bruni S[3], Filieri C[1], Tagliati F[1], Trasforini G[1], Rossi R[1], Beccati MD[4], degli Uberti E[1,2]
[1]University of Ferrara, Section of Endocrinology, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy, [2]University of Ferrara, LTTA, Ferrara, Italy, [3]S. Anna Hospital, Section of Endocrinology, Ferrara, Italy, [4]S.Anna Hospital, Cytopathology, Ferrara, Italy

P253 **PROGNOSTIC VALUE OF POST-OPERATIVE NECK ULTRASOUND FOR PREDICTING RECURRENCES IN DIFFERENTIATED THYROID CANCER PATIENTS WITH INITIAL LYMPH NODES INVOLVEMENT**

Lepoutre-Lussey C[1], Maddah D[1], Golmard J-L[2], Le Henaff V[1], Hoang C[3], Trésallet C[4], Ménégaux F[4], Aurengo A[1], Leenhardt L[1]
[1]Hôpital Pitié-Salpêtrière, Service de Médecine Nucléaire, Paris, France, [2]Hôpital Pitié-Salpêtrière, Service de Biostatistiques et Unité de Recherche Clinique, Paris, France, [3]Hôpital Pitié-Salpêtrière, Service D'anatomopathologie, Paris, France, [4]Hôpital Pitié-Salpêtrière, Service de Chirurgie Endocrinienne, Paris, France

P254 **EFFECT OF PROPHYLACTIC CENTRAL LYMPH NODE DISSECTION ON POSTOPERATIVE STIMULATED THYROGLOBULIN LEVELS AND ON DISEASE PERSISTENCE AND RECURRENCE IN LYMPH NODE NEGATIVE PATIENTS WITH PAPILLARY THYROID CARCINOMA**

Aydoğan Bİ[1], Ünlütürk U[1], Taşkıran B[2], Can F[3], Yüksel B[3], Özkan E[4], Erdoğan MF[1], Güllü S[1], Emral R[1], Başkal N[1], Çorapçıoğlu D[1], Şahin M[1], Küçük Ö[4], Uysal AR[1]
[1]Ankara University School of Medicine, Endocrinology and Metabolism, Ankara, Turkey, [2]Yunus Emre State Hospital, Endocrinology and Metabolism, Ankara, Turkey, [3]Ankara University School of Medicine, Internal Medicine, Ankara, Turkey, [4]Ankara University School of Medicine, Nuclear Medicine, Ankara, Turkey

P255 **THE RELATIONSHIP OF PREOPERATIVE TSH LEVELS AND COEXISTING AUTOIMMUNE THYROID DISEASE WITH TUMOR STAGE AT THE DIAGNOSIS AND RECURRENCE IN DIFFERENTIATED THYROID CARCINOMA PATIENTS**

Taşkıran B[1], Aydoğan Bİ[1], Ünlütürk U[1], Öztürk B[2], Bali E[3], Güllü S[1], Erdoğan MF[1], Emral R[1], Başkal N[1], Çorapçıoğlu D[1], Şahin M[1], Özkan E[3], Küçük Ö[3], Uysal AR[1]
[1]Ankara University School of Medicine, Endocrinology and Metabolism, Ankara, Turkey, [2]Ankara University School of Medicine, Internal Medicine, Ankara, Turkey, [3]Ankara University School of Medicine, Nuclear Medicine, Ankara, Turkey

P256 **WHOLE-BODY DIFFUSION MRI AND SKELETAL LESIONS IN THYROID CANCER: DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS**

Locati LD[1], Potepan P[2], Granata R[1], Gianluca A[3], Civelli EM[2], Bossi P[1], Montin E[2], Licitra LF[1]
[1]Fondazione IRCCS Istituto Nazionale dei Tumori, Medical Oncology, Milan, Italy, [2]Fondazione IRCCS Istituto Nazionale dei Tumori, Radiology, Milan, Italy, [3]Fondazione IRCCS Istituto Nazionale dei Tumori, Radiology-Nuclear Medicine, Milan, Italy

P257 **PATTERN OF NODAL SPREAD ACCORDING TO TUMOR LOCATION OF PAPILLARY THYROID CARCINOMA**

Jeong W-J[1], Hong SN[1], Kim YW[1], Sung M-W[2], Kim KH[2], Ahn S-H[1]
[1]Seoul National University Bundang Hospital, Department of Otorhinolaryngology - Head & Neck Surgery, Seongnam, Republic of Korea, [2]Seoul National University Hospital, Department of Otorhinolaryngology - Head & Neck Surgery, Seoul, Republic of Korea

PO29 Thyroid Cancer Therapeutics Clinical 3

Chair: *Sophie Leboulleux* (France)

P258 **LONG TERM IMPACT OF RADIOIODINE TREATMENT FOR DIFFERENTIATED THYROID CARCINOMA ON PERIPHERAL BLOOD CELL COUNT**

Kneer K[1], Luster M[1], Bommer M[2], Ohlhauser D[1]
[1]Uniklinikum Ulm, Nuklearmedizin, Ulm, Germany, [2]Uniklinikum Ulm, Innere Medizin III, Ulm, Germany

P259 **VALUE OF FIRST THYROGLOBULIN AS A PROGNOSTIC FACTOR IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA**

Zakavi SR[1], Ayati A[1], Mousavi Z[2], Ayati NK[1]
[1]Nuclear Medicine Research Center/ Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran, [2]Endocrine Research Center, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran

P260 **FOLLOW-UP IN PATIENTS WITH ANTIBODY INTERFERENCE IN TG MEASUREMENT: A CONSENSUS STATEMENT**

Verburg FA[1], Luster M[2], Chiovato C[3], Chiovato L[4], Duntas L[5], Elisei R[6], Feldt-Rasmussen U[7], Rimmele H[8], Seregni E[9], Smit JW[10], Theimer C[11], Giovanella L[12]
[1]University Hospital Aachen, Nuclear Medicine, Aachen, Germany, [2]University Hospital Ulm, Nuclear Medicine, Ulm, Germany, [3]Azienda Ospedaliera-Universitaria Pisana, Endocrine Outpatient Clinic, Pisa, Italy, [4]University of Pavia Hospital, Department of Internal Medicine and Endocrinology, Pavia, Italy, [5]Evgenidion Hospital, University of Athens Medical School, Endocrine Unit, Athens, Greece, [6]Department of Endocrinology, University Hospital Pisa, Pisa, Italy, [7]Rigshospitalet, Endocrinology, Copenhagen, Italy, [8]Ohne Schilddruese Leben e.V., Berlin, Germany, [9]Instituto di Tumori, Endocrinology, Milan, Italy, [10]Leiden University Medical Center, Endocrinology, Leiden, Netherlands, [11]Thermo Fisher Scientific, Inc., Hennigsdorf, Germany, [12]Oncology Institute of Southern Switzerland, Department of Nuclear Medicine and PET Centre, Bellinzona, Switzerland

P261 **LIFE EXPECTANCY IS NORMAL IN PATIENTS WITH UICC/AJCC TNM STAGE I, II AND III DIFFERENTIATED THYROID CANCER, BUT CLEARLY REDUCED IN STAGE IV DISEASE**

Verburg FA[1,2], Maeder U[3], Tanase K[2], Thies ED[2], Diessl S[2], Buck AK[2], Reiners C[2], Luster M[4]
[1]University Hospital Aachen, Nuclear Medicine, Aachen, Germany, [2]University Hospital Wuerzburg, Nuclear Medicine, Wuerzburg, Germany, [3]University Hospital Wuerzburg, Comprehensive Cancer Center Mainfranken, Wuerzburg, Germany, [4]University Hospital Ulm, Nuclear Medicine, Ulm, Germany

P262 **PREDICTIVE VALUE FOR DISEASE PERSISTENCE OR EARLY PROGRESSION OF SERUM THYROGLOBULIN LEVELS AT TIME OF 131I REMNANT ABLATION USING RECOMBINANT TSH**

Melo M[1,2], Costa G[3], Ribeiro C[1], Carrilho F[1], Martins MJ[4], Gaspar da Rocha A[2], Soares P[2,5], Carvalheiro M[1]
[1]University Hospital of Coimbra, Department of Endocrinology, Diabetes and Metabolism, Coimbra, Portugal, [2]Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP), Porto, Portugal, [3]University Hospital of Coimbra, Department of Nuclear Medicine, Coimbra, Portugal, [4]University Hospital of Coimbra, Department of Pathology, Coimbra, Portugal, [5]Medical Faculty, University of Porto, Department of Pathology, Porto, Portugal

P263 **EFFECTS OF PILOCARPINE ON SALIVARY GLAND FUNCTION AFTER POSTOPERATIVE RADIOIODINE THERAPY FOR DIFFERENTIATED THYROID CANCER**

Lim J-Y[1], Choi J-S[1], Kim Y-M[1]
[1]Department of Otorhinolaryngology, Inha University College of Medicine, Incheon, Korea, Republic of

P264 **PROGNOSTIC IMPLICATIONS OF THE NUMBER AND RATIO OF METASTATIC LATERAL NODES IN PAPILLARY THYROID CARCINOMA**

Koo MY[1], Lee SK[2], Bae SY[2], Choi MY[2], Choe J-H[2], Kim J-H[2], Kim JS[2]
[1]National Police Hospital, Surgery, Seoul, Korea, Republic of, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Surgery, Seoul, Republic of Korea

P265 **PROGNOSTIC VALUE OF STIMULATED THYROGLOBULIN PRIOR 131I ABLATION IN DIFFERENTIATED THYROID CARCINOMA: A PROSPECTIVE STUDY**

Scheffel RS[1], Zanella AB[1], Dora JM[1], Maia AL[1]
[1]Hospital de Clínicas de Porto Alegre, Thyroid Section, Endocrine Division, Porto Alegre, Brazil

P266 ***Withdrawn***

P267 **SIDE EFFECTS OF TYROSINE KINASE INHIBITORS (TKI) APPLIED IN THYROID CANCER (TC) PATIENTS - ONE CENTER EXPERIENCE**

Krajewska JA[1], Kukulska A[1], Paliczka-Cieslik E[1], Handkiewicz-Junak D[1], Gawlik T[1], Olczyk T[1], Kropinska A[1], Skoczylas A[1], Michalik B[1], Jarzab B[1]
[1]M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Nuclear Medicine and Endocrine Oncology Department, Gliwice, Poland

P268 **PROS AND CONS OF PROPHYLACTIC CENTRAL COMPARTMENT LYMPH NODE DISSECTION IN DIFFERENTIATED THYROID CANCER PATIENTS**

Valerio L[1], Viola D[1], Materazzi G[2], Miccoli P[2], Basolo F[2], Sensi E[2], Faviana P[2], Molinaro E[1], Agate L[1], Pinchera A[1], Elisei R[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy, [2]University of Pisa, Department of Surgery, Pisa, Italy

P269 **METASTATIC THYROID CANCER (TC) UNRESPONSIVE TO CONVENTIONAL THERAPY AND OTHER THYROSINE KINASES INHIBITORS (TKI) TREATED WITH SUNITINIB "OFF-LABEL"**

Cappagli V[1], Bottici V[1], Molinaro E[1], Agate L[1], Viola D[1], Valerio L[1], Mazzeo S[2], Battaglia V[2], Contillo Pontillo B[2], Dal Canto L[3], Vitti P[1], Pinchera A[1], Elisei R[1], Ribechini A[4]
[1]University of Pisa, Endocrinology and Metabolism, Pisa, Italy, [2]University of Pisa, University Radiodiagnostic, Pisa, Italy, [3]AOUP, Pharmacy, Pisa, Italy, [4]University of Pisa, Thoracic Surgery-Section of Thoracic Endoscopy, Pisa, Italy

PO30 Thyroid Cancer Pathogenesis Clincial/ Translational

Chair: *Clara Alvarez* (Spain)

P270 **ASSOCIATION OF PAPILLARY CARCINOMA, AND SOME OF ITS BASIC FEATURES WITH THE PRESENCE OF HASHIMOTO´S THYROIDITIS**

Semenov A[1], Chernikov R[1], Vorobyov S[1], Bubnov A[1], Slepcov I[1], Uspenskaya A[1], Makarin V[1], Timofeeva N[1], Chinchuk I[1], Novokshonov K[1], Karelina J[1], Rusakov V[1], Fedorov E[1], Kulyash A[1]
[1]St. Petersburg Branch Pirogov National Medical & Surgical Center, Endocrine Surgery Department, St.Petersburg, Russian Federation

P271 **PREVALENCE AND INFLUENCE OF OBESITY IN DIFFERENTIATED THYROID CARCINOMA**

Castagna MG[1], Ciuoli C[1], Theodoropoulou A[1], Brusco L[1], Maino F[1], Belardini V[1], Serafini A[1], Memmo S[1], Pacini F[1]
[1]University of Siena, Siena, Italy, Section of Endocrinology and Metabolism, Department of Internal Medicine, Endocrinology and Metabolism and Biochemistry, Siena, Italy

P272 **2D-DIGE PROTEOMIC ANALYSIS IS A USEFUL TOOL IN THE SEARCH OF NEW BIOMARKERS IN THE EPITHELIAL THYROID TUMORS WITH DIFFERENT DEGREES OF MALIGNANCY**

Mato E[1,2], Barceló S[3], González C[1,2], Aulinas A[2], Bell O[1,2], Moral A[4], Pérez JL[4], de Leiva A[1,2]
[1]Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Barcelona, Spain, [2]Hospital Sant Pau, Autonomous University, Endocrinology Department, Barcelona, Spain, [3]Instituto Aragonés de Ciencias de la Salud (ICS), Unidad Mixta de Investigación, Proteomics Unit, Zaragoza, Spain, [4]Hospital Sant Pau, Autonomous University, General Surgery, Barcelona, Spain

P273 **ANAPLASTIC AND POORLY DIFFERENTIATED THYROID CARCINOMA SHOW A LOW PREVALENCE OF KNOWN GENETIC ALTERATIONS**

Alessia T[1], Romei C[1], Molinaro E[1], Agate L[1], Cosci B[1], Vivaldi A[1], Gianì C[1], Pieruzzi L[1], Lorusso L[1], Elisei R[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy

P274 **DIFFERENCIATED THYROID CANCER COEXISTENT WITH CHRONIC THYROIDITIS (HASHIMOTO'S THYROIDITIS) A STUDY ON GENDER DIFFERENCES**

Mitsuhashi T[1], Tomemori T[1], Watanabe R[1], Hiruma K[1], Sakitani E[1], Sugisaki H[1], Yanagi Y[1]
[1]Tokyo Metropolitan Cancer and Infectious Diseases Center KOMAGOME Hospital, Otorhinolaryngology Head and Neck Oncology, Tokyo, Japan

P275 **EXOME WIDE ANALYSIS IN 5 PAPILLARY THYROID CARCINOMAS**

Frasca F[1], Nicolosi ML[1], Gianì F[1], Vella V[2], Cattonaro F[3], Morgante M[3], Vigneri R[1]
[1]University of Catania, Clinical and Molecular Biomedicine, Endocrinology Unit, Catania, Italy, [2]University of Enna 'Kore', Scienze Motorie, Enna, Italy, [3]University of Udine, Istituto di Genomica Applicata, Parco Scientifico e Tecnologico, Udine, Italy

P276 **DNA METHYLATION OF *CBX7* GENE IN PAPILLARY THYROID CARCINOMA**

Chung K-W[1], Park S-Y[2], Lee EK[2], Lee YJ[2], Kim SK[2], Kim TS[2], Jung YS[2], Kim TH[2], Ryu JS[2]
[1]Asan Meical Center, Ulsan University, College of Medicine, Division of Endocrine Sdurgery, Department of Surgery, Seoul, Republic of Korea, [2]National Cancer Center, Center for Thyroid Cancer, Goyang, Republic of Korea

P277 **MATRIX METALLOPROTEINASE-9 (MMP-9) AND TISSUE INHIBITOR OF METALLOPROTEINASE-1 (TIMP-1) OVEREXPRESSION IN PAPILLARY THYROID CARCINOMA: IMPLICATIONS FOR CLINICAL DISEASE PRESENTATION**

Romitti M[1], Ceolin L[1], Ferreira CV[1], Cavalcante S[1], Wajner SM[1], Meurer L[2], Brasil BA[2], Maia AL[1]
[1]Hospital de Clínicas de Porto Alegre/ Universidade Federal do Rio Grande do Sul, Endocrinology Service, Porto Alegre, Brazil, [2]Hospital de Clínicas de Porto Alegre, Pathology, Porto Alegre, Brazil

P278 **PAPILLARY THYROID CARCINOMA WITH SIZE OF UP TO 10 MM - A DIFFERENT CLINICAL ENTITY?**

Stanicic J[1], Jukic T[1], Dabelic N[1], Granic R[1], Kusic Z[1]
[1]University Hospital Centre Sestre Milosrdnice, Dpt of Oncology and Nuclear Medicine, Zagreb, Croatia

P279 **SOMATOMETRIC PARAMETERS AND DAILY HABITS AS RISK FACTORS FOR THYROID CANCER DEVELOPMENT**

Mathiopoulou L[1], Boudina M[1], Chrisoulidou A[1], Mandanas S[1], Panagiotou G[1], Doumala E[1], Iliadou P[1], Tziomalos K[1], Pazaitou- Panayiotou K[1]
[1]Theagenio Cancer Hospital, Endocrinology and Endocrine Oncology, Thessaloniki, Greece

P280 **EYA-SIX TRANSCRIPTIONAL SIGNAL PATHWAY IS INVOLVED IN THYROID CANCER TUMORIGENESIS**

Riesco-Eizaguirre G[1], Miranda S[2], Mendiola M[3], Hardisson D[3], Nistal M[3], Santisteban P[4]
[1]Hospital La Paz, Endocrinology, Madrid, Spain, [2]Instituto de Investigaciones Biomédicas de Madrid, Fisiopatología Endocrina y del Sistema Nervioso, Madrid, Spain, [3]Hospital La Paz, Madrid, Spain, [4]Instituto de Investigaciones Biomédicas de Madrid, Madrid, Spain

PO31 Thyroid Hormone and Reproduction/ Foeto-Maternal Unit

Chair: *Kris Poppe* (Belgium)

P281 **THIOCYANATE FROM MATERNAL SMOKING INHIBITS NIS WITH INCREASED RISK OF IODINE DEFICIENCY IN MOTHER AND CHILD BUT PLACENTAL IODINE TRANSFER SEEMS TO BE UNAFFECTED**

Andersen SL[1], Nøhr SB[2], Wu CS[3], Olsen J[3], Pedersen KM[4], Laurberg P[1]
[1]Department of Endocrinology, Aalborg Hospital, Aalborg, Denmark, [2]Postgraduate Education, Aalborg Hospital Science and Innovative Center, Aalborg, Denmark, [3]Section of Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark, [4]Department of Medicine, Vejle Hospital, Vejle, Denmark

P282 **EVALUATION OF THE THYROID FUNCTION, IODINE URINARY EXCRETION AND THYROID VOLUME IN 300 WOMEN AT FIRST TRIMESTER OF PREGNANCY LIVING IN AN AREA OF MODERATE IODINE DEFICIENCY**

Russo L[1], Bottai S[1], Licari S[1], Frigeri M[1], Gambacciani M[2], Vitti P[1], Pinchera A[1], Tonacchera M[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy, [2]University of Pisa, Department of Reproductive Medicine and Child Development, Pisa, Italy

P283 **THYROID VOLUME AND THYROID HORMONE LEVELS IN PREGNANT WOMEN LIVING IN THE SOFIA AREA**

Ivanova RB[1], Kovatcheva R[1], Kirilov G[1], Ivanova RS[1], Dimitrova V[2]
[1]University Hospital of Endocrinology, Thyroid and Metabolic Bone Diseases, Sofia, Bulgaria, [2]University Hospital of Obstetrics and Gynecology, Sofia, Bulgaria

P284 **DETECTION OF THYROID DISFUNCTION IN EARLY PREGNANCY BY USING A UNIVERSAL SCREENING PROTOCOL**

Diéguez M[1], Aller J[2], Delgado E[2], Lavilla A[2], Pertierra J[2], Rabal A[2], Sánchez C[2], Herrero A[3], Menéndez E[2]
[1]Hospital de Cabueñes, Endocrinology and Nutrition, Gijón, Spain, [2]Hospital Universitario Central de Asturias, Endocrinology and Nutrition, Oviedo, Spain, [3]Complejo Universitario de Salamanca, Endocrinology and Nutrition, Salamanca, Spain

P285 **SEVERE GESTATIONAL HYPOTHYROIDISM DUE TO ANTI-TSH RECEPTOR BLOCKING ANTIBODIES**

Di Bella B[1], Moleti M[1], Presti S[1], Di Mauro F[1], Sturniolo G[1], Violi MA[1], Agretti P[2], De Marco G[2], Tonacchera M[2], Trimarchi F[1], Vermiglio F[1]
[1]Università degli Studi di Messina, Clinico-Sperimentale di Medicina e Farmacologia, Messina, Italy, [2]Università di Pisa, Endocrinologia e Metabolismo, Pisa, Italy

P286 **DOES THE PRESENCE OF THYROID ANTIBODIES AFFECT THE COURSE AND OUTCOME OF PREGNANCY IN TYPE1 DIABETIC WOMEN?**

Vasileiou V[1], Sarantopoulou V[1], Philippou G[1], Lymberi P[1], Sarika L[1], Alevizaki M[1], Anastasiou E[1]
[1]Alexandra Hospital, Diabetes Centre- First Endocrine Section, Athens, Greece

P287 **IODINE STATUS OF PREGNANT WOMEN AND INFANTS IN EASTERN UKRAINE**

Belykh N[1], Mamenko M[1]
[1]Luhansk State Medical University, Department of Postgraduated Education in Pediatrics, Luhansk, Ukraine

P288 **THYROID FUNCTION IN WOMEN UNDERGOING TO CONTROLLED OVARIAN HYPERSTIMULATION**

Del Ghianda S[1], Benelli E[2], Ruggiero M[3], Artini P[3], Simoncini T[3], Loconte E[1], Vitti P[4], Tonacchera M[5]
[1]University of Pisa, Dep of Endocrinology, Pisa, Italy, [2]University of Pisa, School of Medicine, Dep of Endocrinology, Pisa, Italy, [3]University of Pisa, Dep Reproductive Medicine, Pisa, Italy, [4]University of Pisa, Pisa, Italy, [5]University of Pisa, School of Medicine, Pisa, Italy

PO32 Environmental Factors and Drugs Affecting Thyroid Function 2

Chair: *Peter Smyth* (Ireland)

P289 **THYROID FUNCTIONAL STATUS IN CHRONIC KIDNEY DISEASE (CKD)**

Hossain M[1], Hasan M[1], Ahmed P[1], Monoarul Islam AKM[1], Islam Chowdhury N[1], Shah K[1], Begum N[1]
[1]Rajshahi Medical College Hospital, Nuclear Medicine, Rajshahi, Bangladesh

P290 **AMIODARONE INDUCED SUBCLINICAL THYROID DYSFUNCTION - WHAT TO EXPECT DURING FOLLOW UP? IS THERE REASON FOR AMIODARONE WITHDRAWAL?**

Aleksić ŽP[1], Aleksić AZ[2], Mitov VM[2], Jolić AD[2], Vešović DM[3]
[1]Health Center Zaječar, Neclear Medicine, Zaječar, Serbia, [2]Health Center Zaječar, Internal Medicine, Zaječar, Serbia, [3]American School of Medicine, Belgrade, Serbia

P291 **THE EFFECT OF POTASSIUM IODIDE ON RADIOACTIVE IODINE UPTAKE OF THE HEALTHY JAPANESE**

Kunii Y[1], Noh J[1], Mukasa K[1], Sekiya K[1], Iwaku K[1], Matsumoto M[1], Yoshihara A[1], Ohe H[1], Suzuki A[2], Uruno T[2], Ito K[2]
[1]Ito Hospital, Internal Medicine, Tokyo, Japan, [2]Ito Hospital, Surgery, Tokyo, Japan

P292 **THE PITUITARY-THYROID AXIS IN ADULTHOOD IS UNINFLUENCED BY BIRTH WEIGHT. EVIDENCE FROM A STUDY OF EXTREMELY BIRTH WEIGHT DISCORDANT MONOZYGOTIC TWIN PAIRS.**

Brix TH[1], Frost M[2], Petersen I[2], Christiansen L[2], Hegedüs L[1], Christensen K[2]
[1]Odense University Hospital, Endocrinology and Metabolism, Odense, Denmark, [2]University of Southern Denmark, The Danish Twin Registry, Odense, Denmark

P293 **PREVALENCE OF IODINE INTAKE INADEQUACY IN A GROUP OF ELDERLY BRAZILIAN WOMEN.**

Destefani SA[1], Corrente JE[2], Paiva SAR[1], Mazeto GMFS[1]
[1]Botucatu Medical School - Sao Paulo State University - Unesp, Internal Medicine, Botucatu, Brazil, [2]Institute of Biosciences - Sao Paulo State University - Unesp, Biostatistics, Botucatu, Brazil

P294 **INNOVATIVE METHODS OF IODINE PROPHYLAXIS: FROM IODINE-FORTIFIED VEGETABLES TO HUMANS**

Dimida A[1], Frigeri M[1], De Servi M[1], Agretti P[1], De Marco G[1], Ferrarini E[1], Piaggi P[1], Grasso L[1], Aghini-Lombardi F[1], Vitti P[1], Pinchera A[1], Tonacchera M[1]
[1]Department of Endocrinology, Pisa, Italy

P295 **CHARACTERISTICS OF THYROID AUTONOMY BEFORE AND TEN YEARS AFTER INCREASE IN MANDATORY SALT IODIZATION**

Gaberscek S[1], Bajuk V[2], Zaletel K[1], Pirnat E[1], Hojker S[1]
[1]University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Medical Faculty in Ljubljana, Ljubljana, Slovenia

P296 **CHANGES IN THE THYROID GLAND UNDER THE INFLUENCE OF BISPHOSPHONATES**

Luzin V[1], Fomina K[1], Yeryomin A[2], Zakharov A[1], Fastova O[1]
[1]Lugansk State Medical University, Lugansk, Ukraine, [2]Lugansk State Medical University, Human Anatomy, Lugansk, Ukraine

PO33 Hypothyroidism Clinical 2

Chair: *Salvatore Benvenga* (Italy)

P297 **DIFFERENT REQUIREMENT OF LEVOTHYROXINE (LT4) REPLACEMENT THERAPY IN CONGENITAL HYPOTHYROIDISM WITH RESPECT TO ADULT IATROGENIC HYPOTHYROIDISM**

Bagattini B[1], Montanelli L[1], Di Cosmo C[1], Ciampi M[1], Pinchera A[1], Vitti P[1], Tonacchera M[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

P298 **LACTOSE INTOLERANCE: A NOVEL OCCULT CAUSE OF THYROXINE MALABSORPTION**

Virili C[1], Cellini M[2], Santaguida MG[1], Del Duca SC[2], Brusca N[2], Gargano L[3], Centanni M[2,3]
[1]'Sapienza' University of Rome, Experimental Medicine, Rome, Italy, [2]'Sapienza' University of Rome, Dept of Medico-Surgical Sciences and Biotechnologies, Latina, Italy, [3]AUSL Latina, UOC Endocrinologia, Latina, Italy

P299 **FT4 LEVELS DO NOT REFLECT EUTHYROIDISM IN CENTRAL HYPOTHYROID L-T4 TREATED PATIENTS. A THERAPEUTIC TARGET TO BE RECONSIDERED AND IMPLICATIONS FOR TREATMENT**

Gullo D[1], Ielo C[1], Latina A[1], Tita P[1], Marturano I[1], Vigneri R[1]
[1]Garibaldi-Nesima Hospital, University of Catania Medical School, Endocrinology, Catania, Italy

P300 **CONGENITAL HYPOTHYROIDISM CAUSED BY A NOVEL HOMOZYGOUS MUTATION IN THE THYROGLOBULIN GENE**

De Marco G[1], Agretti P[1], Bagattini B[1], Ferrarini E[1], Dimida A[1], Molinaro A[1], Vitti P[1], Pinchera A[1], Tonacchera M[1]
[1]Università di Pisa, Pisa, Italy

P301 **FREQUENCY OF *PDE8B* GENE POLYMORPHISMS IN PATIENTS AFFECTED BY SPORADIC AND FAMILIAR NON-AUTOIMMUNE SUBCLINICAL HYPOTHYROIDISM**

Agretti P[1], Ferrarini E[1], De Marco G[1], Dimida A[1], Niccolai F[1], Molinaro A[1], Pinchera A[1], Vitti P[1], Tonacchera M[1]
[1]Università di Pisa, Pisa, Italy

P302 **TREATMENT OF HYPOTHYROIDISM IN ELDERLY PATIENTS**

Gasparyan E[1], Ostashko G[2], Dimnova S[2], Gasparyan A[3]
[1]I.Mechnikov North-Western State Medical University, Endocrinology, Saint Petersburg, Russian Federation, [2]St. Eugene Hospital № 46, Endocrinology, Saint Petersburg, Russian Federation, [3]Medical Centre 'Professor', Endocrinology, Saint Petersburg, Russian Federation

P303 **THE LINK BETWEEN HYPOTHYROIDISM AND MORTALITY IS EXPLAINED BY COMORBIDITY RATHER THAN HYPOTHYROIDISM PER SE. EVIDENCE FROM A DANISH NATIONWIDE REGISTER-BASED STUDY OF TWINS AND SINGLETONS**

Thvilum M[1], Brandt F[1], Almind D[2], Christensen K[2,3,4], Brix TH[1], Hegedüs L[1]
[1]Odense University Hospital, Department of Endocrinology and Metabolism, Odense C, Denmark, [2]University of Southern Denmark, The Danish Aging Research Center and The Danish Twin Registry, Odense C, Denmark, [3]Odense University Hospital, Department of Clinical Genetics, Odense C, Denmark, [4]Odense University Hospital, Department of Clinical Biochemistry and Pharmacology, Odense C, Denmark

P304 **TRENDS IN THYROID HORMONE PRESCRIBING IN THE UK 2000-2009**

Taylor P[1], Iqbal A[2], Sayers A[3], Greenwood R[4], Dayan C[1]
[1]Cardiff University, CEDS, Cardiff, United Kingdom, [2]University of Sheffield, Department of Endocrinology, Sheffield, United Kingdom, [3]University of Bristol, Bristol, United Kingdom, [4]UHBT, Bristol, United Kingdom

P305 **EXPERIENCE OF THE FIRST YEAR OF NEWBORN SCREENING FOR CONGENITALHYPOTHYROIDISM (CH) IN GEORGIA**

Beridze N[1], Takaishvili R[1], Azikuri T[1], Takaishvili B[1], Mumladze M[1], Iashvili M[2]
[1]Express diagnostics, Tbilisi, Georgia, [2]Georgian Patriarkhat St.Joakim and St.Ann Maternity Home, Tbilisi, Georgia

PO34 Hyperthyroidism Clinical

Chair: *Fausto Bogazzi* (Italy)

P306 **AN AUDIT OF PATIENTS (N=322) UNDERGOING DEFINITIVE TREATMENT OF HYPERTHYROIDISM AT A UK DISTRICT GENERAL HOSPITAL BETWEEN 2002 AND 2010**

Taylor M[1], Skene A[1]
[1]Royal Bournemouth Hospital, Bournemouth, United Kingdom

P307 **LATE MANIFESTATION OF SUBCLINICAL HYPERTHYROIDISM AFTER GOITROGENESIS IN AN INDEX PATIENT WITH A N670S TSH RECEPTOR GERMLINE MUTATION CAUSING FAMILIAL NON-AUTOIMMUNE AUTOSOMAL DOMINANT HYPERTHYROIDISM (FNAH)**

Schaarschmidt J[1], Özerden M[2], Paschke S[1], Jaeschke H[1], Huth S[1], Eszlinger M[1], Meller J[2], Paschke R[1]
[1]University of Leipzig, Department of Internal Medicine, Neurology and Dermatology, Leipzig, Germany, [2]University of Göttingen, Department of Nuclear Medicine, Göttingen, Germany

P308 **THE UTILITY OF RADIOIODINE UPTAKE AND THYROID SCINTIGRAPHY IN THE MANAGEMENT OF HYPERTHYROIDISM**

Hong SI[1]
[1]Kwangju Veterance Hospital, Kwangju, Republic of Korea

P309 **GESTATIONAL HYPERTHYROIDISM IN WOMEN FROM MILD TO MODERATE IODINE DEFICIENCY (ID) AREAS**

Presti S[1], *Moleti M*[1], *Di Bella B*[1], *Sturniolo G*[1], *Di Mauro F*[1], *Violi MA*[1], *Trimarchi F*[1], *Vermiglio F*[1]
[1]Università degli Studi di Messina, Clinico-Sperimentale di Medicina e Farmacologia, Messina, Italy

P310 **EFFICENCY OF RADIOIODINE THERAPY WITH A FIX DOSE OF J-131 IN TOXIC THYROID ADENOMA**

Petrovski Z[1], *Trajkovska K*[1]
[1]Clinical Hospital, Department of Nuclear Medicine, Bitola, the Former Yugoslav Republic of Macedonia

P311 **DIAGNOSIS AND TREATMENT OF HYPERTHYROIDISM : RESULTS OF THE FRENCH SURVEY THYRDEL**

Goichot B[1], *Caron P*[2], *Bouée S*[3], *N'daye N*[1], *Landron F*[4]
[1]Hôpitaux Universitaires de Strasbourg, Internal Medicine, Endocrinology and Nutrition, Strasbourg, France, [2]CHU Toulouse, Endocrinology, Toulouse, France, [3]Cemka-Eval, Epidemiology & Statistics, Bourg la Reine, France, [4]Merck Serono, General Medecine and Specialties, Lyon, France

P312 **THE USEFULNESS OF 99MTC-SESTAMIBI THYROID SCAN IN THE DIFFERENTIAL DIAGNOSIS OF ELEVEN CASES OF AMIODARONE-INDUCED THYROTOXICOSIS**

Souto SB[1], *Vieira T*[2], *Nogueira C*[1], *Carvalho-Braga D*[1], *Pereira J*[2], *Carvalho D*[1]
[1]Centro Hospitalar São João, Endocrinology, Porto, Portugal, [2]Centro Hospitalar São João, Nuclear Medicine, Porto, Portugal

P313 **MOST ASPECTS OF THYROID-SPECIFIC QUALITY OF LIFE WAS MARKEDLY IMPROVED 6 MONTHS AFTER TREATMENT OF GRAVES´ DISEASE**

Cramon P[1], *Bjorner JB*[2], *Hegedüs L*[3], *Bonnema SJ*[3], *Groenvold M*[4], *Rasmussen AK*[1], *Feldt-Rasmussen U*[1], *Watt T*[1]
[1]Rigshospitalet - Copenhagen University Hospital, Dept. of Endocrinology, Copenhagen, Denmark, [2]National Research Centre for the Working Environment, Copenhagen, Denmark, [3]Odense University Hospital, Dept. of Endocrinology, Odense, Denmark, [4]University of Copenhagen, Institute of Public Health Science, Copenhagen, Denmark

P314 **MODERATE ALCOHOL CONSUMPTION MAY PROTECT FROM GRAVES´ HYPERTHYROIDISM - A POPULATION-BASED CASE-CONTROL STUDY**

Carlé A[1], *Pedersen IB*[1], *Knudsen N*[2], *Perrild H*[2], *Ovesen L*[3], *Rasmussen LB*[4], *Jørgensen T*[5], *Laurberg P*[1], *DanThyr, The Danish Investigation of Iodine Intake and Thyroid Diseases*
[1]Department of Endocrinology & Medicine, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark, [2]Endocrine Unit, Medical Clinic I, Bispebjerg Hospital, Copenhagen, Denmark, [3]Department of Internal Medicine, Slagelse Hospital, Slagelse, Denmark, [4]Ministry of Food, Agriculture and Fisheries, National Food Institute, Technical University of Denmark, Copenhagen, Denmark, [5]Research Centre for Disease Prevention and Health, Copenhagen County, Copenhagen, Denmark

PO35 Graves' Disease and Orbitopathy Basic/ Translational

Chair: *Milos Zarkovic* (Serbia)

P315 **BIMATOPROST (PGF2α) EFFECTS ON ADIPOCYTE BIOLOGY? RELEVANT TO GRAVES' ORBITOPATHY**

Draman MS[1], *Grennan-Jones F*[1], *Zhang L*[1], *Kyaw Tun T*[2], *McDermott J*[2], *Moriarty P*[3], *Morris D*[4], *Lane C*[4], *Sreenan S*[2], *Dayan C*[1], *Ludgate M*[1]
[1]Institute of Molecular & Experimental Medicine, School of Medicine, Cardiff University, Cardiff, United Kingdom, [2]Department of Diabetes and Endocrinology, Connolly Hospital, Blanchardstown, Ireland, [3]Royal Victoria Eye & Ear Hospital, Dublin, Ireland, [4]Department of Ophthalmology, Cardiff and Vale University Health Board, Cardiff, United Kingdom

P316 **DOES COMBINED ACTIVATION OF THE TSHR AND THE IGF1-R CONTRIBUTE TO THE PATHOGENESIS OF GRAVES´ ORBITOPATHY?**

Grennan-Jones FA[1], *Zhang L*[1], *Draman MS*[1], *Lane C*[2], *Dayan CM*[1], *Ludgate M*[1]
[1]Cardiff University, Institute of Molecular and Experimental Medicine, Cardiff, United Kingdom, [2]Cardiff and Vale University Health Board, Department of Opthalmology, Cardiff, United Kingdom

P317 **HIF-1 DEPENDENT GENE EXPRESSION IS INVOLVED IN PATHOGENESIS OF GRAVES´ ORBITOPATHY**

Berchner-Pfannschmidt U[1], *Müller M*[1], *Fandrey J*[2], *Steuhl K-P*[1], *Eckstein AK*[1]
[1]Klinik für Augenheilkunde/Vorderer Augenabschnitt, Universität Duisburg-Essen, Essen, Germany, [2]Institut für Physiologie, Universität Duisburg-Essen, Essen, Germany

P318 **INHIBITION OF THE ACID SPHINGOMYELINASE/ CERAMIDE SYSTEM PREVENTS HALLMARKS OF GRAVES OPHTHALMOPATHY (GO)**

Meyer zu Hörste M[1,2], Ströher E[1], Zhang Y[2], Röck K[3], Fischer JW[3], Berchner-Pfannschmidt U[1], Gulbins E[2], Eckstein A[1]
[1]University of Duisburg-Essen, Ophthalmology, Essen, Germany, [2]University of Duisburg-Essen, Molecular Biology, Essen, Germany, [3]University of Duesseldorf, Pharmacology and Clinical Pharmacology, Duesseldorf, Germany

P319 **BIOCHEMICAL CHARACTERIZATION OF AUTOANTIBODIES TO THE IGF1-RECEPTOR**

Minich W[1], Welsink T[1], Schwiebert C[1], Koehrle J[1], Eckstein A[2], Schomburg L[1]
[1]Charité Universitätsmedizin Berlin, CVK, Institute for Experimental Endocrinology, Berlin, Germany, [2]University Hospital Essen, Department of Ophthalmology, Essen, Germany

PO36 Thyroid Gland Development/ Thyroid Hormone Synthesis

Chair: *Mikael Nilsson* (Sweden)

P320 **REGULATION OF THE SODIUM IODIDE SYMPORTER GENE EXPRESSION BY RESVERATROL**

Giuliani C[1], Di Santo S[1], Bucci I[1], Monaco F[1], Napolitano G[1]
[1]University 'G. D'Annunzio' Chieti-Pescara, Dept. of Medicine and Sciences of Aging, Chieti, Italy

P321 **IDENTIFICATION OF MUTATIONS OF GENES INVOLVED IN THYROID HORMONE SYNTHESIS IN PATIENTS WITH CONGENITAL HYPOTHYROIDISM**

Kumorowicz-Czoch M[1], Hermanns P[2], Madetko-Talowska A[3], Tylek-Lemanska D[4], Pohlenz J[2], Starzyk J[1]
[1]Department of Pediatric and Adolescent Endocrinology, Chair of Pediatrics, Polish-American Institute of Pediatrics, Jagiellonian University Medical College, Cracow, Poland, [2]Childrens Hospital of the University of Mainz, Molecular Endocrinology, Mainz, Germany, [3]Division of Medical Genetics, Chair of Pediatrics, Polish-American Institute of Pediatrics, Jagiellonian University Medical College, Cracow, Poland, [4]Division of Mass Screening and Metabolic Diseases, University Children's Hospital, Cracow, Poland

P322 **SCREENING OF MUTATION IN HOMEOBOX GENES *HOXA3*, *HOXB3*, *HOXD3* AND *PITX2*, WHICH ARE POTENTIALLY RELATED TO THYROID DEVELOPMENT, IN FOUR PATIENTS WITH FAMILIAL AND SPORADIC THYROID HEMIAGENESIS**

Kizys MML[1], Nesi-França S[2], Cardoso MG[3], Harada MY[1], Soares F[1], Chiamolera MI[1], Dias da Silva MR[1], Maciel RMB[1]
[1]Universidade Federal de Sao Paulo, Medicine, Sao Paulo, Brazil, [2]Universidade Federal do Parana, Pediatrics, Curitiba, Brazil, [3]Universidade Federal de Sao Paulo, Biochemistry, Sao Paulo, Brazil

P323 **THYBE1 IS A LONG NON-CODING RNA TIGHTLY REGULATED IN THYROID FOLLICULAR CELLS**

D'Onofrio B[1], D'Andrea B[1], De Menna M[1], De Vita G[1], Di Lauro R[1]
[1]Università di Napoli Federico II, Biologia e Patiologia Cellulare e Molecolare, Napoli, Italy

P324 **MORPHOMETRIC CHANGES OF THE THYROID GLAND AGAINST INFLUENCE OF GLUCOCORTICOIDS AND ZOLEDRONIC ACID 'ZOMETA'**

Luzin V[1], Fomina K[1], Yeryomin A[1], Zakharov A[1], Fastova O[1]
[1]Lugansk State Medical University, Human Anatomy, Lugansk, Ukraine

P325 **THE COMBINED EFFECT OF GLUCOCORTICOIDS AND ZOLEDRONIC ACID ON THE THYROID GLAND**

Luzin V[1], Fomina K[1], Yeryomin A[1], Zakharov A[1], Fastova O[1]
[1]Lugansk State Medical University, Human Anatomy, Lugansk, Ukraine

PO37 Clinical Thyroidology

Chair: *Roussanka Kovatcheva* (Bulgaria)

P326 **PREVALENCE OF VITAMIN D DEFICIENCY IN SUBJECTS WITH THYROID DYSFUNCTION**

Borissova A-MI[1], Shinkow A[2], Vlahov J[2], Dakovska L[2], Metalova T[2], Svinarov D[3], Kasabova I[3]
[1]Medical University Sofia, Clinic of Thyroid and Metabolic Bone Disorders, Clinical Center of Endocrinology, Laboratory of Clinical Pharmacology, University Hospital 'Alexandrovska', Sofia, Bulgaria, [2]Medical University Sofia, Department of Thyroid and Metabolic Bone Diseases, Sofia, Bulgaria, [3]Medical University Sofia, Laboratory of Clinical Pharmacology, University Hospital 'Alexandrovska', Sofia, Bulgaria

P327 **THYROID AND THYMIC EXERESIS IN SURGERY OF HYPERPARATHYROIDISM**

Diaconescu MR[1], Glod M[1], Costea I[1], Grigorovici M[2], Diaconescu S[3]
[1]'Gr T Popa' University of Medicine and Pharmacy, Surgery, Iasi, Romania, [2]CF Universitary Hospital, Pathology, Iasi, Romania, [3]'Gr T Popa' University of Medicine and Pharmacy, Pediatrics, Iasi, Romania

P328 **ASSOCIATION OF NEONATAL THYROID-STIMULATING HORMONE (TSH) CONCENTRATIONS WITH PSYCHOSOCIAL, INTELLECTUAL AND PSYCHOMOTOR DEVELOPMENT OF PRESCHOOL CHILDREN**

Trumpff C[1,2], Vanderfaeillie J[1], Vandevijvere S[2,3]
[1]Vrije Universiteit Brussel, Brussels, Belgium, [2]Scientific Institute of Public Health, Brussels, Belgium, [3]Université Libre de Bruxelles, Brussels, Belgium

P329 **PATHOLOGY OF THYROID GLAND IN PATIENTS WITH ACROMEGALY**

Khyzhnyak O[1], Mykytyuk M[2], Karachentsev I[3], Sulima T[3], Alekseeva I[3]
[1]Institute for Endocrine Pathology Problems, Clinical Endocrinology, Kharkiv, Ukraine, [2]Institute for Endocrine Pathology Problems, Kharkiv, Ukraine, [3]Institute for Endocrine Pathology Problems, Clinical, Kharkiv, Ukraine

P330 **MATERNAL AND FOETAL RAT´S HYPOTHYROIDISM DURING GESTATION AND LACTATION UNBALANCES CORTICAL VGLUT1-VGAT IMMUNOREACTIVITY AND ALTERS ATTENTION DEFICIT AND ANXIETY**

Navarro D[1], Mayvi A[1], Navarrete F[1], Giner M[1], Pacheco P[1], Morreale de Escobar G[2], Manzanares J[1], Berbel P[1]
[1]Inst. de Neurociencias, Sant Joan D´Alacant, Spain, [2]Inst. Investigaciones Biomedicas de Madrid, Madrid, Spain

P331 **SHORT-TERM EFFECTS OF BISPHOSPHONATES ON BONE TURN-OVER MARKERS IN GLUCORTICOID PULSE-THERAPY FOR GRAVES'OPHTHALMOPATHY**

Borzì G[1], Muscia V[1], Le Moli R[1], Furneri MT[1], Padova G[1]
[1]University of Catania, Biomedicine, Clinical and Molecular, Catania, Italy

Congress General Information

Venue

Palazzo dei Congressi di Pisa
Via Matteotti, 1
56124 Pisa

Smoking is strictly prohibited in the entire building.

Oral Presentations

All conference rooms are fully equipped with up-to-date presentation systems. Powerpoint is the preferred format for presentations.

Opening Times of Media Check

Saturday:	7:30-18:30
Sunday:	7:30-19:00
Monday:	7:30-15:30
Tuesday:	7:30-17:30
Wednesday:	7:30-12:30

All presenters are requested to hand in their lecture at least 1 hour before the scheduled talk, or the day before if your talk is early the next morning.

Poster Displays

Maximum Poster sizes are 120 cm high and 90 cm wide.
Mounting material will be available on site. All poster boards will be numbered. Staff will assist you in locating your poster wall and setting up your poster.
Poster discussion sessions are from 12.00-13.00 from Sunday to Tuesday. Your poster should be in place well before discussion time. See below for a time guide:
P1–P121: Sunday 9th from 8.30 to be removed by 18.00
P122–P245: Monday 10th from 8.30 to be removed by 16.00
P246–P331: Tuesday 11th from 8.30 to be removed by 18.00

Authors must be present at their poster session.

Thank you for your understanding that posters that have not been removed by the above mentioned times cannot be stored.

Programme Changes

The organisers cannot assume liability for changes in the programme due to external or unforeseen circumstances.

Language

The official congress language is English.

Name Badges

Entrance to the Congress area will be limited to badge holders only.
If the badge is lost, please contact the Congress registration desk.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Published by S. Karger AG, Basel

Accessible online at:
www.karger.com/etj

Congress Lunches

Lunch will be provided in the exhibition area, and for the satellite symposium attendees in the Main Auditorium.

Congress Material

The Congress participants who have pre-registered will receive the congress material, together with their name badge from the Pre-Registered desk of the Congress Secretariat.

Climate and Clothing

First weeks of September are usually still summery in Italy, so you can expect the weather to be pleasant. The average maximum temperature is around 27° C. Pisa has a warm climate, rendered mild by the sea air even in late summer.

Currency

The official currency in Italy is the Euro.

Banks and Exchange

Banks are open from Monday to Friday, from 8:30 am to 1:30 pm and from 2:45 pm to 3:45 pm. Money can also be changed in exchange desks across the city. Most hotels, restaurants and shops accept foreign currency and credit cards. ATMs are located throughout the city and at the conference premises.

Electricity

The electricity supply is 220 volts, 50 Hz. Foreign appliances may require adapter.

Health

Free first aid and hospital services are available to all citizens of Europe who have a special card (EHIC, European Health Insurance Card, formerly E111) issued by the health authority of the relative country. Visitors from other countries are advised to take out special insurance for the duration of the trip, to avoid the cost of possible medical treatment. American visitors may find out that reimbursement of medical expenses incurred abroad is covered by their private insurance. Medicines can only be obtained in the pharmacies (farmacia, marked by a green or red cross) which are usually open from 8:30 to 13:00 and from 16:30 to 20:00. At night and on public holidays pharmacies are not open; however, you can find a list of those open on afore-said days.

Italian Time and Date

Pisa is located in the Middle European Time Zone, GMT +1. However, during the congress we will be in summer time (or CET) i.e. GMT +2.
In Italy all dates are written: day, month, year (thus 8/9/12 means 8th September 2012).

Telephone

The prefix for Pisa is 050. The international code for Italy is 39. To make an international call from Italy start with 00 and add the complete international number.

Tips

Prices include service in bars and restaurants, but tips are always welcome.

Visas

Citizens of countries in the European Union and the European Economic Area do not need a visa for Italy.
We strongly recommend that you consult the official website of the Italian Ministry of Foreign Affairs http://www.esteri.it/visti/index_eng.asp for updated and detailed information for foreigners regarding entrance visas for Italy and permits of stay. Foreign participants should contact the Italian Embassy or Consulate in their home country as soon as possible to determine their particular visa requirements. Participants requiring visas must initiate the application process at least 3 months prior to their departure date. The conference organizers cannot assist participants with their visa application process.

Tourism Tax

From March 1st 2012, the City Council of Pisa introduced, according to the resolution N°56 December 21st 2011, the tourism tax applied to non-residents overnight staying, for a maximum of 3 consecutive nights from the first Sunday of November until the Sunday before Easter and for a maximum of 5 nights from Monday before Easter to the first Sunday of November.
The amount is € 2 per person per night for the 5/4 stars hotel and € 1,5 per person per night for the 3 stars hotels, to be paid in cash upon departure.

Reaching Pisa

By air: The airport of Pisa 'Galilei', 2 km from the city center, serves national and international airlines. It is possible to reach Pisa directly with daily flights from London, Paris and other important European cities, or through connections with domestic flights from Rome and Milan airports. Another suitable international airport is that of Florence 'Peretola', about 80 km from Pisa.
By train: The central railway station of Pisa (Pisa Centrale) is an important junction of the Italian railway system. It can be easily reached from all major Italian cities. The Palazzo dei Congressi is about one kilometer away from the central railway station.
By car: Pisa is directly connected to the Italian motorway network, and can be reached by an uninterrupted motorway journey starting from all Italian border crossing points. It is advisable to leave the motorway at Pisa Nord station, and then to proceed southward until reaching the banks of the river Arno, where road signs to the Palazzo dei Congressi are found.
By bus:

Transfers from/to the Airport
The bus LAM red will carry you directly from the airport to the central railway station every 20 minutes on working days and every 30 minutes on Sunday.
Taxi from the airport to the railway station will cost approx. 10 Euro.

Transfers from/to the Conference Site
Bus LAM blue and bus n. 13 connect the central railway station to the Conference Centre every 15 minutes on working days and once an hour on Sunday. You can also hire a taxi at Pisa airport or Pisa train station. At Pisa airport the taxi pick up area is just in front of you when you exit the airport building straight ahead of the arrival gate. At Pisa central train station taxis departure is on your left hand side exiting the train station building.

Radio taxi phone number: +39 050 541600.

Welcome Reception

Saturday, 8th September, 19.30

Stazione Leopolda
Piazza Guerrazzi
56125 Pisa

It is located a few minutes from Pisa central railway station and at walking distance from the Palazzo dei Congressi.

The Leopolda station is one of the first railway stations built in Italy. It is is a large neo-Renaissance building designed by the architect Enrico Presenti, and from here started the Linea Leopolda, the train for Pisa and Livorno. It was named after the Habsburg-Lorraine Grand Duke Leopold II of Tuscany, who built it in the 1844.
The station, although only opened in 1847, was already transformed into a freight terminus in 1860, as passenger traffic had been moved to the Maria Antonia station which was more centrally located. From 1929 it housed the fruit and vegetable market. In recent years, this station which is a good example of railway architecture has become an exhibition and cultural center, hosting any kind of events. The historical hall represents the core of the whole complex and it may be used for meetings, exhibitions, shows and social events.

Price per person: included in the fee for registered participants and registered accompanying persons

ETA Excursion to The Charterhouse of Calci

Monday, 10th September

16.45 Departure from the Palazzo dei Congressi by bus
Return by bus to all the conference hotels or nearby for the hotels placed in the historical centre and not accessible by bus.

The monumental monastery of Calci, just 10 kms from Pisa, was founded in 1366 by Carthusian monks.
In the last years of the XIV century the Refectory, the Chapterhouse, the Church, the friars' cells and the rooms of the lay brothers were finished. In 1425, the Charterhouse definitively became a centre with a great prestige and political power with the acquisition of the ancient and once very rich Benedictine monastery in the isle of Gorgona.
Later, the convent went through numerous other enlargement works by benefiting from the continuous donations that the most illustrious Pisan families gave in the hope to grant themselves their indulgence in Paradise.
In the XVII century, the cloister and the fountain were carried out. Its current appearance, yet, is due to the works carried out between 1764 and 1797 above all and they were carried by the prior Alfonso Maria Maggi, thanks to whom many painters were called to decorate old and new rooms with their frescoes. The Pisan painter Pietro Giarré listed the names of lineages and merchant families who contributed to these works. He reproduced their emblems inside fake niches created by Luigi Pochini at the end of XVIII century.
Napoleon's laws that caused the disappearance of all the religious brotherhoods, suppressed the Charterhouse in 1808 and it became part of the state property. Yet, the Carthusian order kept living there until 1972.
Its central nave and its marble façade are marvellous examples of local 17th century Baroque. Its frescoes are still among the most important in Tuscany. It is today one of

Accessible online at:
www.karger.com/etj

the most interesting national museums. In the huge monumental building you will visit the private chapels, the main church, the refectory, the cloisters and the Carthusian cells.
Since 1981 one wing of the complex houses the Natural History Museum of Pisa University. The museum exhibits very ancient mineralogical, palaeontologic and zoological collections, including some pieces dating back to the 16th century. The museum features also an interesting scientific library.
The zoological collections are certainly the most catching and include dinosaurs, animals coming from all over the world and insects. Very suggestive is the gallery reserved to the skeletons of cetaceans, which is situated in a wonderful panoramic hallway in the ancient barns and represents the most important collection existing in Italy and one of the largest collections in Europe.

The open buffet dinner will take place in the charterhouse courtyard.

Price per person: 50 €

Gala Dinner
Tuesday, 11th September, 20.00

National Museum of San Matteo Cloister
Piazza San Matteo in Soarta, 1
56127 Pisa

It is located on the banks of the Arno River, at walking distance from the Palazzo dei Congressi.

The National Museum of San Matteo is one of the most important European museums in the field of medieval art due to the quantity and the relevance of works it houses. It hosts numerous masterpieces of paintings and sculptures from the early medieval age, as well as archaeological and ceramic treasures.
The museum is situated in the ancient convent of Saint Mathew, on the small square San Matteo in Soarta, which dates from the early XI century. The building that houses the museum is striking in itself, as in many places the walls still show the original paintings and decorative patterns that were applied in the late Middle Ages. Some of these geometric patterns, highly in vogue at the time, show remarkable similarities to the patterns on the Islamic bowls of the ceramic collection, hinting at the influence of the Islamic world on coastal Italy at the time.
The Matteo National Museum boasts a complete series of works by the leading 12th and 17th century Pisan and Tuscan masters and a flourishing collection of archaeological and earthenware artefacts.
The Croci dipinte (painted crosses) cycle represents 12th and 13th century painting, all deriving from the oldest town churches, with works by Berlinghiero Berlinghieri, Giunta Pisano and the Master of San Martino.
The 14th and 15th century painting section features works by Francesco di Traino, Lippo Menni, Buonamico Buffalmacco, Spinello Aretino, Taddeo di Bartolo and other great painters of the age. Further 15th century works are represented by Masaccio, Gentile da Fabriano, Beato Angelico, Benozzo Gozzoli and Domenico Ghirlandaio, glazed earthenware by the Della Robbia school of art and the renowned bust-relic of San Lussorio, by Donatello.
Of particular interest are the sculptures from various churches in Pisa, brought here to preserve them from increasing environmental pollution and replaced by copies in their original positions. The polyptych by Simone Martini, from the Church of Santa Caterina d'Alessandria, the Natività by Tino di Camaino and the Madonna del Latte by brothers Andrea and Nino Pisano (c. 1340), from the Church of Santa Maria della Spina, are considered masterpieces of 12th–15th century Pisan sculpture.

The museum also displays important low relief wooden sculptures. The 13th and 14th century pieces feature works by the Sienese Francesco di Valdambrino.
The illuminated manuscripts section contains pieces from the 12th and 14th century, including the illustrated bible, Bibbia di Calci, dating back to 1168.
There is also a noteworthy collection of medieval Pisan and Islamic ceramic basins were once used to decorate the external walls of the Pisan churches and are evidence of the trade industry between the Maritime Republic and the North African countries.

Price per person: 80 € (formal dress)

Tours

Pisa – Half Day Walking Tour (min 25 participants)
Sunday, 9th September
Monday, 10th September
Tuesday, 11th September

Departure at 9.30 am from the congress venue
Duration: approx 3 hrs
Price per person: € 20

After a panoramic walking along the beautiful riversides the tour will move through Ponte di Mezzo, the old market Piazza delle Vettovaglie, Borgo Stretto, the commercial street of Pisa since XIII century, the Church of Saint Michael and Piazza dei Cavalieri, surrounded by a noble complex of XVI and XVII century buildings transformed by Vasari for Cosimo I of Medici, that constituted the political centre of the Ancient Maritime Republic of Pisa.
The tour will continues with the famous Piazza dei Miracoli where you will discover the celebrated Leaning Tower, dating back to 1174, the Baptistery , the Monumental Cemetery and the splendid Cathedral (interior visit), an unequalled masterpiece of Romanesque art carried out between the 11th and 12th centuries.

The rate includes: English speaking guide, Cathedral entrance ticket.

Florence – Full Day Tour (min 25 participants)
Monday, 10th September

Departure at 9 am from the congress venue
Duration: approx 8 hrs
Price per person: € 55

Situated on the banks of the Arno river, in a harmonic frame of hills, Florence is universally well-known for the extraordinary wealth and high quality of its monuments and art treasures. Birth-place of Dante and cradle of Italian language and literature, Florence has retained its role as an important center for culture and art and is today one of the main destination of the international tourism.
The tour includes the visit of the fascinating Piazzale Michelangelo where one can enjoy a breath-taking view, the Cathedral, the greatest religious monument of the city, Piazza della Signoria, wide and solemn square, theatre of the main events of Florence since Middle ages, Ponte Vecchio, the oldest and most famous bridge of Florence, built on three arches in 1345 and renowed for its goldsmith shops.
After the guided tour free time for lunch and walking round the fashion streets of Florence, where you can finds shops and boutiques of the most important Italian designers.

The rate includes: bus, taxes for entrance in Pisa and Florence city centres, tour leader, English speaking guide.
Lunch is not included

Lucca – Full Day Tour (min 25 participants)
Sunday, 9th September
Monday, 10th September

Departure at 9 am from the congress venue
Duration: approx 8 hrs
Price per person: € 45

Lucca is an ancient city with Roman origins that still maintains the urban structure and the remains of the first fortifications. Today the old center of the town is a huge pedestrian area with narrow lanes, squares and old monuments creating a unique atmosphere.
The guided tour includes, among the others, the 12th century Basilicas of St. Michael and St. Frediano, the Cathedral of San Martino with the famous burial monument of Ilaria del Carretto by Iacopo della Quercia (15th century), the old market square, formerly a Roman amphitheatre (2nd century), the medieval Via Fillungo, main axis of the historic core, the Torre Guinigi, which is 44 metres high and has a characteristic that makes it unique: a wonderful holm oak planted on its summit, which is an excellent example of a 15th century townhouse.
After the guided tour free time for lunch and shopping.
It 's very romantic to take a walk or rent a bike and ride along the ancient walls that have been transformed into a park and enjoy the splendid landscape of the city and its many bell towers.

The rate includes: bus, taxes for entrance in Pisa and Lucca city centres, tour leader, English speaking guide, entrance ticket (Ilaria del Carretto).
Lunch is not included

Volterra & S. Gimignano – Full Day (min 25 participants)
Tuesday, 11th September

Departure at 9 am from the congress venue
Duration: approx 8 hrs
Price per person: € 60

Volterra is the town of the legendary Etruscans and the snow-white alabaster.
The guided tour includes the most important treasures like Arco Etrusco, the 2300-year-old Etruscan gateway, the Roman theatre which dates back to the Augustan Age, the Duomo and Piazza dei Priori, one of the most interesting medieval squares in Italy.
San Gimignano rises on a hill, dominating the Elsa valley with the outline of its towers that dates back to the 12th and 13th centuries.
The tour includes the visit of Piazza della Cisterna ,where it is possible to admire the monumental well built in 1271, Piazza del Duomo with its Palazzo del Vecchio Podestà, the Palazzo del Popolo and the Palazzo Nuovo del Podestà which is presently the Town Hall.

The rate includes: bus, taxes for entrance in Pisa, Volterra and S. Gimignano city centres, tour leader, English speaking guide.
Lunch is not included

The organizers reserve the right to cancel tours if the minimum number of participants is not reached.

Pisa General Information

Arno River

Pisa is an historic town in Tuscany, near the mouth of the Arno river. Once a city of political and cultural importance, Pisa is now most famous for one of its architectural masterpieces, the Leaning Tower.
Travelling through in the 1760s, notoriously critical Tobias Smollett found Pisa a 'fine old city' and admired the town's elegant palaces and 'majestic solitude'.
Modern Pisa - away from the tourist hub - still has a quietness and an air of a town that has seen greater days. A thousand years ago, the naval town ruled a miniature empire, including Corsica, Sardinia and the Balearics. An influential power, Pisa was also the home of mathematician Fibonacci and the celebrated Galileo Galilei. Like Rome, Venice and Amalfi, Pisa's pride came before its fall, and as rival Genoa conquered the seas, and the **Arno river** silted up, Pisa's light began to fade. Today Pisa is an important university town, with a population of 100,000, and a major tourist destination.

Campo dei Miracoli

Daytrippers flock in to marvel at the Leaning Tower of Pisa. Pisa's principal tourist attractions are grouped together in the **Campo dei Miracoli**, the Field of Miracles. It's hard to believe the place is real; the tourists flocking around are the only thing that gives the surreal scene a touch of reality. The setting is a flat space, green with lawns, at the edge of the town centre. Here rise the town's cluster of monuments, all architecturally exquisite, and all leaning at different angles. There is a grand Romanesque cathedral, a large striped baptistry, and, of course, the Leaning Tower. Also in the Campo dei Miracoli, another curious sight is the Campo Santo, the Holy Field. This is a cloistered cemetery, said to have been laid with earth brought back from the Holy Land by the Crusaders.
Bombing in the Second World War destroyed some of the works of art that were stored in the surrounding buildings; some frescoes remain, however.

Santa Maria della Spina

In the same area are two museums, the Museo del Duomo (cathedral museum) and the Museo delle Sinopie, which contain art and sculpture from the monuments. Elsewhere in Pisa you can wander peaceful streets, admire the town's palazzi and university buildings, shop in the market areas, and admire bridges and churches. Among the most attractive churches are **Santa Maria della Spina**, a Gothic masterpiece on the banks of the Arno, and the octagonal Sant'Agata.
The Museo di San Matteo contains art by local artists and others, including the Pisano family, Fra Angelico and Brueghel.
For those with an interest in the Romantic poets, Shelley's body was brought ashore at Gombo, close to Pisa, and cremated on the beach.

Knight's Square *(Piazza dei Cavalieri)*

The **Knights' Square** (*Piazza dei Cavalieri*) is one of the most important landmarks in Pisa, and the second main square of the city. After the middle of 16th century the square became the headquarters of the Order of the Knights of St. Stephen. Now it is a centre of education, being the main house of the 'Scuola Normale di Pisa', a higher learning institution part of the University. The square, known as Square of the seven streets was the political heart of the city, where the Pisans used to discuss their problems or celebrate their victories. Since 1140 the square became the center of Pisa Comune, with buildings and churches belonging to the different magistracies, including the city administrator. After the victory of the People of Pisa in 1254, the Palace of the People and the Elders was built on the square by joining some pre-existent buildings *The Captain of the People* was housed in the near *Clock Palace* (since 1357), which incorporated some previous existing towers.

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/etj

European
Thyroid Journal

Map of Pisa

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Published by S. Karger AG, Basel

European
Thyroid Journal

Eur Thyroid J 2012;1(suppl 1):75–208
DOI: 10.1159/000339890

Published online: August 15, 2012

36TH ANNUAL MEETING
OF THE EUROPEAN
THYROID ASSOCIATION
PISA / CONGRESS PALACE
8/12 SEPTEMBER 2012

36th Annual Meeting of the European Thyroid Association

Abstracts

Pisa, Italy, September 8–12, 2012

Guest Editors
Theo Visser, Rotterdam, The Netherlands
Paolo Vitti, Pisa, Italy

KARGER

Basel · Freiburg · Paris · London · New York · New Delhi · Bangkok ·
Beijing · Tokyo · Kuala Lumpur · Singapore · Sydney

European Thyroid Journal

Presenting authors are underlined

OP1 Topic Highlights

OP1

CLINICAL AND BIOCHEMICAL ACTIVITY IN THE EXAM TRIAL, A PHASE 3 STUDY OF CABOZANTINIB (XL184) IN PATIENTS WITH HEREDITARY AND NON-HEREDITARY MEDULLARY THYROID CARCINOMA (MTC)

Elisei R[1], *Mueller S*[2], *Schöffski P*[3], *Brose M*[4], *Shah M*[5], *Licitra L*[6], *Jarzab B*[7], *Medvedev V*[8], *Kreissl MC*[9], *Niederle B*[10], *Cohen E*[11], *Wirth L*[12], *Ali H*[13], *Clary D*[14], *Mangeshkar M*[14], *Ball D*[15], *Nelkin B*[15], *Sherman S*[16], *Schlumberger M*[17z]

[1]University of Pisa, Department of Endocrinology, Pisa, Italy, [2]University Hospital of Essen, Essen, Germany, [3]UZ Leuven, Leuven, Belgium, [4]University of Pennsylvania Health System, Philadelphia, United States, [5]Ohio State University Medical Center, Columbus, United States, [6]Istituto Nazionale dei Tumori, Milano, Italy, [7]Centrum Onkology, Instytut im. M. Sklodowskiej-Curie oddzial w Gliwicach, Gliwicach, Poland, [8]Medical Radiology Research Center of RAMS, Obnisk, Russian Federation, [9]University Hospital of Wuerzburg, Wuerzburg, Germany, [10]Medical University of Vienna, Vienna, Austria, [11]University of Chicago Medical Center, Chicago, United States, [12]Massachusetts General Hospital, Boston, United States, [13]Henry Ford Health System, Detroit, United States, [14]Exelixis, South San Francisco, United States, [15]John Hopkins Hospital and Health System, Baltimore, United States, [16]MD Anderson Cancer Center, Houston, United States, [17]Institut Gustave Roussy, Paris, France

Objectives: MTC accounts for 5–8% of thyroid cancers and represents an unmet medical need. We conducted a Phase 3 study of cabozantinib (an oral inhibitor of MET, VEGFR2, and RET) versus placebo in patients with progressive, unresectable, locally advanced or metastatic MTC.

Methods: Patients with MTC and documented RECIST progression within 14 months of screening were randomized 2:1 to receive cabozantinib or placebo. Prior treatment with tyrosine kinase inhibitors, including RET inhibitors, was permitted. Tumor assessments, including serum levels of calcitonin and carcinoembryonic antigen (CEA), occurred every 12 weeks. The primary efficacy measure was progression-free survival (PFS), assessed by an independent review committee using RECIST.

Results: A total of 330 patients were randomized to cabozantinib (140 mg freebase qd; n=219) or placebo (n=111). At the primary PFS analysis, statistically significant PFS prolongation of 7.2 months was observed. Median PFS for cabozantinib was 11.2 months versus 4.0 months for placebo (HR 0.28, 95% CI 0.19–0.40, p< 0.0001). The 12-month progression-free landmark estimate is 47.3% for cabozantinib and 7.2% for placebo. ORR was 28% for cabozantinib versus 0% for placebo. The most frequent grade ≥3 adverse events were diarrhea, palmar-plantar erythrodysaesthesia, fatigue, hypocalcemia, and hypertension. At Week 12, mean calcitonin and CEA levels had decreased 45% and 24% respectively for patients on cabozantinib, but had increased 57% and 89% for patients on placebo. Of subjects achieving calcitonin biochemical partial or complete response, 56% also achieved partial tumor response per RECIST. For subjects with calcitonin biochemical progressive or stable disease, only 3% and 12%, respectively, had a tumor response.

Conclusions: The study met its primary objective of demonstrating substantial PFS prolongation with cabozantinib versus placebo in a patient population with documented progressive MTC. Reductions in the levels of the serum tumor markers calcitonin and CEA correlated with the radiographic tumor response.

OP2

EFFICACY AND SAFETY OF THREE DIFFERENT CUMULATIVE DOSES OF INTRAVENOUS METHYLPREDNISOLONE FOR MODERATE-TO-SEVERE AND ACTIVE GRAVES' ORBITOPATHY (GO): A MULTICENTER, RANDOMIZED, DOUBLE-BLIND CLINICAL STUDY OF 159 PATIENTS

Bartalena L[1], *Krassas G*[2], *Wiersinga WM*[3], *Marcocci C*[4], *Salvi M*[5], *Daumerie C*[6], *Bournaud C*[7], *Stahl M*[8], *Sassi L*[1], *Veronesi G*[9], *Azzolini C*[10], *Boboridis KG*[11], *Mourits MP*[12], *Soeters MR*[3], *Baldeschi L*[12], *Nardi M*[13], *Currò N*[14], *Boschi A*[15], *Bernard M*[16], *von Arx G*[17], *European Group on Graves' Orbitopathy (EUGOGO)*

[1]University of Insubria, Clinical & Experimental Medicine, Varese, Italy, [2]Panagia General Hospital, Endocrinology, Diabetes & Metabolism, Thessaloniki, Greece, [3]Academic Medical Center, Endocrinology & Metabolism, Amsterdam, Netherlands, [4]University of Pisa, Endocrinology & Metabolism, Pisa, Italy, [5]University of Milan, Medical Sciences, Milan, Italy, [6]Université catholique de Louvain, Internal Medicine, Brussels, Belgium, [7]GHE-Hospices Civils de Lyon and Lyon 1 University, Endocrinology & Nuclear Medicine, Lyon, France, [8]Kantonsspital, Endocrinology & Metabolism, Olten, Switzerland, [9]University of Insubria, Clinical & Experimental Medicine, Epidemiology & Preventive Medicine, Varese, Italy, [10]University of Insubria, Surgical & Morphological Sciences, Section of Ophthalmology, Varese, Italy, [11]Ahepa Hospital, Ophthalmology, Thessaloniki, Greece, [12]Academic Medical Center, Amsterdam, Netherlands, [13]University of Pisa, Neuroscience, Section of Ophthalmology, Pisa, Italy, [14]Ospedale Maggiore Policlinico, Ophthalmology, Milan, Italy, [15]Université Catholique de Louvain, Ophthalmology, Brussels, Belgium, [16]GHE-Hospices Civils de Lyon and Lyon 1 University, Neuro-Ophthalmology Outpatient Clinics, Lyon, France, [17]Interdisziplinaires Zentrum fur Endokrine Orbitopathie, Ophthalmology, Olten, Switzerland

Glucocorticoids are the first-line treatment for moderate-to-severe and active GO, and the intravenous (iv) route seems to be more effective and better tolerated than the oral route. The optimal therapeutic regimen of iv glucocorticoids is still undefined. The EUGOGO group performed the first multicenter, randomized, double-blind trial to evaluate efficacy and safety of three different cumulative doses of iv methylprednisolone (2.25, 4.98, 7.47 grams distributed in 12 weekly infusions) in 159 patients with moderate-to-severe and active GO. Efficacy was assessed at 12 weeks, objectively by blinded ophthalmologists and subjectively by blinded patients [using a GO-specific quality-of-life (GO-QoL) questionnaire]. Overall ophthalmic improvement was more frequent using 7.47 grams (27of 52 patients, 52%) than 4.98 grams (19 of 54 patients, 35%; p=0.03) or 2.25 grams (15 of 53 patients, 28%; p=0.01). Clinical activity score improved by at least two points in 81% of the 7.47-gram group, 83% of the 4.98-gram group, and 58% of the 2.25-gram group. The 7.47-gram dose achieved the best improvement in ocular motility (particularly elevation and abduction). Palpebral aperture and exophthalmos decreased significantly in a minority of patients, with no differences between groups. QoL improved most using 7.47 grams, although not reaching statistical significance. Dysthyroid optic neuropathy (DON) developed in several patients in all groups. Major adverse events were slightly more frequent using the highest dose, but occurred also with the lowest dose. Among patients whose GO improved at 12 weeks, 9/27 (33%) in the 7.47-gram group, 4/19 (21%) in the 4.98-gram group, and 6/15 (40%) in the 2.25-gram group had relapsing GO after methylprednisolone withdrawal at the exploratory 24-week visit. In conclusion, the 7.47-gram dose is optimal, offering a reasonable balance between efficacy and adverse events. The risk of developing DON or relapses of GO after treatment withdrawal is not completely abolished by high methylprednisolone doses.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Published by S. Karger AG, Basel
2235–0640/12/0015–0075$38.00/0

Accessible online at:
www.karger.com/etj

OP3

DEFECTIVE VASCULAR DEVELOPMENT IS ASSOCIATED WITH ABNORMAL THYROID ORGANOGENESIS IN ZEBRAFISH

Opitz R[1], Maquet E[1], Antonica F[1], Costagliola S[1]
[1]IRIBHM, Université Libre de Bruxelles, Brussels, Belgium

Thyroid gland organogenesis relies on a complex interplay of intrinsic and extrinsic factors regulating the multiple morphogenic events from thyroid specification within ventral foregut endoderm throughout functional thyroid differentiation at a site distant from its origin. However, particularly the identity and source of extrinsic signals influencing thyroid morphogenesis remains still enigmatic. Given their coordinated spatial development, cardiac mesoderm and blood vessels represent prime candidates to influence thyroid development. In this study, we used transgenic zebrafish embryos to examine the spatiotemporal relationship between thyroid morphogenesis and pharyngeal vasculature development. Live imaging of *tg(tg:mCherry; myl7:EGFP)* embryos showed that the thyroid primordium adopts a position close to the heart outflow tract during early thyroid morphogenesis. Approximately 10 hours after detachment from the pharyngeal floor, the thyroid starts to expand rostrally along the pharyngeal midline concurrent with a major remodeling of the hypobranchial vasculature. Four-dimensional imaging of live *tg(tg:mCherry; kdrl:EGFP)* embryos revealed that endothelial cells of the forming hypobranchial artery (HA) make intimate contact with thyroid tissue during this initial phase of rostral expansion. Moreover, confocal microscopy of transgenic embryos throughout subsequent development corroborate the view that the paired HA tightly demarcates thyroid tissue localization in zebrafish larvae. We next used 3D reconstruction of confocal images to examine thyroid morphogenesis in various zebrafish models displaying defective vascular development. In general, we found a strong correlation between defective vessel remodeling and abnormal thyroid positioning. Importantly, these mutant and morphant studies confirmed a critical role of the HA for guiding thyroid relocalization. In *ltbp3* morphants, for example, thyroid tissue failed to expand rostrally but instead extended laterally along the course of a highly dysplastic HA. Collectively, our data highlight the value of transgenic zebrafish models as innovative tools to delineate the relationship between thyroid and cardiovascular development.

OP4

IMPACT OF THE THYROCYTE-SELECTIVE INACTIVATION OF THE *MEN1* GENE ON THE BASAL AND TSH-STMULATED GROWTH OF THE THYROID GLAND

Selmi-Ruby S[1], Du Payrat J[1], D'orazio T[1], Bonnavion R[1], Zhang CX[1], Rousset B[1], Borson-Chazot F[1]
[1]CRCL Inserm U1052, Université Lyon 1, Faculté de Médecine RTH-Laennec, Lyon, France

Multiple endocrine neoplasia type1 (MEN1) is an inherited predisposition syndrome characterized by an increased risk of endocrine tumors development mainly parathyroid, pituitary and pancreatic islets. However, it has recently reported an increased frequency of thyroid tumors in MEN1 syndrome. To understand the function of menin in thyroid gland, we generated mice that *Men1* gene was disrupted selectively in thyrocytes and examined the physiopathological and functional consequences on the basal and TSH-stimulated thyroid growth. Menin-deficient (named:Thyr-*Men1*$^{-/-}$) mice were generated by crossing mice carrying floxed-Men1 alleles with mice expressing Cre-recombinase selectively in thyrocytes. Thyroid phenotype of mice was analyzed at 4, 8 and 12-month of age. PCR analysis showed that *Men1*^{flox} allele excision was selective in thyroid of mice expressing Cre-recombinase. Immunohistochemical analysis revealed no menin-staining in thyrocytes of Thyr-Men1$^{-/-}$ mice indicating a complete recombination of *Men1*^{flox} allele whereas menin was mainly localized into the nucleus of thyrocytes in wild-type mice. In basal conditions, thyroid parameters (thyroid size - histology and hormonal status) were similar in Men1-deficient and control mice of 2-month-old. Interesting at 8 months of age, Men1-deficient mice begun to develop a progressive thyroid hypertrophy without any alteration in the structure of follicles and hormonal status (serum TSH and T4 concentrations). At 12 months of age, the increase in thyroid weight in Thyr-Men1$^{-/-}$ mice was 1.5-fold higher than in wild-type mice. Under TSH-stimulation (perchlorate treatment-1% in drinking water), wild-type mice developed a goiter. The goiter weight progressed with aging and was 2-fold higher in Thyr-Men1$^{-/-}$ compared to control mice, although TSH levels were similar in both genotypes. Histological examination of thyroid revealed that the changes in goiter weight were related to thyroid cell number.

In conclusion, our data suggest that *Men1* gene could act as a negative regulator controlling the basal and the TSH-stimulated growth of the thyroid gland.

OP5

MYOCARDIAL INFARCTION INDUCES AN UNEXPECTED CARDIAC MICRORNA SIGNATURE OF PLURIPOTENCY, ASSOCIATED WITH IMPAIRED THYROID-HORMONE SIGNALING

Janssen R[1], Zuidwijk M[1], Mulders J[2], Muller A[1], Oudejand C[2], Simonides W[1]
[1]Institute for Cardiovascular Research / VU University Medical Center, Department of Physiology, Amsterdam, Netherlands, [2]VU University Medical Center, Department of Clinical Chemistry, Amsterdam, Netherlands

Introduction: Remodeling of the stressed left ventricle (LV) after myocardial infarction (MI) is accompanied by alterations in gene expression aimed at maintaining contractile function. We showed earlier that the thyroid-hormone degrading enzyme deiodinase type III (DIO3) is stably re-induced in cardiomycytes following MI as part of this compensatory response, causing a local hypothyroid condition. The mechanisms driving post-MI remodeling are only partly understood and here we investigated the possible involvement of microRNAs.

Methods: Using the mouse MI model, total RNA was isolated from the remodeling LV one week following surgery. LV tissue from sham-operated mice was used as controls. All 641 currently known mouse microRNAs were analyzed using the Taqman Megaplex rodent array. Data were analyzed using RQ-manager and DataAssist.

Results: 506 microRNAs were successfully quantified of which 107 were significantly ($p < 0.05$) up- or downregulated following MI compared to controls. Surprisingly, 33 microRNAs that were upregulated are encoded in the imprinted Dlk1-Dio3 genomic region. This was associated with significant upregulation of Dio3 mRNA expression, confirming earlier results.

Conclusions: Our analysis of post-MI LV shows a distinct microRNA-signature originating from the imprinted Dlk1-Dio3 region that has recently been identified as a hallmark of pluripotency. Together with the induction of DIO3 protein expression, this suggests that stressed cardiomyocytes re-induce a fetal gene program, comparable with that of a cardiac-progenitor-cell phenotype, of which reduction of thyroid-hormone signaling is an integral part. The concerted upregulation of a large set of microRNAs from the Dlk1-Dio3 region indicates a novel mechanism in LV remodeling, possibly involving other aspects of cardiac thyroid-hormone signaling.

OP6

PROTEOMICS DIFFERENTIATE BETWEEN GRAVES' ORBITOPATHY AND DRY EYE SYNDROME – A PROSPECTIVE AND CONTROLLED STUDY

Matheis N[1], Grus FH[2], Knych I[1], Breitenfeld M[1], Kahaly GJ[1]
[1]Gutenberg University Medical Center, Department of Medicine I, Mainz, Germany, [2]Gutenberg University Medical Center, Experimental Ophthalmology, Mainz, Germany

Objectives: An altered tear protein profile has been reported in Graves' Orbitopathy (GO). In this prospective, controlled study we aimed to determine specific proteins for GO and differentiate between GO, the common dry eye (DE) syndrome and healthy controls (C).

Methods: After complete ophthalmic and endocrine investigation of 120 subjects in a university joint thyroid-eye clinic, tear fluid proteins were analysed and identified using matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) technology.

Results: Thirty patients with GO (mean age 43.3 years, 23 female), 30 patients with GO+DE (51.9 yrs., 25 fem), 30 patients with DE (54.7 yrs., 23 fem) and 30 C (45.6 yrs., 27 fem) were investigated. A total of 30 proteins sig-

nificantly differed in all four study groups. Sixteen proteins (53%) significantly differed between GO and DE and seven (23%) between GO+DE and GO alone. Nine (30%) proteins significantly differed between GO and C and 11 (36%) between DE and C. Compared to C, the proteins calgranulin A (S10A8) and transcription activator BRG1 (SMCA4) were down-regulated in GO (p=0.004/ p=0.002) but up-regulated in DE (p< 0.001/p< 0.001). The proteins Midasin (MDN1, p=0.03), POTE ankyrin domain family member I (POTEI, p=0.02) and Proline-rich protein 1 (PROL1, p=0.03) were up-regulated in GO vs. C. The deregulated proteins in GO like S10A8 and SMCA4 correlated negatively with the clinical activity (r=-0.78, p< 0.0001) and clinical severity (r=-0.79, p< 0.0001) scores of GO. A Pathway analysis software (©2012 ingenuity systems Inc., USA) determined that SMCA4 and S10A8 are involved in inflammatory pathways, SMCA4 is involved in the AMPK signaling pathway and S10A8 is expressed by macrophages in chronic inflammations.

Conclusions: Proteins that differentiate GO, GO+DE, DE and C were identified. They are involved in inflammatory pathways. Subsequently further evaluation such as microarray technique, proteomics may become a useful diagnostic tool for GO.

OP2 Young Investigator Session

OP7

HYPOXIA-INDUCIBLE FACTOR 2α (HIF-2α) EXPRESSION CORRELATES WITH CLINICALLY AGGRESSIVE THYROID TUMOURS. *IN VITRO*, HYPOXIA-MODULATED TARGETS ARE REGULATED BY BOTH HIF-1/HIF-2 AND PROMOTE RADIO-RESISTANCE

Burrows N[1,2], Resch J[2], Brabant G[2], Williams K[1]
[1]University of Manchester, Hypoxia and Therapeutics group, School of Pharmacy, Manchester, United Kingdom, [2]Med Clinic I – University of Lübeck, Experimental and Clinical Endocrinology, Lübeck, Germany

Background: The HIF-signalling pathways are associated with aggressiveness, treatment-resistance and poor prognosis in many cancers. HIF-1 and HIF-2 are transcription factors activated by both low oxygen environments (hypoxia) and by the PI3K/MAPK pathways. HIF-1 has been associated with aggressiveness and metastasis in thyroid-carcinoma and HIF-2α is expressed in range of thyroid-carcinoma cell lines.

Objectives: To determine the clinical expression profile of HIF-2α, to assess if HIF-modulated targets are specifically regulated by HIF-1 or HIF-2 and to assess if the HIF-pathways contribute to radio-resistance.

Methods: HIF-2α expression was assessed by immuno-histochemistry on human samples of papillary (PTC), follicular (FTC) and anaplastic (ATC) thyroid-carcinomas. *In vitro* studies were performed under varying oxygen-tensions and cell lines were representative of PTC, FTC and ATC. To ablate HIF function, HIF-1α/-2α siRNA studies were undertaken and effects on expression of hypoxia-regulated targets (VEGF, CA-9, GLUT-1) were assessed at the mRNA/protein level. For radiation studies, siRNA-transfected cells and cells expressing a dominant-negative variant of HIF (dnHIF) were irradiated and fixed 1/24h post irradiation. Radiation-induced double-stranded breaks (DSBs) were assessed by analysis of γH2AX expression. Clonogenic survival was analysed in irradiated dnHIF versus WT cells.

Results: Clinically, HIF-2α expression was significantly higher in ATC samples versus FTC/PTC. Variable expression was observed within the same tumour subtype, from very intense to weak staining. siRNA studies revealed that hypoxia/anoxia-induced VEGF was specifically regulated by HIF-1α in the cell panel, whereas HIF-mediated regulation of CA-9 and GLUT-1 was variable between cell types. Inhibition of HIF by dnHIF increased radiation-induced DNA-DSBs and reduced clonogenic survival under anoxia. siRNA studies revealed that the observed increase in radiation-induced DNA-DSBs was specifically mediated by HIF-1α or -2α, depending on cell-type.

Conclusions: HIF-2α expression is associated with aggressive phenotype/ transition in thyroid-carcinoma. HIF-mediated regulation of downstream targets differed between the two HIF-isoforms, depending on cell-type. The HIF-pathway also contributes to radio-resistance, which has important therapeutic implications.

OP8

THYROID HORMONE AND TRα1 FORM A NEUROGENIC SWITCH REPRESSING *SOX2* IN THE ADULT NEURAL STEM CELL NICHE

Remaud S[1], Lopez-Juarez A[1], Hassani Z[2], Morvan G[1], Demeneix B[1]
[1]Muséum National d'Histoire Naturelle, UMR CNRS 7221, Evolution des Régulations Endocriniennes, Département Régulations, Développement et Diversité Moléculaire, Paris, France, [2]King's College London, Centre for the Cellular Basis of Behaviour, The James Black Centre, London, United Kingdom

The adult subventricular zone (SVZ) neural stem cell (NSC) niche contains mixed populations of stem cells, transit amplifying progenitor cells and migrating neuroblasts. Deciphering how endogenous signals, such as hormones, affect the balance between these cell types is essential for understanding the physiology of niche plasticity and homeostasis. We show that Thyroid Hormone (T3) and its receptor, TRα1, are directly involved in maintaining this balance in the SVZ of adult mouse brain. Using fluorescent immunohistochemistry on brains of euthyroid adult mice, we observed that TRα1 expression was absent from stem cells, appears in progenitors and is strongly maintained in the more committed cells, i.e. the doublecortin positive (DCX+) neuroblasts. To address the role of TRα1 in neural stem cell commitment, we modulated expression levels of TRα1 using i*n vivo* gain and loss of function experiments. We demonstrate first, that TRα1 in presence of T3 directly represses *Sox2,* a key factor involved in stem cell maintenance. Secondly, TRα1 overexpression within the SVZ niche stimulates emergence of DCX+ migrating neuroblasts. Consistent with these results, in mice lacking TRα *(TRα$^{0/0}$)* SOX2+ cell numbers increase in the SVZ. Finally, a lack of T3 (hypothyroidism) increases proportions of cells in interphase and decreases proportions of transit amplifying progenitors, showing a role for T3 in the exit from quiescence.

Thus, in the adult SVZ, T3/TRα1 favour NSC commitment and progression towards a migrating neuroblast phenotype; This transition correlates with T3/ TRα1 dependent transcriptional repression of *Sox2*. To our knowledge, this is the first description of an endogenous, hormonal, signalling pathway acting on NSC commitment and migration.

OP9

FACILITATION OF MEMORY ACQUISITION AND RETENTION IN MOUSE BY 3-IODOTHYRONAMINE

Musilli C[1], Manni ME[1], De Siena G[1], Saba A[2], Marchini M[2], Zucchi R[2], Raimondi L[1]
[1]Università di Firenze, Firenze, Italy, [2]Università di Pisa, Pisa, Italy

Objectives: 3-iodothyronamine (T1AM) is a novel chemical messenger which has been shown to produce several functional effects, including modulation of energy metabolism, insulin secretion and feeding behavior. In the present investigation we evaluated whether intracerebral injection of T1AM can modify learning capacity in mouse.

Methods: T1AM was injected i.c.v. into male mice, at dosages ranging from 0.13 to 4.0 μg/Kg. An equivalent amout of vehicle was injected in control mice. After 30 min memory acquisition, pain threshold, and curiosity were evaluated by the following tests: passive avoidance paradigm, novel object recognition, jumping on hot plate, movements and curiosity on the hole-board platform. In parallel experiments ERK1/2 activation, CREB activation and c-fos expression were determined in different brain areas by Western blot technique and T1AM concentration was measured in brain homogenate by HPLC coupled to tandem mass spectrometry.

Results: At dosages ≥ 1.32 μg/Kg, T1AM significantly improved learning capacity (P< 0.001). This effect occurred without producing analgesia or increasing locomotor activity. At the dosages which proved to be effective on learning, T1AM actually decreased pain threshold and increased curiosity. The effects observed in passive avoidance and object recognition tests were retained after 24 hours. After T1AM administration ERK2 activation was detected in hippocampus, hypothalamus and mesencephalon, while no changes in c-fos expression and CREB activation were observed. In control mice overall brain T1AM content averaged 0.4±0.1 pmol/g, and after administration of 1.32 μg/Kg exogenous T1AM it increased to 13.1±0.1 pmol/g, whereas T3 and T4 brain levels were unchanged.

Conclusions: Intracerebral administration of exogenous T1AM at dosages able to produce a 30-fold increase in physiological brain content activated ERK2 and enhanced memory acquisition and retention. These results might be consistent with a role for T1AM in learning and/or in memory disorders.

OP10

MIR-218 IS A MARKER OF OXIDATIVE PHOSPHORYLATION PROCESS IN ONCOCYTIC THYROID TUMOURS

Carat S[1], Guillotin D[2], Le Pennec S[2], Houlgatte R[1], Savagner F[2]
[1]Inserm U915, Nantes, France, [2]Inserm U694, Angers, France

Oncocytic thyroid tumours are mitochondrial-rich tumours presenting efficient oxidative phosphorylation (OXPHOS). This process needs a cross-talk between mitochondrial and nuclear genomes controlled at transcriptional level by the PGC-1 family of coactivators (PGC-1α, PGC-1β, and PRC). These coactivators may also control the expression of several miRNA that were previously shown to be differentially expressed in oncocytic tumours. To explore the relation between miRNA and PRC overexpression observed in these tumours, we have used cDNA and miRNA microarrays on a PRC-knock down cellular model. Moreover, chromatin immunoprecipitation with PRC antibody were used on cell lines and oncocytic thyroid tumours to confirm promoter interactions. We showed that PRC directly targeted 12 miRNA, five of which were involved in the control of the OXPHOS process. In particular, miR-218 appeared to control mitochondrial biogenesis and OXPHOS efficiency. The link between miR-218 effects and the impairment of mitochondrial biogenesis was explored by quantitative measurements of miR-218 target genes and mitochondrial respiratory chain activity. In thyroid tumours, measuring miR-218 expression related to PRC and PGC-1α expression level in 10 oncocytic tumours compared to 10 follicular adenomas and 10 papillary carcinomas, confirmed the interest for miR-218 as a marker for OXPHOS efficiency. We have identified a new biomarker for mitochondrial biogenesis in oncocytic thyroid tumours related to the feedback control of the OXPHOS process. Moreover, our findings demonstrate that PRC and several miRNA cooperate in the fine regulation of an essential metabolic pathway.

OP11

CLINICAL PHENOTYPE OF A NEW TYPE OF THYROID HORMONE RESISTANCE CAUSED BY MUTATION OF THE T3 RECEPTOR TRα1

van Mullem A[1], van Heerebeek R[1], Chrysis D[2], Visser E[1], Medici M[1], Andrikoula M[3], Tsatsoulis A[3], Visser TJ[1], Peeters R[1]
[1]Erasmus MC, Internal Medicine, Rotterdam, Netherlands, [2]University of Patras, Department of Pediatrics, Division of Endocrinology, Patras, Greece, [3]Universiy of Ioannina, Department of Endocrinology, Ioannina, Greece

Objectives: The biological action of T3 is mediated by its binding to nuclear receptors, in particular TRα1 and TRβ1. TRα1 is the major isoform in brain, heart and bone. Although TRα1 has already been characterized decades ago, no patients with mutations in this receptor have been identified until very recently. The phenotype of the first patients indicates that mutations in TRα1 are associated with abnormal thyroid hormone (TH) but normal TSH levels, growth retardation, delayed bone development and constipation. In the current study we describe the detailed clinical phenotype of two patients (father and daughter) with a heterozygous inactivating mutation in TRα1 (Phe397fs406X) as well as the effects of LT4 treatment.

Methods: Both patients have low (F)T4, high T3, low rT3 and normal TSH levels, in combination with high cholesterol, and low-normal GH and IGF-1 levels. Clinical characteristics include hypothyroid symptoms, growth retardation due to delayed bone development, mildly delayed mental and motor development, and constipation. Because of clinical hypothyroidism, patients were treated with LT4. To evaluate treatment effects, LT4 was withdrawn for 35 days.

Results: Treatment with LT4 resulted in normalization of serum (F)T4, persistently high T3 and suppression of TSH levels. LT4 also induced a transient increase in growth (in the girl), normal defecation pattern and lowering of cholesterol. Despite the high T3 levels, the patients have a normal heart rate suggesting partial TH resistance of the heart. The highly elevated T3/rT3 ratio suggests altered peripheral TH metabolism. At 8 years of age, the girl was treated in addition with GH, which normalized IGF-1 but did not increase growth.

Conclusions: In conclusion, mutations in TRα1 are associated with abnormal TH levels, constipation and a delayed bone development. Only partial normalization of the phenotype is achieved by LT4 treatment; growth and bone development remain delayed.

OP12

TWO NOVEL CHIMERIC TSH RECEPTOR BIOASSAYS MEASURING THYROID-STIMULATING AND BLOCKING AUTOANTIBODIES DIFFERENTIATE THYROIDAL VERSUS ORBITAL INVOLVEMENT IN PEDIATRIC GRAVES' DISEASE – A MULTICENTER TRIAL

Diana T[1], Bossowski A[2], Sawicka B[2], Borysewicz-Sanczyk H[2], Pietrewicz E[2], Ziora K[3], Bossowska A[4], Kanitz M[1], Kim J[5], Olivo PD[5], Kahaly GJ[1]
[1]Gutenberg University Medical Center, Department of Medicine I, Mainz, Germany, [2]Medical University in Bialystok, Department of Pediatrics, Endocrinology, Diabetology with the Cardiology Division, Bialystok, Poland, [3]Medical University of Silesia, Department of Pediatrics in Zabrze, Katowice, Poland, [4]Internal Affair and Administration Ministry Hospital, Department of Cardiology, Bialystok, Poland, [5]Diagnostic Hybrids, Inc, R & D, Athens, United States

Objectives: Scarce data are available regarding the clinical utility of TSH receptor (TSHR) bioassays in children with autoimmune thyroid disease (AITD). The objective of this multicenter study was to detect thyroid stimulating (TSAb) and blocking (TBAb) autoantibodies in a large collective of pediatric samples with AITD.

Methods: Both bioassays utilize a CHO cell line expressing a chimeric TSHR and a CRE-dependent luciferase. TSAb were measured with a FDA-cleared test (Thyretain) and results were expressed as percentage of specimen-to-reference ratio (SRR%). TBAb were measured as percent inhibition in luciferase expression relative to a bovine TSH control. Positive percent inhibition reveals blocking activity whereby negative percent inhibition reveals stimulatory activity. Thyroid binding inhibiting immunoglobulins (TBII, ECLIA, Roche) were measured in all samples.

Results: A total of 173 serum samples from 30 pediatric patients with Graves' disease (GD, 28 female, mean age ± SEM 12.9±0.7 years, 11 with orbitopathy, GO), 62 with Hashimoto's thyroiditis (HT, 52 female, 13.4±0.4 yrs.) and 40 healthy controls (C, 18 female, 12.1±0.8 yrs.) were evaluated for the presence of TSAb and TBAb. All untreated GD patients were TSAb positive whereas two were TBII negative. TSAb and TBII were detected in 46 (90%) and 39 (77%) of 51 GD samples, respectively. Mean serum TSAb levels were SRR% 419±19.4 and 239±84.4 (p=0.002) in untreated and treated GD children, respectively. In contrast to TBII, TSAb levels were markedly higher (p=0.03) in children with (SRR% 439±27) vs. without (330±39) GO. Thyroid-stimulatory activity in GD children with vs. without GO (-107.2 vs. -69.5%, p=0.02) was also noted in the TBAb bioassay. All HT and C were TSAb negative whereas one hypothyroid child with HT was TBAb positive.

Conclusions: These innovative data in a large pediatric AITD collective demonstrate the clinical usefulness of the novel bioassays and the close association between TSAb and GO.

OP13

NEW SOMATIC MUTATIONS AND CLONAL EVOLUTION IN AGGRESSIVE PAPILLARY THYROID CARCINOMA REVEALED BY WHOLE-TRANSCRIPTOME DEEP SEQUENCING

Le Pennec S[1], Gacquer D[1], Detours V[1], Maenhaut C[2]
[1]IRIBHM – ULB, Bruxelles, Belgium, [2]IRIBHM – ULB – Welbio, Bruxelles, Belgium

Global transcriptome sequencing in cancer cells enable the systematic discovery of somatic mutations like non synonymous Single Nucleotides Variants (nsSNVs) that may contribute to carcinogenesis. To determine the phylogenetic relationships between the primary and metastatic tumor sites

and to identify new mutated genes involved in the development and progression of papillary thyroid cancer (PTC), we performed paired-end massively parallel sequencing of cDNA (RNA-seq) on seven different samples (primary tumor, lymph nodes and pleural metastases) from the same patient for which an aggressive PTC had been diagnosed.

Our computing analysis identified 192 novel nsSNVs. Two categories of mutations were identified. The largest category corresponded to mutations detected in all the samples and represented putative "founder mutations" present in the primary cancer cells before the development of metastatic lesions. Other nsSNVs are only detected in one or more of the metastases examined and corresponded to putative "progressor mutations".

Only a small fraction of the mutations in a tumor are driver mutations that confer a selective growth advantage to the cell. We therefore searched to identify those driver mutations in our samples. SIFT and Polyphen-2 algorithms predicted some of these nsSNVs being damaging for protein function. We next used different resources to identify the nsSNVs that are located in putative "cancer genes": Cosmic database, PubMed literature, CGPrio algorithm... This allowed us to select some nsSNVs as best-candidates for further validation by Sanger sequencing in the same samples as well as for investigation in other PTC and metastases.

This study demonstrates that the development of PTC metastases is associated with the addition of new mutations. We are currently searching for the presence of some of these new mutations in a large panel of PTC samples to test whether these selected individual nsSNVs are actually frequent driver mutations for PTC carcinogenesis and progression.

OP14

IGSF1 GENE DELETION CAUSE CENTRAL HYPOTHYROIDISM AND MACROORCHIDISM WITH DECREASED OF TSH BIOACTIVITY

Escudero A[1], Gorbenko D[2], Barrio R[3], Vallespín E[4], Nevado J[4], De Graaff L[2], Lapunzina P[4], Hokken-Koelega A[2], Moreno JC[1]

[1]Institute for Medical and Molecular Genetics (INGEMM). La Paz University Hospital, Thyroid Molecular Laboratory, Madrid, Spain, [2]Pediatric Endocrinology, Sophia Children's Hospital. Erasmus University Medical Center, Rotterdam, Netherlands, [3]Ramón y Cajal University Hospital, Pediatric Endocrinology, Madrid, Spain, [4]Institute for Medical and Molecular Genetics (INGEMM). La Paz University Hospital, Structural Genomic Laboratory, Madrid, Spain

Central Congenital Hypothyroidism (CCH)is caused by a TSH deficiency. Known molecular bases of CCH involve mutations in only the TSHB and TRHR genes. IGSF1 has been proposed as a membrane receptor for Inhibin-B. Activins-Inhibins are a complex system of endo- and autocrine factors with opposing effects and important roles in pituitary and reproductive organs, but unreported actions on the thyroid axis.

Objective: To investigate the molecular cause of CCH-macroorchidism using genome-wide genetic techniques.

Methods: A patient with X-linked CCH-macroorchidism was studied with complete hormonal and clinical follow-up. Comparative Genomic Hybridization (CGH)-arrays were performed on the DNA of patient and his family. TSH bioactivity was assayed in vitro by a cell-based luciferase reporter assay using patient's serum.

Results: CCH was diagnosed by neonatal clinical hypothyroidism (sTSH:1.4mU/L; FT4:7.2pmol/L). Poor TSH response at TRH test indicated pituitary hypothyroidism. Excessive testicular growth was detected from 3 years of age (3–4ml Prader). GnRH test showed stimulation of FSH and LH, but discordantly low testosterone levels. Normal puberty started at 12.5 years with initial testicular volume of 8 ml (N:2), reaching 40 ml at the end of puberty (N:20–25). Inhibin-B (500ng/L; N:200–400) and Antimullerian hormone (48µg/L; N:5–9) were markedly elevated, suggesting increased Sertoli cell mass. CGH-array showed an hemizygous 200Kb deletion of the entire IGSF1 gene in the patient, inherited from his heterozygous mother. Both patient and mother showed a significantly low TSH bioactivity, which did not increase by TRH physiological stimulus.

Conclusions: IgSF1 is a novel candidate gene for central hypothyroidism with reduced TSH bioactivity. Elevated Inhibin-B and normal FSH levels suggest Inhibin-B resistance. IgSF1 defects may disturb pituitary and testicular functions through disruption of the counter-balancing effect of Inhibin-B over Activin-A derived signaling pathways in targets cells.

OP3 Clinical Thyroidology

OP15

MENTAL VULNERABILITY IS HIGH IN PREVIOUSLY TREATED HYPER AND HYPOTHYROIDISM

Perrild H[1], Knudsen N[1], Bjergved L[1,2], Carle A[3], Bulow I[3], Vejbjerg P[1], Laurberg P[3], Ovesen L[4], Rasmussen L[5], Jørgensen T[2]

[1]Bispebjerg University Hospital, Department of Endocrinology, Copenhagen, Denmark, [2]Research Centre for Prevention and Health, The Capital region of Denmark, Glostrup, Denmark, [3]Aalborg Hospital, Aarhus University Hospital, Department of Endocrinology, Aalborg, Denmark, [4]Slagelse Hospital, Department of Gastroenterology, Slagelse, Denmark, [5]National Food Institute, Department of Nutrition, Copenhagen, Denmark

Aim: To investigate whether the presence of overall mental vulnerability, as well as psychosomatic or mental symptoms or personal traits, is associated with present or previous thyroid dysfunction in subjects randomly selected from two regions in Denmark.

Methods: Random samples from the general population were drawn from the Civil Registration System. The samples were restricted to certain age groups within the spectrum 18- 65 years. Participants answered questionnaires followed by a personal interview including four validated scales to evaluate different aspects of mental vulnerability. Thyroid function was evaluated from blood samples.

Results: In all 8,021 subjects participated. In Participants, now euthyroid, mental vulnerability was significantly associated with previous hyper- or hypothyroidism, compared with euthyroid participants without previous or present thyroid disease. The 12 item scale: Previous hypothyroidism (n:84): 2,9 (95% confidence interval 2,4 to 3,3) vs euthyroid and without previous thyroid disease (n:7150) 2,0 (95% confidence interval 1,9 to 2,0) ($p< 0.001$) and previous hyperthyroidism (n:105): 2,9 (95% confidence interval 2,5 to 3,3) vs euthyroid and without previous thyroid disease (n:7150): 2,0 (95% confidence interval 1,9 to 2,0).($p< 0.001$)). Further analysis, using the three other item scales, indicates that psychosomatic symptoms and mental symptoms, but not interpersonal problems (that is personal traits), were significantly associated to previous hyper- and hypothyriodism.

No association with mental vulnerability was found among subjects with unknown biochemical hypo- (n:23) or hyperthyroidism (n:46), mild (subclinical) hyperthyroidism (n:255) or mild (subclinical) hypothyroidism (n:358).

Conclusions: Our data suggest that patients with previous hyper- and hypothyroidism have persistent mental vulnerability, primarily dominated by psychosomatic and mental symptoms, whereas no association. was found with personal traits. In this unselected population sample, mental vulnerability was not found in subjects with overt or mild (subclinical) hyper- or hypothyroidism, unknown to the patient. This Study is part of the DanThyr study.

OP16

THE ASSOCIATION BETWEEN HYPERTHYROIDISM AND MORTALITY IS NOT EXPLAINED BY PRE-EXISTING CO-MORBIDITY, BUT INFLUENCED BY GENETIC CONFOUNDING. EVIDENCE FROM A DANISH NATION-WIDE REGISTER-BASED STUDY OF TWINS AND SINGLETONS

Brandt F[1], Almind D[2], Christensen K[2,3,4], Green A[5], Hegedüs L[1], Brix TH[1]

[1]Odense University Hospital, Department of Endocrinology and Metabolism, Odense, Denmark, [2]University of Southern Denmark, The Danish Aging Research Center and The Danish Twin Registry, Odense, Denmark, [3]Odense University Hospital, Department of Clinical Genetics, Odense, Denmark, [4]Odense University Hospital, Department of Clinical Biochemistry and Pharmacology, Odense, Denmark, [5]University of Southern Denmark, Odense Patient data Exploratory Network, Institute of Clinical Research, Odense, Denmark

Context: Hyperthyroidism is associated with potentially lethal conditions, such as stroke. However, the impact of pre-exisitng co-morbidity on the link between hyperthyroidism and mortality remains at large unanswered. Further since both hyperthyroidism and longevity are partly inherited, the issue of genetic confounding needs to be addressed.

Objective: To investigate whether hyperthyroidism is associated with an increased mortality, and, if so, whether the association is influenced by pre-existing co-morbidity and/or genetic confounding.

Methods: Observational cohort study using record-linkage data from nation-wide Danish health registers. 4850 singletons and 926 twins from same sex pairs diagnosed with a first episode of hyperthyroidism were identified. Individuals with hyperthyroidism were matched with 4 non-hyperthyroid controls for age and sex and same sex twin pairs discordant for hyperthyroidism were identified. The degree of co-morbidity was evaluated by using the Charlson score (CS). This score includes 19 different disease categories. Cases and controls were followed over a mean time of 10 years (range 0–31 years) and the hazard ratio (HR) for mortality was calculated using Cox regression analyses adjusted for CS.

Results: In singletons there was a significantly increased mortality in individuals diagnosed with hyperthyroidism (HR 1.37; 95% CI 1.30–1.46), which was similar after adjustment for pre-existing co-morbidity (HR 1,28; 95% CI 1.21–1.36). In twin pairs discordant for hyperthyroidism the twin with hyperthyroidism had an increased risk of mortality compared to the healthy co-twin (HR 1.43; 95% CI 1.09–1.88). Zygosity had a major impact, there was an increased risk of mortality in dizygotic twins (HR 1.80; 95% CI 1.27–2.55), whereas the effect of hyperthyroidism vanished in the monozygotic twins (HR 0.95; 95% CI 0.60–1.50).

Conclusions: Hyperthyroidism is associated with increased mortality independent of pre-existing co-morbidity. The study of same sex twin pairs discordant for hyperthyroidism suggests that genetic confounding influences the association between hyperthyroidism and mortality.

OP17

AGE AND GENDER SUBSTANTIALLY INFLUENCE THE RELATIONSHIP BETWEEN THYROID STATUS AND LIPOPROTEIN PROFILE: RESULTS FROM A LARGE CROSS-SECTIONAL STUDY

Tognini S[1], Polini A[1], Pasqualetti G[1], Ursino S[1], Ferdeghini M[2], Monzani F[1]

[1]University of Pisa, Internal Medicine, Pisa, Italy, [2]Universty of Verona, Morphological and Biomedical Sciences, Verona, Italy

Background: Conflicting data are reported on the association between mild thyroid failure and lipid profile. We assessed the possible influence of gender and age on this relationship.

Methods: 2308 consecutive patients (1874 F, mean age 47±4.1 years) received a complete clinical workup. Thyroid status and lipoprotein profile were assessed after an overnight fast. Patients were divided into subgroups according to age (1st: 10–29, 2nd: 30–49, 3rd: 50–64, 4th: >65 years) and TSH values (1st: < 0.36; 2nd: >0.36 and < 3.6; 3rd: >3.6 and < 10.0; 4th: >10.0 mIU/l).

Results: The prevalence of autoimmunity was significantly higher in women than men (p=0.0002) but no gender difference in TSH frequency distribution was observed. Total (TC) and LDL cholesterol (LDLc) values (p< 0.003) as well as LDL/HDLc ratio (p< 0.03) were significantly elevated in unselected women of the 4th TSH group but also in those of the 3rd TSH group older than 50 years (p< 0.02 Vs euthyroid women). Among unselected men only those of the 4th TSH group had significantly elevated triglyceride (TG) (p< 0.0001) but not cholesterol values. However, men of the 3rd and 4th TSH groups older than 65 years showed significantly higher TC, LDLc values and LDL/HDLc ratio too (p< 0.03 Vs euthyroid men). In the final model of stepwise regression analysis, which explained almost 40% of serum TC and LDLc variations, age had the highest standardized coefficient (0.37), followed by TSH (0.20 and 0.11, respectively) and FT4 (-0.10).

Conclusions: This study, while confirming a gender differentiation in the relationship between thyroid function and lipid profile, firstly documents that the impact of mild thyroid impairment on lipid parameters is substantially influenced by age in both genders. Our data may, at least partially, explain the conflicting results on the relationship between slightly elevated TSH value and circulating lipid parameters.

OP18

HYPOTHYROIDISM IS ASSOCIATED WITH CURRENT BUT NOT WITH INCIDENT HYPERTENSION

Ittermann T[1], Tiller D[2], Meisinger C[3], Agger C[4], Nauck M[1], Rettig R[1], Hofman A[5], Jorgensen T[4], Linneberg A[4], Witteman JCM[5], Franco OH[5], Greiser KH[2], Werdan K[2], Döring A[3], Kluttig A[2], Stricker BHC[5], Völzke H[1]

[1]University of Greifswald, Greifswald, Germany, [2]Martin-Luther-University Halle-Wittenberg, Halle, Germany, [3]German Research Center for Environmental Health, München, Germany, [4]University of Copenhagen, Copenhagen, Denmark, [5]Erasmus Medical Center, Rotterdam, Netherlands

Background: Recent data from a large population-based study in children and adolescents suggests that serum thyroid-stimulating hormone (TSH) levels are associated with arterial blood pressure and hypertension. These results are in agreement with some, but not all population-based studies in adults. Discrepancies in results might be explained by intake of drugs, different iodine supplies and sizes of populations investigated. In addition, it is currently not clear, whether an association between TSH and hypertension exists longitudinally rather than only cross-sectionally. Thus, our aim was to investigate both the cross-sectional and longitudinal associations between thyroid function and arterial blood pressure in a large consortium of cohort studies in adults.

Material and methods: Data from five population-based studies were pooled resulting in 17,023 individuals being available for cross-sectional and 10,048 individuals for longitudinal analyses. Associations of baseline serum TSH levels with baseline blood pressure or hypertension were analyzed by multivariable median or logistic regression models. Multivariable median or Poisson regression models were used to investigate associations of baseline serum TSH levels with 5-year-change in arterial blood pressure or incident hypertension.

Results: There was a cross-sectional association of serum TSH levels with arterial blood pressure (p< 0.001) and hypertension (odds ratio=1.76; 95% confidence interval=1.24 - 2.50; p=0.002). Serum TSH levels, however, were not consistently associated with a 5-year-change in blood pressure or incident hypertension.

Conclusion: Hypothyroidism is associated with current hypertension and blood pressure but not with 5-year-change in blood pressure and incident hypertension. This argues for an only short-term effect of thyroid hormone levels on arterial blood pressure or a spurious association that need further evaluation in population-based studies.

OP19

THE EFFECT OF HYPOTHYROIDISM ON COLOUR VISION: A PROSPECTIVE STUDY

Cakir M[1], Ozturk B[2], Turan E[1], Gonulalan G[1], Polat I[3], Gunduz K[2]
[1]Konya University Meram School of Medicine, Division of Endocrinology and Metabolism, Konya, Turkey, [2]Konya University Meram School of Medicine, Department of Ophthalmology, Konya, Turkey, [3]Konya University Meram School of Medicine, Department of Internal Medicine, Konya, Turkey

Objective: In mice during early development period, thyroid hormone (TH), is an important regulator of retinal cone spectral identity. Additionally, it has been shown that TH controls retinal cone opsin expression hence the protein of colour vision in adult rodents. The aim of this study was to evaluate the effect of hypothyroidism on colour vision in adult overt hypothyroid patients before and after euthyroidism is achieved.

Methods: Thirty-eight (31 females, 7 males) overt hypothyroid subjects were included in the study. The etiologies of hypothyroidism included Hashimoto's thyroiditis and thyroid surgery for nodular goiter. Ophthalmological examination including visual acuity, intraocular pressure measurement, biomicroscopy and fundus examination were performed for all patients and those with any ocular pathology that may affect visual acuity and colour vision were excluded from the study. To evaluate the status of colour vision a special test called Chromatest was used. Chromatest is a software program analyzing the age-corrected tritan (blue-yellow) colour contrast threshold (TCCT) and protan (red-green) colour contrast threshold (PCCT).

Results: To date, seventeen (13 females, 4 males) patients have been re-examined after a median period of 90 (89–195) days. On admission, median thyroid function test values were as follows; free T3: 2.76 (1.43–3.34) [(normal range 2.5–3.9)] pg/dl, free T4: 0.51 (0.15–0.6) [(normal range 0.61–1.12)] ng/dl and TSH: 25.7 (9.41–100) [(normal range 0.34–5.6)] µIU/ml. Median serum TSH level after euthyroidism was 1.26 (0.37–5.53) µIU/ml. On Chromatest results, there was a significant decrease in TCCT ($p< 0.001$) and PCCT ($p=0.001$) which clinically translates into improved colour vision after euthyroidism.

Conclusions: Our study is a first in English literature in terms of examining the effect of hypothyroidism on colour vision in adults. The results of completed examination of seventeen subjects show, TCCT and PCCT decrease hence colour vision significantly improves after euthyroidism is achieved in hypothyroid subjects.

OP20

REDUCTION OF LEVOTHYROXINE (L-T4) REQUIREMENTS IN HYPOTHYROID OBESE PATIENTS AFTER BARIATRIC SURGERY

Martinelli S[1], Pinchera A[1], Fierabracci P[1], Piaggi P[2], Tamberi A[1], Basolo A[1], Ceccarini G[1], Marsili A[1], Scartabelli G[1], Landi A[2], Vitti P[1], Santini F[1]
[1]University of Pisa, School of Medicine, Endocrinology Unit, Obesity Center, Pisa, Italy, [2]University of Pisa, Department of Electrical Systems and Automation, Pisa, Italy

L-T4 needs in hypothyroid patients are usually estimated based on total body weight, and proper adjustment of the replacement dose in hypothyroid obese subjects after weight loss is an important clinical issue.

Aim of this study was to evaluate changes in the l-T4 dose after bariatric surgery in patients affected by acquired hypothyroidism.

We analyzed 51 obese hypothyroid subjects (48 F, 3 M, mean age ± SD: 47 ± 10 years), 8 after thyroidectomy, 4 after radioiodine therapy and 39 with autoimmune hypothyroidism, before and 28.6 ± 7.9 months after bariatric surgery.

The body mass index at the time of surgery ranged between 34 and 60 Kg/m^2 (45 ± 6 Kg/m^2). Twenty-two subjects underwent gastric bypass, 24 gastric banding and 5 sleeve gastrectomy, with a mean weight loss of 29.5 ± 14.6 Kg.

The mean total daily dose of l-T4 before-surgery was 126.9 ± 45.9 mcg/die (1.11 ± 0.38 mcg/Kg per die). After weight loss, a significant decrease in the total l-T4 dose occurred (-8.2%, $p=0.001$) while the pro-Kg dose underwent a significant increase (+25.5%, $p< 0.001$). The latter increase was directly related to the amount of weight lost ($p< 0.001$). No significant differences in the variation of the dose of l-T4 among the three types of surgery were found. There was no association between reduction of circulating leptin and variation of the l-T4 dose, suggesting no relationship between l-T4 requirements and the fat mass.

In conclusion: 1) In obese hypothyroid subjects, weight loss achieved through bariatric surgery requires a reduction in the daily dose of l-T4.

2) The amount of l-T4 reduction is proportional to the weight lost and is not influenced by the type of surgical procedure.

3) The reduction of l-T4 dose is independent of reduced fat mass and may be related to reduced lean mass.

OP21

TAZ DOES NOT RESCUE THE LUNG PROMOTER ACTIVITY OF A NOVEL NKX2-1 MUTATION IN A BOY WITH SEVERE LUNG EMPHYSEMA

Moya CM[1], Garzón L[2], Luna C[3], Simón R[4], Zaballos MA[5], Santisteban P[6], Gallego E[2], Moreno JC[1]
[1]INGEMM- Institute for Medical and Molecular Genetics. 'La Paz' University Hospital, Thyroid Molecular Laboratory, Madrid, Spain, [2]'12 de Octubre' University Hospital, Paediatric Endocrinology, Madrid, Spain, [3]'12 de Octubre' University Hospital, Paediatric Pneumology and Allergy, Madrid, Spain, [4]'12 de Octubre' University Hospital, Neuropediatric, Madrid, Spain, [5]Biomedical Research Institute, Endocrine Physiopathology and Nervous System, Madrid, Spain

Background: NKX2-1 is a transcription factor expressed in thyroid, brain and lung. NKX2-1 defects cause primary hypothyroidism, neurological disorders and respiratory distress, with large variability in the presence/severity of the phenotypes. Recently, it was suggested that different domains of NKX2-1 may exert differential functions. TAZ is a co-activator of NKX2-1 with large expression in the lung.

Objective: To identify the pathogenic mechanisms of a Thyroid-Brain-Lung syndrome in a boy with life-threatening lung emphysema.

Patient and methods: Male of 14 years, diagnosed with hypothyroidism at neonatal screening (TSH 224 µU/L; FT4 0.6ng/dl) with gland in situ. Severe respiratory disease from birth evolved into chronic bronchopathy. Thoracic scan showed extensive lung destruction, and biopsy indicated emphysema, and interstitial fibrosis. He has chorea from 9 months of age and psychomotor retardation. PCR and direct sequencing of NKX2-1. Site-directed mutagenesis of NKX2-1. Co-transfection of wildtype, N-terminal (224insG) or C-terminal (825delC) mutations with 3 luciferase reporters containing thyroid, lung and brain promoters, with or without TAZ cDNA. Luciferase assays and confocal microscopy.

Results: We identified a novel de novo heterozygous mutation in NKX2-1 (c.224insG; p.V75fsX408), the most amino-terminally located so far. The mutant shows nuclear location. However, its capacity to activate thyroid, lung and brain promoters is abolished. Of note, and clearly contrasting with a carboxy-terminal NKX2-1 mutation identified in patients without lung problems, the 224insG mutant is incapable to activate the pulmonary promoter, even in cotransfection with the lung coactivator TAZ.

Conclusions: We confirmed that mutation c.224insG is causing the NKX2-1 syndrome in this patient. Our studies suggest that mutations that modify interactions between NKX2-1 and TAZ may cause the most severe respiratory problems in the Thyroid-Brain-Lung syndrome, and shape TAZ as an important modifier gene in this disorder.

OP22

PERIPHERAL TISSUE BIOMARKERS IN RESISTANCE TO THYROID HORMONE

Moran C[1], Schoenmakers N[1], Mitchell C[1], Talbot F[1], Watson L[1], Lyons G[1], Raymond-Barker P[1], Taylor K[2], Halsall D[2], Chatterjee K[1]
[1]University of Cambridge, Institute of Metabolic Science, Cambridge, United Kingdom, [2]University of Cambridge, Clinical Biochemistry, Cambridge, United Kingdom

Thyroid hormones (TH) regulate lipid metabolism, deiodinase enzyme activity and possibly copper levels in rodents and humans. We measured fasting lipid, copper, TH and reverse T3 (rT3) in subjects with Resistance to Thyroid Hormone (TRbeta mutations), thyrotoxicosis and healthy controls. Copper was markedly raised in thyrotoxics (n=22, mean 21.8 mol/L) com-

pared to RTH subjects (n=58, mean 17.07 mol/L, p 0.05 x 10^{-3}) and healthy controls (n=107, 17.5 mol/L, p=0.0012). Copper levels fell following treatment (mean 18.6 mol/L, p=0.048). rT3 levels were higher in the thyrotoxic patients (n=29, 94.6 ng/dl) than in RTH subjects (n=82, 68.1 ng/dl; p=0.012 x 10^{-2}) and healthy controls (n= 32, 24.4 ng/dl; p=0.009 x 10^{-8}) and declined markedly following treatment (preRx 62.4 ng/dl, postRx 25 ng/dl (p=0.03).

RTH subjects exhibited lower FT3 levels than thyrotoxic subjects (13.3pmol/L vs 32.9 pmol/L; p=0.019 x 10^{-12}), such that their FT4/FT3 ratio is higher (2.8 vs 1.96; p=0.013 x 10^{-4}) but FT3/rT3 ratio is lower (0.21 vs 0.33; p=0.0151 x 10^{-5}) than in hyperthyroidism.

Higher total cholesterol (5.18 mmol/L vs 4.85 mmol/L; p=0.036), and LDL cholesterol (3.32 vs 2.93; p=0.003), but lower HDL (1.19 vs 1.49; p=0.06 x 10^{-6}) and higher triglycerides (1.50 vs 1.05; p=0.008 x 10^{-3}) was seen in RTH subjects (n=93) versus healthy controls (n=113), resulting in higher cholesterol: HDL ratios in this disorder (4.63 vs 3.34; p= 0.018 x 10^{-7}).

Our observations, showing a lack of comparable elevation in circulating copper, free T3 and rT3 in RTH versus thyrotoxicosis, substantiate the utility of these biomarkers in quantifying peripheral tissue refractoriness to TH action in RTH. Our findings indicate mixed dyslipidaemia in RTH and we have previously described insulin resistance and reduced vascular compliance in this disorder; it is possible that their coexistence with dyslipidaemia and steatosis, defines a subset of RTH patients at excess cardiovascular risk.

OP4 Thyroid Cell Biology

OP23

PAX8 EXPRESSION IS REQUIRED FOR THE DIFFERENTIATION OF THYROID FOLLICULAR CELLS

Marotta P[1], *Amendola E*[1], *De Luca P*[1], *Zoppoli P*[1], *Di Lauro R*[1,2], *De Felice M*[1,2]
[1]Biogem, Ariano Irpino (Av), Italy, [2]University Federico II, DBPCM, Napoli, Italy

Studies on both animal models and patients affected of thyroid dysgenesis have demonstrated that the transcription factor Pax8 is required for the normal morphogenesis of the thyroid. However, the specific role of this factor in the mature thyroid has not been addressed. In Pax8$^{-/-}$ mice the thyroid anlage disappears around E11.5, before the onset of functional differentiation and the rudimentary gland present at birth is devoid of follicular cells. To elucidate the role of Pax8 in follicular cells it is necessary to inactivate the gene in a manner that allows formation of a mature thyroid. We have generated a conditional knock-out mouse harboring a Pax8 allele in which exons encoding for the paired domain are flanked by LoxP sites (Pax8^{fl}). This allele of Pax8 is functioning but can be disrupted by CRE ricombinase. These mice have been crossed with Pax8^{CRE} mice, expressing CRE in the thyroid. By this process, we have obtained Pax8$^{fl/CRE}$ mice in which the Pax8 gene becomes disrupted in thyroid tissue. In Pax8$^{fl/Cre}$ embryos the developing thyroid is correctly located and the size of the gland appears to be similar to that of wild type embryos. The expression of a number of genes such as Titf1, Foxe1, Tg and NIS appears unaffected. However, after birth, Pax8$^{fl/CRE}$ animals show a hypoplastic gland devoid of follicular structure. Gene expression profile shows that the expression of many thyroid specific genes, required for both hormone production and regulative functions, is completely abolished in the absence of Pax8. Furthermore, in the thyroid gland of these mice there is an increased apoptosis, thus confirming the role of Pax8 in controlling cell survival (Fagman H, 2010) These data demonstrate, in a physiological context, that Pax8 plays a key role in the control of both survival and differentiation of the thyroid follicular cells.

OP24

PAX8 IS A SURVIVAL FACTOR FOR THYROID CELLS AND IS INVOLVED IN THE CONTROL OF CELL PROLIFERATION

Di Palma T[1], *de Cristofaro T*[1], *Filippone MG*[1,2], *Pierantoni GM*[2], *Fusco A*[1,2], *Zannini M*[1]
[1]Institute of Experimental Endocrinology and Oncology (IEOS)-CNR, Naples, Italy, [2]University of Naples 'Federico II', Dpt. of Cellular and Molecular Biology and Pathology, Naples, Italy

The transcription factor Pax8, a member of the *Paired-box* gene family, has been demonstrated to be a critical regulator required for proper development and differentiation of thyroid follicular cells. Intriguingly, the analysis of Pax8$^{-/-}$ mice revealed that in the absence of this transcription factor, at E11.5 the thyroid primordium appears much smaller than the wild-type one, and at E12.5 the follicular cells are essentially undetectable. Such phenotype is very suggestive of a requirement of Pax8 for the survival of thyroid cell precursors. Despite being Pax8 well-characterized with respect to its role in regulating genes involved in thyroid differentiation, its involvement in cell growth and survival remains unclear. Hence, to shed light on this new interesting putative role of Pax8, we analyzed whether its up-regulated expression is sufficient to promote cell growth in the FRTL-5 thyroid cell line. Indeed, we demonstrate that Pax8 overexpression significantly increases the fraction of FRTL-5 cells in the S phase of the cell cycle. This result is further supported by a delay in the accumulation of the well known inhibitors p21$^{Waf1/Cip1}$ and p27^{Kip1}, involved in G1/S phase of the cell cycle. In parallel, to examine a possible Pax8 involvement in apoptosis we inhibited its expression in FRTL-5 thyroid cells by RNA interference. Interestingly, we show that upon Pax8 silencing the cells undergo apoptosis and this occurs through a pathway involving caspase-3 activation and cleavage of poly(ADP)ribose polymerase (PARP-1). In conclusion, our data suggest that in thyroid cells Pax8 plays an important role sustaining cell survival and inducing cell growth by directly regulating the cell cycle.

OP25

DYNAMIC CHANGES OF LAMININ EXPRESSION AND BASEMENT MEMBRANE ORGANIZATION IN THE DEVELOPING THYROID

Johansson E[1], *Johansson BR*[2], *Nilsson M*[1]
[1]Sahlgrenska Cancer Centre, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [2]Electron Microscopy Unit, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Objectives: Basement membranes (BM) underlying epithelia constitute physical and biochemical barriers that separate the epithelium from the stromal compartment. Dissolution of BM and altered cell-matrix interactions are recognized in e.g. embryonic tissue patterning and tumour invasiveness. Here we investigated for the first time BM dynamics in the embryonic thyroid.

Methods: Mouse embryos were collected from ages E10.5 to E15.5 for immunostaining of laminin, a major BM constituent, and for transmission electron microscopy. Thyroid progenitor cells of both thyroid anlagen, the midline thyroid bud and the paired ultimobranchial bodies (UBs), were identified by Nkx2.1/TTF-1 expression. The investigated times cover the entire process from the delamination of anlagen in foregut endoderm, via migration and fusion of primordial tissues, to the early differentiation of thyroid follicles and parafollicular C cells in the prospective lobes.

Results: Laminin formed continuous BMs that enveloped each thyroid primordium until E12.5. At these early stages of thyroid morphogenesis no laminin was detected in the interior of the cell masses, indicating that only peripheral progenitor cells had contact with BM. Coinciding with thyroid fusion (E13.5) the BM became ultrastructurally disrupted and laminin discontinuous as cells from the two anlagen started to mix. At the same time laminin deposits were observed inside the UB. From E14.5 and onwards laminin reorganized around the pre-follicular parenchyma and early follicles.

Conclusions: We conclude that the emerging thyroid anlagen in mouse embryos remain distinct structures, each of them separated from surrounding mesenchyme by a laminin+ BM, before the fusion stage. The approach of follicular and C cell precursors starting by fusion of the midline thyroid and UB involves pattern-specific degradation of preformed BM and neosynthesis of laminin. Together this suggests that thyroid organogenesis leading to a

composite endocrine gland is regulated by cell-matrix interactions in a distinct spatiotemporal fashion.

OP26

GLOBAL NOTCH PATHWAY PERTURBATIONS AS A NOVEL MODEL OF THYROID DYSGENESIS IN *ZEBRAFISH*

Marelli F[1], Porazzi P[2], Benato F[3], Argenton F[3], Tiso N[3], Persani L[1,4]
[1]IRCCS Istituto Auxologico Italiano, Endocrinology and Metabolic Disorders, Cusano Milanino, Italy, [2]Childen's Hospital of Philadelphia, Philadelphia, United States, [3]University of Padua, Padua, Italy, [4]University of Milan, Milan, Italy

Objectives: The mechanisms underlying the early steps of thyroid development and the pathogenesis of thyroid dysgenesis (TD) are largely unknown. Using the zebrafish model we evaluated the role of Notch pathway in thyroid organogenesis.

Methods: transgenic lines UAS:NICD crossed with hsp70:GAL4 and *mib*-mutants were used to study the overexpression and the impairment of the Notch pathway on thyroid development. Whole-mount in situ hybridization and immunostaining were used to evaluate the expression of thyroid markers and the proliferation/apoptosis rates.

Results: the overexpression of the Notch intracellular domain (NICD), results in thyroid hypoplasia, with the absence *nkx2.1a*-expressing cells (ortholog of human-*NKX2.1*), a reduction of *pax2a* (paralog of human-*PAX8*) expression and a significant decrease of *tg*-positive cells. On the contrary, an impaired Notch signaling resulted in an increased expression of thyroid-related genes. The thyroid hypoplasia in NICD over-expressing embryos vs the thyroid expansion in *mib*-mutants could be explained by two different mechanisms: 1) differences in proliferation rate or apoptosis of thyroid precursors; 2) alterations in the recruitment of thyroid precursor. To investigate the first hypothesis, we carried out phospho-histone H3 (PH3) and activated caspase-3 (AC-3) immunostaining. We did not observe any significant difference in proliferation (PH3 analysis) or apoptosis (AC-3 analysis) in the thyroid cells expressing *pax2a*, neither in NICD over-expressing embryos or *mib*-mutants at 24 hpf.

Conclusions: These results indicate that a conserved Notch signaling defines the thyroid-precursor cell number; alterations of Notch function are sufficient to induce or prevent the development of thyroid cells. We then propose a model in which, when thyroid primordium forms, the Notch signaling is necessary for endodermal precursor differentiation in thyrocytes, limiting the number of cells committed to a thyroid fate. The Notch signal is therefore involved in the early step of thyroid differentiation and its derangements might be involved in the pathogenesis of TD.

OP27

MOLECULAR FUNCTIONS OF THE DNAJC17 PROTEIN, A CANDIDATE MODIFIER FOR CONGENITAL HYPOTHYROIDISM

Ferrandino G[1], Spadaro O[1], Di Campli A[2], Luini A[2], de Franciscis V[3], De Felice M[1,4], Di Lauro R[1,4]
[1]IRGS, Biogem, Ariano Irpino (AV), Italy, [2]Istituto di Biochimica delle proteine del CNR, Napoli, Italy, [3]Istituto di Endocrinologia ed Oncologia Sperimentale del CNR, Napoli, Italy, [4]Università di Napoli Federico II, Dipartimento di Biologia e Patologia Cellulare e Molecolare, Napoli, Italy

The contemporary presence of heterozygous null mutations in Nkx2-1 and Pax8 genes induces hypothyroidism in the B6 mouse strain, while the SV129 strain harboring the same mutations does not develop the disease [1]. Dnajc17 has been identified as a candidate modifier gene responsible for the different susceptibility of the two strains to the development of hypothyroidism, since the amino acid in position 273 is a Phenylalanine in the B6 strain, while it is a tyrosine in SV129 and in all other organism investigated. Furthermore, mice homozygous for null mutation in the DNAjC17 gene die early in embryogenesis, demonstrating that this gene plays essential functions [2]. In order to better characterize the physiological function of Dnajc17, we demonstrated that its RNA binding domain is functional. Synthetic RNA oligonucleotides binding to DNAjc17 have been obtained by SELEX and an RNA sequence motif recognized by the Dnajc17 protein has been identified. We have also knocked-down the gene in Hela cells and demonstrated an effect on the actin cytoskeleton, that appears more organized with a resulting increased adhesion to the substrate and alterations in morphology toward a fibroblast-like appearance. Given the early lethality of the Dnajc17 KO mice, we investigated the expression of the gene in mouse ES cells and demonstrated that it is expressed at noticeable levels. We are setting up a conditional KO strain to study the specific role of this gene in the thyroid gland.

1. Amendola, E., et al., *A mouse model demonstrates a multigenic origin of congenital hypothyroidism.* Endocrinology, 2005. **146**(12): p. 5038–47.
2. Amendola, E., et al., *A locus on mouse chromosome 2 is involved in susceptibility to congenital hypothyroidism and contains an essential gene expressed in thyroid.* Endocrinology, 2010. **151**(4): p. 1948–58.

OP28

INVOLVEMENT OF NITRIC OXIDE IN IODINE DEFICIENCY-INDUCED ANGIOGENESIS: ROLE OF NOS3 AND OF RYANODINE RECEPTORS

Craps J[1], Vanderstraeten J[1], Lobysheva I[2], Balligand J-L[2], Sonveaux P[2], Gilon P[3], Colin IM[1], Gerard A-C[1]
[1]UCL, Pôle de Morphologie, Bruxelles, Belgium, [2]UCL, Pôle de Pharmacologie Expérimentale, Bruxelles, Belgium, [3]UCL, Pôle d'endocrinologie, diabète et nutrition, Bruxelles, Belgium

Iodine deficiency (ID) induces angiogenesis via a ROS-HIF-1α-VEGF pathway. Among ROS, nitric oxide (NO) is a key regulator of vasodilation and angiogenesis. Our goal was to study the involvement NO in ID-induced ROS-HIF-1α-VEGF pathway and the role of Ca^{++} in ID-induced nitric oxide synthase 3 (Nos3) activation. ID was induced in vitro (PCCL-3, FRTL-5, human thyrocytes in primary cultures) and in mice (LID/perchlorate). The role of NO was assessed by L-NAME-induced NOS inhibition and by SNAP (a NO donor). Nos3 phosphorylation on serine1177 (activation, pSNos3) and on threonine495 (inactivation, pTNos3) and HIF-1α protein were detected by WB, VEGF-A mRNA by qRT-PCR, and VEG-A protein by WB and immunohistochemistry. NO production was measured in vitro by EPR (Electron Paramagnetic Resonance) spin trapping. The thyroid blood flow was measured by laser Doppler. In vitro, ryanodine was used to inhibit (10μM) or to activate (1nM) the RYR Ca^{++} channels. Ca^{++} involvement was studied either by BAPTA-AM (intracellular Ca^{++} chelator), or by thapsigargin (a potent inducer of Ca^{++} release), or by measuring the free cytosolic Ca^{++} concentration ($[Ca^{2+}]$c) in perifused cells loaded with fura-PE3. Both in vitro and in vivo, Nos3 was activated by ID (increased pSNos3 and decreased pTNos3) while ID-induced VEGF-A mRNA and protein expression was inhibited by L-NAME. In vitro, ID increased NO release, but L-NAME inhibited ID-induced HIF-1α protein and SNAP increased VEGF-A mRNA. LID/perchlorate-induced thyroid blood flow, VEGF-A mRNA and protein expression was inhibited by L-NAME in vivo. Although no major $[Ca^{2+}]$c change was observed, ryanodine (10μM) decreased ID-induced HIF-1α, pSNos3 and VEGF-A expression, while when used at 1nM, ryanodine increased pSNos3. BAPTA-AM inhibited pSNos3, as well as ID-induced HIF-1α protein, and thapsigargin increased VEGF-A mRNA expression. In conclusion, NO plays a major role in ID-induced angiogenesis through a RYR dependent activation of pNOS3.

OP29

CA^{2+}-BINDING PROTEIN EXPRESSION IN PRIMARY HUMAN THYROCYTES

Lorenz S[1,2], Krohn K[1]
[1]University of Leipzig, Medical Faculty, Interdisciplinary Center for Clinical Research, Leipzig, Germany, [2]University of Leipzig, Medical Faculty, Division of Endocrinology and Nephrology, Leipzig, Germany

We previously described the regulation Ca^{2+}-binding proteins (CaBP) from the S100 and annexin family in FRTL-5 by TSH and their effect on the Ca^{2+}-signal transduction of other GPCRs by Ca^{2+} buffering. We therefore analyzed expression of CaBP (S100A4, S100A6, ANXA2), FOS and TPO in primary human thyrocytes (hThy) derived from autonomous functioning nodules (AFTN), cold thyroid nodules (CTN) and surrounding tissues (ST) in response to TSH and signaling pathways involved in CaBP expression using RT-qPCR and Western blotting. We further examined the impact of CaBP expression on Ca^{2+} signaling in hThy using Ca^{2+} imaging. Finally we studied the Ca^{2+}-

buffering mechanism in HEK293 cells using S100A4 mutants deficient in Ca^{2+} and protein binding. CaBP expression showed a high inter-patient variability in hThy. We found a strong correlation of CaBP expression with FOS expression and the differentiation of individual cultures, determined by the induction of TPO. CaBP expression was upregulated in well differentiated hThy from ST, but not CTN- and AFTN-hThy. CaBP and FOS were coregulated in ST and CTN. The expression of ANXA2 was regulated by PKA and MEK1/2, while S100 proteins are additionally regulated by PI3-K. Forskolin was unable to mimic the effects of TSH. Triiodothyronine induced expression of S100 proteins in a dose-dependent manner. ANXA2 and S100A4 affected resting Ca^{2+} levels in TSH-unstimulated hThy. S100A4 expression increased Ca^{2+} responses to repeated ATP stimulation, while S100A6 increased the first Ca^{2+} response. In TSH-stimulated hThy the effects of CaBP expression were obscured by unknown TSH effects. Analysis of S100A4 mutants showed that the EF-hand and the dimerization interface are necessary for Ca^{2+}-buffering.

CaBP expression in hThy differs between ST, CTN and AFTN and is dependent on the degree of differentiation as well as PKA, PI3-K, MEK and TH-receptor signaling. CaBP expression modulates Ca^{2+} signals from other receptors by protein interactions.

OP30

INTRATHYROID REARRANGEMENT IN SPACE ENVIRONMENT

Albi E[1], Curcio F[2], Spelat R[2], Lazzarini A[2], Lazzarini R[1], Cataldi S[1], Loreti E[3], Ferri I[3], Ambesi-Impiombato FS[2]
[1]Sphingolipid Club - CRABioN Research Centre, Perugia, Italy, [2]University of Udine, Dipartimento di Scienze Mediche e Biologiche, Udine, Italy, [3]University of Perugia, Institute of Pathologic Anatomy and Histology, Perugia, Italy

Accumulating evidence show that in normal thyroid gland there is an intrathyroid regulation among follicular and parafollicular cells. We have previously demonstrated that during space missions, follicular cells in culture released microdomains of membrane constituted by cholesterol and sphingomyelin containing TSHreceptor, thus inducing impairment of TSH-TSHR interaction and consequently lack of response to TSH treatment resulting in the release of low cAMP levels. To study whether the molecular changes of follicular cells could be present also *in vivo,* influencing parafollicular cells and/or vice-versa, we took the opportunity of shifting to *in vivo* research, by joining the "Tissue Sharing" experiment headed by Dr. R. Cancedda, thus participating to the Space Shuttle/ISS 90 days mission inside the Mice Drawer System (MDS) facility developed by the Italian Space Agency. In this longest-duration animal experiment in the history of Space exploration, we have investigated the possible changes of thyroid tissue structure on histological microsections of wild-type (WT) and Pleiotrophin transgenic (PTN-TG) mice stainied with hematoxylin-eosin whereas immunohistochemical analysis was used to highlight calcitonin production. Control animals were maintained in the same conditions in the vivarium of Genoa, Italy. Results showed that WT spaceflight mice presented a more homogenous thyroid tissue structure with ordered follicles, a reduction of interfollicular space with evident loss of parafollicular cells and strong reduction of immunopositivity for calcitonin compared with thyroid gland of control mice. The overexpression of PTN in spaceflight animals did not change the characteristics of follicles present in thyroid gland of PTN-TG maintained in the vivarium but reduced strongly the loss of parafollicular cells observed in WT mice thyroid. In conclusion, we suppose that modifications of follicular cells during space mission, regulated in turn by hypothalamus, are responsible for parafollicular cell changes, possibly playing a key role in osteoporotic damages observed in astronauts after long-term space missions.

OP5 Autoimmunity

OP31

CORTICOSTEROIDS AND RAPAMYCIN INHIBIT TH1 AND TH2 CHEMOKINES SECRETION, INDUCED BY CYTOKINES, IN ORBITAL CELLS OF PATIENTS WITH GRAVES' OPHTHALMOPATHY

Ferrari SM[1], Fallahi P[1], Ruffilli I[1], Di Domenicantonio A[1], Sellari Franceschini S[2], Ferrannini E[1], Antonelli A[1]
[1]University of Pisa, School of Medicine, Department of Internal Medicine, Pisa, Italy, [2]University of Pisa, School of Medicine, Otorhinolaryngology Unit, Pisa, Italy

Objectives: The T helper (Th)1 and Th2 chemokines are secreted under the influence of cytokines in fibroblasts, preadipocytes and myoblasts from orbital cells in Graves' ophthalmopathy (GO). Until now, no study has evaluated the effects of corticosteroids or rapamycin on the secretion of chemokines in GO orbital cells.

Method: The effects of increasing concentrations of corticosteroids or rapamycin, on Th1 [chemokine (C-X-C motif) ligand 10 (CXCL10)] and Th2 [chemokine (C-C motif) ligand 2 (CCL2)] secretion in primary cultures of fibroblasts, preadipocytes and myoblasts from the orbits of GO patients were tested.

Result: In primary cultures of fibroblasts, preadipocytes and myoblasts from GO patients, CXCL10 was undetectable in the supernatant. Interferon(IFN)-gamma dose-dependently induced CXCL10 release, whereas tumor necrosis factor(TNF)-alpha alone had no effect. However, the combination of TNF-alpha and IFN-gamma had a significant synergistic effect on CXCL10 secretion. GO fibroblasts, preadipocytes and myoblasts produced in basal condition low amounts of CCL2. TNF-alpha dose-dependently induced CCL2 release, whereas IFN-gamma alone had no effect. However, the combination of TNF-alpha and IFN-gamma had a significant synergistic effect on CCL2 secretion. Treatment of GO fibroblasts, preadipocytes and myoblasts with increasing concentrations of corticosteroids or rapamycin (in a pharmacological range), added at the time of IFN-gamma and TNF-alpha stimulation, dose-dependently inhibited CXCL10 and CCL2 release.

Conclusion: Corticosteroids or rapamycin, in a pharmacological range, play an inhibitory role both on Th1 (CXCL10) and Th2 (CCL2) chemokines, in GO orbital cells, suggesting the therapeutic effect of these drugs could be exerted, at least in part, through this mechanism.

OP32

OXIDATIVE STRESS OF EYE MUSCULAR CELLS IN GRAVES' OPHTHALMOPATHY IS ASSOCIATED TO DOWN-REGULATION OF CAVEOLIN-1 AND UPREGULATION OF TYPE III-DEIODINASE

Van Regemorter E[1], Van Regemorter V[1], Marique L[1], Senou M[1], de Bournonville M[1], Delacourt V[1], Behets C[1], Lengelé B[1], Brichard S[2], Boschi A[3], Daumerie C[2], Many M-C[1]
[1]UCL, MORF, Bruxelles, Belgium, [2]UCL, Endocrinologie, Bruxelles, Belgium, [3]UCL, Ophthalmology, Bruxelles, Belgium

Oxidative stress, a hallmark of Graves' ophthalmopathy (G0), has been described in orbital fibroblasts. In this study, it was analysed in the muscular cells in relation with the expression of caveolin-1 (Cav-1) and type III-deiodinase (D3). Indeed, Cav-1 is involved in glucose transport and utilization via regulation of Glut-4 translocation. D3, increased in hyperthyroidism, inactivates T4 and T3, lowering the T3 supply to the muscular cells.

Orbital muscles and adipous tissues were obtained from GO patients (n = 5–8) or control patients operated for strabismus or at autopsy (n = 6). They were processed for a morphological analysis and immunohistochemical detection of 4-hydroxynonenal (HNE, a marker of lipid peroxidation), caspase-3 (a marker of apoptosis), Cav-1, Cav-3 and D3. In G0, the orbital muscular cells were dissociated by fibro-adipous tissue and/or infiltration of immune cells. The HNE labeling was strongly increased in muscular cells and adipocytes

from G0 patients, as compared to controls. This was indicative of an oxidative stress, leading to apoptosis of muscular cells, as shown by an increase of caspase-3 labeled nuclei in G0 (15 ± 1%) versus controls (2,7 ± 0.4%). The expression of Cav-1 was low or absent in G0 muscular cells, while its level was unmodified in adipocytes or endothelial cells. No change was observed in the expression of Cav-3, specific of the muscular cells. The expression of D3 was strongly increased in nearly 100% of the muscular cells from G0 patients, as compared to controls, while it was unchanged in adipocytes.

Our morphological study demonstrates that in G0, the muscular cells themselves are the targets of an oxidative stress. This could be due to a reduced supply of glucose, through down regulation of Cav-1, and of T3, through upregulation of D3, glucose and T3 being both essential substrates to maintain the cell homeostasis.

OP33

RELATIONSHIP BETWEEN USE OF IODIZED SALT AND THYROID AUTOIMMUNITY AFTER UNIVERSAL IODINE PROPHYLAXIS: THE 2010 PESCOPAGANO SURVEY

Provenzale MA[1], *Frigeri M*[1], *Puleo L*[1], *Antonangeli L*[1], *Rago T*[1], *Fiore E*[1], *Tonacchera M*[1], *Grasso L*[1], *Pinchera A*[1], *Aghini-Lombardi F*[1], *Vitti P*[1]

[1]University of Pisa, Endocrinology, Pisa, Italy

Objectives: We carried out a survey in a community after iodine prophylaxis to investigate whether the use of iodized salt may affect the prevalence and distribution of thyroid autoimmunity.

Methods: The study group included 1146 subjects who underwent medical exam, thyroid ultrasound, measurement of thyroid hormones, TSH, anti-thyroglobulin (TgAb) and anti-thyroperoxidase (TPOAb) antibodies and urinary iodine excretion (UIE). According to clinical diagnosis subjects were classified as normal (Normals, n=664), or as affected by diffuse/nodular goiter (Goiters, n=293), autoimmune thyroid disease (ATD, n=179) or other thyroid diseases (n=10).

Results: Out of 1146 subjects, 784 (68.4%) declared to use iodized salt every day (IS-users), while 316 (27.6%) never used iodized salt (IS-non-users) and 46 (4.0%) did not answer the question. UIE was significantly higher in IS-users (median 101 µg/L, interquartile range, IR, 62–164 µg/L) than in IS-non-users (median 91 µg/L, IR, 48–126 µg/L, p=0.02). The distribution of thyroid diseases was not significantly different between IS-users and IS-non-users. In IS-users, positive thyroid autoantibodies (TAb) were more frequent than in IS-non-users (168/769, 21.8% vs 47/309, 15.2%, p=0.01), both for TgAb (128/769, 16.6% vs 33/309, 10.7%, p=0.01) and TPOAb (120/769, 15.6% vs 34/309, 11.0%), although in the last case this difference was not statistically significant (p=0.05). Positive TAb were significantly more frequent in IS-users than in IS-non-users in Goiters (25/181, 13.8 vs 3/66, 4.5%, p=0.04), while this difference was not significant in Normals (46/468, 9.8% vs 15/200, 7.5%).

Conclusions: After iodine prophylaxis, UIE is significantly higher in IS-users than in IS-non-users. The use of iodized salt is associated with an increased frequency of TAb, but this relationship is significant only in goitrous and not in normal subjects.

OP34

CHARACTERIZATION OF A NOVEL DETECTION BIOASSAY FOR THYROID BLOCKING ANTIBODY

Li Y[1], *Kim J*[1], *Larrimer A*[1], *Klausen R*[1], *Yu L*[1], *Diana T*[2], *Kahaly GJ*[2], *Olivo PD*[1]

[1]Diagnostic Hybrids, Inc. (A Quidel Company), R&D, Athens, United States, [2]Gutenberg University Medical Center, Thyroid Research Laboratory, Mainz, Germany

Objective: There is no uniform method for detecting thyroid-blocking immunoglobulin (TBI). To address this gap, we developed a TBI bioassay based on a CHO cell line that constitutively expresses a chimeric human TSH receptor and a cAMP-inducible luciferase gene.

Methods: Chimeric TSHR CHO cells were grown at 37°C for 15–18 hours and then treated with bTSH, monoclonal thyroid blocking antibody K1-70, and/or patient serum. After incubation for 3 hours, TBI was measured as a function of luciferase activity relative to bTSH alone and expressed as percent inhibition.

Results: Using 1200+ replicates of 350 control sera and 100+ replicates of low concentrations of K1-70, we found the limits of Blank and Detection of the TBI bioassay to be 30.2% and 43.4%, inhibition, respectively. Intra-assay and inter-assay precision CVs were < 10% and < 15%, respectively. There was no cross-reactivity with glycoproteins at two-fold physiological levels. Using K1-70, the TBI bioassay was nearly 20-fold more sensitive than a TRAb assay (Kronus). The chimeric human TSHR gene and its expression were determined and measured by real-time PCR and RT-PCR. Cell surface expression of the chimeric TSHR, assessed by flow cytometry, demonstrated equivalent binding of the K1-70 and M22 (stimulating) human monoclonal antibodies to the receptor. This result supports the use of chimeric TSHR CHO cells in both thyroid stimulating immunoglobulin (TSI) and TBI bioassays. Protein G was used to demonstrate that the blocking activity was due to IgG. Testing 250+ serum samples, from auto-immune thyroid disease (AITD) patients and controls, revealed four result types: -60 to +40% inhibition (TBI negative); +40–80% inhibition (low positive); +80–100% inhibition (high positive); and ≥60% inhibition (potentially TSI positive).

Conclusion: The new bioassay sensitively, specifically, and reliably detects TBI and TSI. Studies are ongoing to assess the prevalence of TBI in patients with various AITD.

OP35

TGAB OF PATIENTS WITH SUBACUTE THYROIDITIS ARE RESTRICTED TO A MAJOR B CELL EPITOPE

Ricci D[1], *Montanelli L*[1], *Altea MA*[1], *Pucci A*[1], *Pinchera A*[1], *Vitti P*[1], *Latrofa F*[1]

[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

Introduction: TgAb are a common finding in patients with subacute thyroiditis (ST). We evaluated whether the epitope pattern of TgAb that arise in this condition resembles that of autoimmune thyroid disease (AITD) or non-autoimmune thyroid disease (non-AITD).

Methods: Sera were collected from 10 patients with ST, 45 patients with Hashimoto´s thyroiditis (HT) (AITD) and 19 patients with Non Toxic Multinodular Goiter (NTMG) (non-AITD). Serum TgAb binding to Tg was inhibited by a panel of four recombinant human TgAb-Fab, recognizing Tg epitope regions A-D. The ability of single TgAb-Fab to inhibit the binding of serum TgAb to Tg was evaluated in ELISA. Percent of Tg binding inhibition was calculated comparing the binding of serum TgAb in presence of each TgAb-Fab with that in its absence. Results were compared by Kruskall-Wallis and Mann-Whitney tests.

Results: The inhibitions were 56.0±19.0 (median±IQR) (ST), 49.0±32.0 (HT) and 25.0±23.0 (NTMG) by TgAb-FabA, 0.0±14.0 (ST), 28.0±39.0 (HT) and 9.0±16.0 (NTMG) by TgAb-FabB, 6.5±26.0 (ST), 23.0± 32.0 (HT) and 6.5±20.0 (NTMG) by TgAb-FabC and 1.0±8.0 (ST), 12.0±28.0 (HT) and 1.0±15.0(NTMG) by TgAb-FabD. Inhibitions were significantly different in the three groups of patients by all four TgAb-Fab ($p< 0.05$). The levels of inhibition were significantly lower in ST than in HT for TgAb-Fab B, C and D ($p< 0.05$), similar for TgAb-Fab A. At variance, comparing ST with NTMG, the level of inhibition was significantly higher for TgAb-Fab A ($p< 0.05$), similar for TgAb-Fab B, C and D. As expected, the levels of inhibition were higher in HT than in NTMG by all four TgAb-Fab ($p< 0.05$).

Conclusions: TgAb of ST are restricted to a B cell epitope that is immunodominant in both AITD and non-AITD, whereas other epitopes are recognized at a lower level compared with other thyroid diseases.

OP36

RISK FACTORS FOR POST-OPERATIVE DIPLOPIA IN PRIMARY GAZE AFTER REHABILITATIVE ORBITAL DECOMPRESSION FOR GRAVES' ORBITOPATHY

Leo M[1], *Lenzi R*[2], *Marinò M*[1], *Latrofa F*[1], *Sisti E*[1], *Altea MA*[1], *Profilo MA*[1], *Megna L*[3], *Mazzi B*[1], *Pinchera A*[1], *Vitti P*[1], *Marcocci C*[1], *Sellari-Franceschini S*[2], *Rocchi R*[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Unit of Endocrinology, Pisa, Italy, [2]University of Pisa, Department of Neuroscience, Unit of Otolaryngology, Pisa, Italy, [3]University of Pisa, Department of Neuroscience, Unit of Ophthalmology, Pisa, Italy

Patients with moderate-severe Graves' orbitopathy (GO) rather frequently require rehabilitative surgery after medical therapy. Diplopia is the most common side effect of orbital decompression (OD). The aim of this study was to identify risk factors for development of post-operative diplopia in primary gaze and the influence of the surgical approach on this outcome.

Methods: Retrospective evaluation of 247 patients with GO treated with medial and lateral (MLD) or lateral (LD) OD between January 2002 and December 2009.

Results: The overall prevalence of post-operative diplopia in primary gaze was 55/247 (22.3%), with a statistically significant difference ($p< 0.001$) between patients with (36/113, 31.2%) and without (19/134, 14.2%) pre-operative diplopia in secondary gaze. The surgical procedure influenced the outcome in patients without pre-operative diplopia (17.8% after MLD and 0% after LD, $p=0.02$), but not in patients with preoperative diplopia in secondary gaze (33.3% after MLD and 26.1% after LD, $p=0.5$). Overall, proptosis reduction was 5.7±2.2 mm (1–11 mm), after MLD and 4.0±1.6 mm (1–8 mm) after LD ($p< 0.001$). Fifty-one/55 patients with constant, post-operative diplopia in primary gaze after OD underwent squint surgery, which was successful in all but two. Four patients refused squint surgery. Patients were also interviewed for satisfaction in terms of recovery of their appearance and ocular function: more than 85% of patients reported a good to excellent post-operative satisfaction for both items.

Conclusions: Pre-operative diplopia in secondary gaze is a risk factor for the development of diplopia in primary gaze after OD, independently of the surgical approach (MDL versus LD). In absence of diplopia, MDL but not LD seems to be associated with its development in primary gaze. Reduction in proptosis after MLD is greater than that after LD. Most patients were satisfied for the results of both facial appearance and ocular function after OD.

OP6 Thyroid Cell Biology and Cancer

OP37

THE THYROID OXIDATIVE CAPACITY IS ENHANCED BY THE TH2 CYTOKINES, IL-4 AND IL-13, THROUGH INCREASED EXPRESSION OF THE DUAL OXIDASE 2 AND ITS MATURATION FACTOR DUOXA2

De Deken X[1], *Raad H*[1], *Eskalli Z*[1], *Hoste C*[1], *Corvilain B*[1], *Miot F*[1]
[1]Université Libre de Bruxelles, IRIBHM - DUOXLab, Brussels, Belgium

Context: The dual oxidases (DUOX) 1 and 2 constitute the major components of the thyroid H2O2-generating system required for thyroid hormone synthesis. With their maturation factor, DUOXA1 or DUOXA2, they share the same bidirectional promoter allowing co-expression of DUOX/DUOXA in the same tissue. However, the molecular mechanisms regulating their transcription in the human thyroid gland have not been fully characterized.

Objectives: The effects of TSH in addition to the main cytokines involved in Hashimoto thyroiditis (IFN-γ) and Graves's diseases (IL-4/IL-13) have been investigated on the transcriptional regulation of *DUOX* and their corresponding *DUOXA* genes in thyroid cells.

Methods: *DUOX*/*DUOXA* mRNA level was measured by quantitative RT-PCR in human and mouse primo-cultured thyrocytes incubated 48 h with TSH or the Th1/Th2 cytokines. DUOX protein expression along with the amount of H2O2 generated were also evaluated.

Results: No significant induction of *DUOX*/*DUOXA* transcript expression could be measured after TSH treatment except for *DUOX1* which showed a weak (1.5-fold) but significant ($p< 0.01$) induction. Thyrocytes exposed to Th2 cytokines, IL-4 and IL-13, showed up-regulation of *DUOX2* (4.7± 0.8 and 3.9 ± 0.8 fold) and *DUOXA2* (38.6 ± 10.3 and 14.7 ± 3.0 fold) genes. The expression of *DUOX1, DUOXA1* and the main thyroid differentiation markers (*TPO*, *NIS*, *TG* and *TSHr*) was not modified by the Th2 cytokine treatment. *DUOX2*/*DUOXA2* induction was rapid and associated with a significant (10-fold) increase of calcium-stimulated extracellular H2O2 generation. IFN-γ treatment slightly inhibited *DUOX* gene expression and repressed the Th2 cytokine-dependent DUOX2/DUOXA2 expression. Analysis of the IL-4 signaling pathway revealed that the JAK1-STAT6 cascade activated by the IL-4 type 2 receptor is required for DUOX2/DUOXA2 induction.

Conclusions: The present data open new perspectives to better understand the pathophysiology of thyroid autoimmune diseases considering DUOX2-mediated oxidative damages.

OP38

DNA MICROARRAY AND MIRNA ANALYSES REINFORCE THE CLASSIFICATION OF FOLLICULAR THYROID TUMOURS

Jacques C[1], *Guillotin D*[1], *Franc B*[2], *Malthiery Y*[1], *Savagner F*[1]
[1]Inserm U694, Angers, France, [2]Laboratoire d'Anatomopathologie, Hopital A PAré, Boulogne Billancourt, France

Our goal was to search for new molecular markers of the mitochondrial implication in the thyroid tumorigenesis. Using gene expression and miRNA microarrays as well as qPCR analysis, we explored several collections of thyroid samples representing 4 classes of thyroid tumours; benign follicular tumours (FTA), oncocytic variants of follicular tumours (OT), papillary thyroid carcinomas (PTC) and tumours of uncertain malignant potential (TUMP).

Our transcriptomic analysis highlighted disturbances between the control and the tumoral tissues and between tumour types and selected 13 genes relevant to discriminate FTA, OT and PTC. The 13 genes are implicated in the tumorigenesis process (TP53, HOXA9, RUNX1, MYD88, CITED, CCNE1 and IL1A), the mitochondrial metabolism (MRPL14, MRPS2, MRPS28 and COX6A1) and thyroid metabolic pathways (CaMKIINalpha and TPO). The miRNA analysis revealed specific differential expression for each tumour type, in accordance with modulation of gene expression revealed in our transcriptomic analysis.

Our data reinforce the classification of the follicular thyroid tumours presently established by the World Health Organization. We propose a panel of 13 genes and 10 miRNA as new biomarkers for OT, FTA and PTC classes that could serve to reclassify TUMP.

OP39

CAMP MAY NOT ALWAYS BE A PROLIFERATION SIGNAL IN THYROID CANCER CELLS

Grassi ES[1], *Dicitore A*[2], *Borghi MO*[3,4], *Vitale G*[1,2], *Persani L*[1,2]
[1]Università degli studi di Milano, Dipartimento di Scienze Mediche, Milan, Italy, [2]Istituto Auxologico Italiano, Laboratory of Endocrine and Metabolic Research, Milan, Italy, [3]Istituto Auxologico Italiano, Laboratory of Immunology, Milan, Italy, [4]Università degli studi di Milano, Dipartimento di Medicina Interna, Milan, Italy

Objectives: Poorly differentiated (PDTCs) and anaplastic (ATCs) thyroid carcinomas are a small subset of thyroid tumors associated with poor prognosis accounting for a significant part of the morbidity and mortality of this disease. Site-selective cAMP-analogs inhibit the growth of a wide variety of scarcely differentiated neoplasia and are interesting candidates for thyroid cancer therapy.

Methods: In this work we studied the effects of two cAMP-analogs based treatments, 8-Cl-cAMP and the association of 8-PIP-cAMP and 8-HA-cAMP (PKA I-selective), on a panel of 9 cell lines representative of thyroid cancer spectrum, from well-differentiated to anaplastic ones. We evaluated the effects

on cell growth and investigated the mechanism of action by the study of principal intracellular signaling pathways.

Results: 8-Cl-cAMP had a significative anti-proliferative effect on all the cell lines (50–80% growth inhibition) while PKA I-analogs showed a preferential action on the less differentiated ones (40–75% growth inhibition).

Further studies have been performed on two cell lines (SW579, HTC/C3) representative of PDTCs. Results show that:

- 8-Cl-cAMP causes significative variations in cell-cycle progression and induces apoptosis as determined by FACS and Annexin-V/propidium-iodide staining while PKA I-analogs have only slight effects on cell-cycle without apoptosis induction.
- Both therapies are able to significatively influence intracellular signaling pathways. First of all both treatments reduce the activation level of Akt, one of the principal regulator of cell proliferation; moreover preliminary data show an involvement of lipid peroxidation as well as p38 pathway in cAMP-analogs antiproliferative action. Furthermore PKA I-analogs reduce ERK1/2 activation in SW579 cell line but not in the BRAFV600E carrier HTC/C3.

Conclusions: This results show that cAMP-analogs are able to significantly regulate principal signaling pathways involved in cell proliferation, acting at different levels. In conclusion, 8-Cl-cAMP can represent a wide-spectrum proapoptotic anticancer drug, while PKA I-analogs seem to preferentially inhibit scarcely differentiated cells.

OP40

GENOME-WIDE LINKAGE ANALYSIS TO IDENTIFY GENES INVOLVED IN THYROID GROWTH AND NEOPLASIA

Bakhsh ADQ[1,2], Hamshere M[3], Gregory J[4], Kirov G[3], Williams D[5], Ludgate M[1]

[1]Cardiff University, Institute of Molecular & Experimental Medicine, Cardiff, United Kingdom, [2]Institute of Molecular & Experimental Medicine, Endocrinology, Cardiff, United Kingdom, [3]Cardiff University, Psychological Medicine & Neurology, Cardiff, United Kingdom, [4]Institute of Molecular & Experimental Medicine, Department of Child Health, Cardiff, United Kingdom, [5]Cambridge University, Strangeways Laboratory, Cambridge, United Kingdom

Objectives: Nodular thyroid disease, prevalence 2–6%, is a risk factor for thyroid cancer. In a family with euthyroid multinodular (MNG) of adolescent onset, progressing to papillary cancer, candidate genes were eliminated by sequencing (PAX8, NIS) or microsatellite analysis (MNG 14q/Xp/3q; familial non-medullary thyroid cancer 19p/2q/1q) suggesting a novel cause. Our aim was to identify gene changes underlying the pathology using genome wide linkage analysis.

Methods: Genomic DNA from 18 individuals (8 affected) was hybridized to Affymetrix GenechipTM Human Mapping 10K 2.0 Arrays. Results were analysed with Affymetrix GDAS 3.0 software to produce a call rate of ~92%. Extensive quality control steps were performed (PLINK, GRR etc) prior to linkage analysis, which used Merlin software in a multipoint dominant disease model.

Results: A dominant LOD score of 2.16 was obtained on 12 Mega base pairs (Mbp) on chromosome 20 (comprises 53 genes), based on a disease model with 0.01 allele frequency, 50% penetrance for males and 90% for females, both age >12. The same region gave a multipoint nonparametric LOD score of 3.01. Haplotype analysis was employed to identify a possible disease locus and reduced the region of interest to 3.7 Mbp, which encodes 10 genes. Analysis of copy number variation in an affected individual (Illumina Human 660W-Quad) revealed an intronic deletion of ~1000 bp in one copy of a gene in the region of interest. The deletion is present in about 1% of 280 Caucasians and has not been detected in >500 people of other ethnicities, suggesting that it is rare.

Conclusions: We have identified a novel genetic locus for goitre and PTC. Future studies using RNA/protein from thyroids of affected family members will determine whether the deletion produces exon skipping or affects gene expression or function In depth sequencing will also identify other possible variations of significance to pathogenesis.

OP41

METABOLIC ENGINEERING OF IODINE CONTENT IN ARABIDOPSIS

Landini M[1], Tonacchera M[2], Gonzali S[1], Agretti P[3], Dimida A[4], Vitti P[3], Alpi A[5], Pinchera A[4], Perata P[1]

[1]Scuola S Anna Pisa, Plant Lab, Pisa, Italy, [2]University of Pisa, School of Medicine, Dep of Endocrinology, Pisa, Italy, [3]University of Pisa, School of Medicine, Pisa, Italy, [4]University of Pisa, Pisa, Italy, [5]University of Pisa, Dep Crop Plant Biology, Pisa, Italy

Objective: Iodine deficiency affects two billion people worldwide. Iodized salt is the most common approach for iodine supplementation. Since iodine salts may be volatile, losses during storage and food cooking may occur. The sodium-iodide symporter (NIS) drives iodide across the basolateral membrane of the thyrocytes. While essential for human health, iodine function in plants is unknown. We attempted to increase iodine content in Arabidopsis thaliana plants by overexpressing the human NIS protein.

Methods: Whole coding sequence of *human NIS* (*hNIS*) was obtained by PCR from the plasmid pcDNA3-hNIS2. The amplified *hNIS* was inserted in a genetic cassette. For plant transformation, the pBIN-*hNIS* binary vector was used. The plasmid was introduced into the *Agrobacterium tumefaciens* GV3101 strain.

Results: Several transgenic lines were obtained. Line 16 was selected. Trace amount of ^{125}I as NaI was fed to wild type (WT) and to NIS transgenic plants, kept at different temperatures. NIS plants accumulated more radioactive iodine especially when plants were kept at 30°C. Nitrate is an essential nutrient for plants, but can negatively affect the activity of NIS. While decreasing nitrate level from 5 to 0.5 mM had a negative impact on the basal level of ^{125}I uptake in WT plants, it increased iodine content in NIS plants, in line with its negative effect on NIS transporter. We also found that HOL-1, a halide methyltransferase, determined iodine volatilization and the inability of Arabidopsis plants to retain iodine. NIS plants were then crossed with hol-1 mutants and an increased iodine accumulation was obtained.

Conclusions: An increased iodine uptake, as obtained by hNIS overexpression, can result in a final higher iodine content only if volatilization is removed. Biofortification of crops with iodine would represent a cost-effective way to control its deficiency, since iodine in food stuffs is readily bioavailable (up to 99%) and assimilated.

OP42

RNA-SEQ PROVIDES ISOFORM SPECIFIC MIRNA EXPRESSION DATA WHICH REQUIRE ISOFORM SPECIFIC QPCR VERIFICATION

Stokowy T[1,2], Swierniak M[1], Wojtas B[1], Danch M[2], Krohn K[3], Fujarewicz K[2], Jarzab B[1], Paschke R[4], Eszlinger M[4]

[1]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Nuclear Medicine and Endocrine Oncology Department, Gliwice, Poland, [2]Silesian University of Technology, Institute of Automatic Control, Gliwice, Poland, [3]University of Leipzig, Interdisziplinares Zentrum fur Klinische Forschung, Leipzig, Germany, [4]University of Leipzig, Klinik fur Endokrinologie und Nephrologie, Leipzig, Germany

About 20% of thyroid FNAC show an indeterminate result, which does not allow a discrimination of malignant and benign follicular thyroid tumors. Four recently published papers (Weber et al., Nikiforova et al., Rossing et al. and Kitano et al.) proposed miRNA markers to improve the diagnosis of follicular thyroid cancer (FTC) and follicular thyroid adenoma (FA). Limited overlap between papers results let us to question if the suggested methodology is appropriate for thyroid tumor markers selection.

Therefore, the aim of this study was to evaluate FTC and FA for more specific miRNA markers by next generation sequencing (NGS) to better discriminate indeterminate results. 20 samples (10 FTC and 10 FA) were analyzed with small RNA Illumina high throughput sequencing and microarrays. Counting of small RNA isoforms in RNA-Seq data and Reads Per Million normalization were performed with implemented Perl software. The sequences present in at least half of the 20 samples were kept for further analysis.

There was low correlation between NGS and microarray results. In addition, qPCR data also showed lack of correlation compared to NGS results. However, reanalysis of the NGS data revealed the existence of closely related

miR family isoforms. Adding the NGS results of the miR isoforms for the 6 miR families studied in detail (with high, medium and low expression) did show correlation of NGS data with qPCR data for these families.

Microarray and conventional miRNA qPCR expression analysis apparently provide expression data for miRNA families, whereas NGS miRNA expression analysis provides miRNA isoform specific miRNA expression data. Therefore, NGS miRNA expression profiling provides a higher specificity due to the detection of miRNA isoforms but requires isoform specific qPCR verification strategies.

OP7 Pregnancy and Iodine

OP43

THYROGLOBULIN ANTIBODIES: AN ADDED VALUE IN THE DETECTION OF THYROID AUTOIMMUNITY IN FEMALE PATIENTS OF INFERTILE COUPLES?

Unuane D[1], *Haentjens P*[1], *Schiettecatte J*[1], *Tournaye H*[1], *Velkeniers B*[1], *Poppe K*[1]
[1]University Hospital UZ-Brussel, Free University Brussels (VUB), Endocrinology, Centre for Reproductive Medicine and Centre for Outcomes Research and Laboratory for Experimental Surgery, Brussels, Belgium

Objective: To determine the prevalence of thyroid autoimmunity (TAI), assessed by the presence of anti-thyroglobulin antibodies (Tg-Abs) and thyroid peroxidase antibodies (TPO-Abs), in women of infertile couples.

Methods: Prospective cohort study. All women of couples consulting for infertility were screened for the presence of Tg-Abs and TPO-Abs. The cause of infertility, thyroid function, BMI, and smoking habits were systematically recorded.

Results: Of a total of 992 women (mean age ± SD: 32 ± 5 years), 16% (163/992) were TAI +. The distribution of antibodies was as follows: 5% had only positive Tg-Abs (48/992); 4% only TPO-Abs (41/992) and 8% had both TPO- and Tg-Abs (74/992). Table 1 lists thyroid function (serum TSH, FT4), age, and BMI in 976 women with - and without TAI, after exclusion of 16 patients treated with L-Thyroxine. Compared to the TAI- group, TSH values were significantly higher in the TAI+ group and in the subgroups with only positive Tg-Abs and with positive Tg- and TPO-Abs. The percentage of women with a serum TSH value between 2.5–4.2 mIU/L or > 4.2 mIU/L was significantly higher in the TAI + group, compared to the TAI- group (21.3% versus 12.2% and 8% versus 1.1%; p< 0.001). The causes of infertility, BMI, and smoking habits were comparable in TAI+ and TAI- women.

Conclusions: This prospective cohort study confirms and extends our knowledge on the high prevalence of TAI in women of infertile couples. Measuring only TPO-Abs fails to detect 5% of TAI+ women, i.e. those with only Tg-Abs, who also have a higher serum TSH and may thus be at risk to develop thyroid dysfunction during subsequent pregnancy.

Table 1 (for Abstract OP43).

	All patients n=976	TAI – n=826	TAI + n=150	Only Tg Abs+ n=47	Only TPO Abs+ n=40	TPO & Tg Abs+ n=63
TSH (mIU/L) *	1.49 [1.02]	1.47 [0.94]	1.83 [1.44] °	1.90 [0.85] °	1.38 [1.56]	1.86 [1.59] ^
fT4 (ng/L) *	11.8 [1.9]	11.8 [1.9]	11.7 [2.2]	11.8 [2.1]	11.5 [2.7]	11.8 [2.1]
Age (years) #	32.5 ± 5.6	32.6 ± 5.6	32.4 ± 5.5	31.7 ± 5.4	34.1 ± 6.1	31.8 ± 5.0
BMI (kg/m²) #	24.6 ± 5.2	24.6 ± 5.3	24.4 ± 5.0	25.6 ± 4.8	24.5 ± 5.0	23.4 ± 5.0

Legend to Table1:
* median [IQR]
# mean ± SD
°p < 0.001 versus TAI -
^p = 0.012 versus TAI -

OP44

THYROID HORMONE LEVELS IN NORMAL PREGNANCY ARE ASSOCIATED WITH ALTERED METABOLIC PARAMETERS

Knight B[1,2], *Shields B*[1], *Hattersley A*[1,2], *Vaidya. B*[3,4]
[1]PCMD (University of Exeter), Peninsula NIHR Clinical Research Facility, Exeter, United Kingdom, [2]RD&E NHS Foundation Trust, Exeter, United Kingdom, [3]RD&E NHS Foundation Trust, Dept of Diabetes and Endocrinology, Exeter, United Kingdom, [4]PCMD (University of Exeter), Exeter, United Kingdom

Objectives: In euthyroid healthy adults thyroid hormones are known to be associated with obesity, insulin resistance, glycaemia, and dyslipidaemia. Little is known of similar associations in pregnancy. We aimed to assess the associations between thyroid function and these features of the metabolic syndrome in non-diabetic Caucasian pregnancies.

Methods: Detailed anthropometry and fasting biochemistry was available on 965 euthyroid participants of the Exeter Family Study of Childhood Health. Correlations were assessed between TSH, FT4, FT3, and FT3/FT4 Ratio and maternal BMI, sum of skinfolds, fasting plasma glucose (FPG), HbA1c, fasting lipid profile and insulin resistance (measured by HOMA -R). Bonferroni adjustments were made to p- values to account for multiple testing.

Results: Participants had mean (SD): age 30.1(5.3) years and BMI 28.0(4.6) kg/m^2. TSH was not correlated with any of the measures. FT4 was negatively associated with: obesity (BMI: r= -0.23, sum of skinfolds r= -0.23 p< 0.001 for both), glycaemia (FPG: r= -0.13, HbA1C: r=-0.14, p< 0.01 for both), insulin resistance (FPI: r=-0.16, HOMA -R: r=-0.16, p< 0.001 for both) and triglycerides(r=-0.17, p< 0.001) but not HDL or LDL cholesterol. FT3/FT4 ratio was positively associated with obesity (BMI: r=0.41, sum of skinfolds: r=0.37, p< 0.0001 for both), glycaemia (FPG: r= 0.24, HbA1C: r=0.21, p< 0.0001 for both), insulin resistance (FPI: r=0.34, HOMA -R: r=0.34, p< 0.0001 for both) and triglycerides (r=0.2, p< 0.001). The T3/T4 ratio was not associated with HDL and LDL cholesterol. Multivariate regression analysis identified: FT4 independently associated with BMI(β= -0.05, p= 0.001), HbA1c (β= -0.39, p=0.02) and triglycerides(β= -0.20, but not HOMA-R(β= -2.32, p= 0.7), and FT3/FT4 ratio independently associated with BMI(β= 0.004, p< 0.001), HbA1c(β= 0.015, p=0.001) and triglycerides(β=0.005, p=0.0.049) but not HOMA-R(β= 0.38, p= 0.06).

Conclusion: Decreasing FT4 and increasing FT3/FT4 Ratio in pregnancy is associated with increased obesity, triglycerides and glycaemia in singleton, non-diabetic pregnant Caucasian women.

OP45

THE TYPE 2 DEIODINASE THR92ALA POLYMORPHISM SEEMS TO BE A MARKER OF INCREASED INSULIN RESISTANCE DURING PREGNANCY: A GENETIC ASSOCIATION STUDY

Dora JM[1], Wajner S[1], Costa JD[1], Pinto Ribeiro RV[1], Lopes MG[1], da Silva AV[1], Leiria L[1], Crispim D[1], Maia AL[1]
[1]Hospital de Clínicas de Porto Alegre, Endocrine Division, Porto Alegre, Brazil

Background: The type 2 deiodinase (D2) activates thyroxine into triiodothyronine, playing a key role for local thyroid hormone regulation in peripheral tissues. The D2 enzyme is expressed in the placenta and might interfere in fetal-maternal thyroid hormone homeostasis. Previous studies have shown that a D2 polymorphism (Thr92Ala) is associated with reduced D2 activity, increased insulin resistance and type 2 diabetes risk.

Objective: To evaluate whether the D2 Thr92Ala polymorphism is associated with disrupted placental D2 activity, and whether it affects glycemic control and gestational outcomes.

Methods: Consecutive singleton pregnant patients, 18–45 year-old, were invited to participate. All participants underwent genotyping of the D2 Thr92Ala polymorphism. Placental sample biopsies were obtained at obstetrical delivery, and assayed for D2 mRNA and activity levels. Glucose homeostasis, thyroid function and gestational outcomes were evaluated.

Results: A total of 233 patients were included. Clinical and laboratorial baseline characteristics were similar among D2 genotype groups. No differences were observed on D2 placental mRNA levels, but the 92Ala genotype displayed decreased placental activity (0.35±0.15 vs 1.96±1.02 fmol/mg. protein/min., for Ala/Ala vs Thr/Ala-Thr/Thr genotypes, respectively; $p< 0.001$). Thyroid hormones and maternal fasting glucose did not differ among D2 Thr92Ala genotypes. However, those with the Ala/Ala genotype displayed a tendency towards increased 2-hour glucose at the 75g-OGTT as compared to Thr/Ala-Thr/Thr patients (115±31 vs 104±26 mg/dL, $p=0.07$). There were no differences on gestational outcomes.

Conclusions: Placental D2 activity is markedly reduced in pregnant patients harboring the D2 Ala92Ala genotype. Moreover, the D2 Thr92Ala polymorphism seems to be a marker of increased insulin resistance during pregnancy, a finding that needs to be confirmed in a larger sample of patients. (FIPE, CNPq)

OP46

IODINE-CONTAINING MULTIVITAMINS FAIL TO CORRECT IODINE DEFICIENCY IN BELGIAN PREGNANT WOMEN

Vandevijvere S[1], Amsalkhir S[2], Mourri Bensouda A[2], Van Oyen H[1], Moreno-Reyes R[2]
[1]Scientific Institute of Public Health, Department of Public Health and Surveillance, Brussels, Belgium, [2]Hôpital Erasme, Université Libre de Bruxelles, Department of Nuclear Medicine, Brussels, Belgium

Introduction: Pregnancy induces profound changes in thyroid function and iodine metabolism leading to thyroid stimulation. Low iodine intake during pregnancy may cause thyroid dysfunction in pregnant women and their newborn.

Objective: To determine iodine status among Belgian pregnant women during the first and third trimester of pregnancy and to asses the determinants of iodine status one year after the introduction of bread fortification with iodised salt.

Methods: Women in the first and third trimester of pregnancy were selected according to a multi-stage proportionate-to-size stratified sampling design. Urine samples were collected and a general questionnaire was completed face-to-face with the study nurse. Median urinary iodine concentration (UIC) in µg/L and in µg per g creatinine were determined.

Results: The median UIC among the pregnant women (n=1311) was 124.1 µg/L and 122.6 µg/g Cr when corrected by urinary creatinine. The median UIC in the first trimester (118.3 µg/L) was significantly lower than in third trimester (131.0 µg/L) but significantly higher than among women of child-bearing age (84.8 µg/L). Intake of iodine-containing supplements was reported by 60.8% of the women and 57.4% of the women took this supplement daily. The risk of iodine deficiency was significantly higher in younger women, in women not taking iodine-containing supplements, in women with low consumption of dairy products and during autumn. Pregnant women with higher BMI had a higher risk of iodine deficiency but the risk was lower in women who reported alcohol consumption during pregnancy.

Conclusion: The median UIC during pregnancy indicates iodine deficiency in Belgium. The low iodine intake in women of child-bearing age precludes the correction of iodine deficiency in pregnant women supplemented with multivitamins containing 150 µg of iodine as currently recommended in Belgium.

OP47

GLOBAL IODINE STATUS IN 2011 AND TRENDS OVER THE PAST DECADE

Andersson M[1], Karumbunathan V[1], Zimmermann MB[1]
[1]Swiss Federal Institute of Technology (ETH) Zürich, Department of Health Sciences and Technology (D-HEST), Zurich, Switzerland

Salt iodization has been introduced in many countries to control iodine deficiency. Our aim was to assess global and regional iodine status as of 2011 and compare it to previous WHO estimates from 2003 and 2007. Using the network of national focal points of the International Council for the Control of Iodine Deficiency Disorders as well as a literature search, we complied new national data on UIC to add to existing data in the WHO VMNIS Micronutrients Database. The most recent data on urinary iodine concentrations (UIC), primarily national data in school-age children (SAC), were analyzed. The median UIC was used to classify national iodine status and the UIC distribution to estimate the number of individuals with low iodine intakes by severity categories. Survey data on UIC cover 96.1% of the world's population of SAC, and since 2007, new national data are available for 58 countries including Canada, the United Kingdom, the US and Pakistan. At the national level, there has been major progress: from 2003 to 2011: the number of iodine-deficient countries decreased from 54 to 32 and the number of countries with adequate iodine intake increased from 67 to 105. However, globally, 29.8% (95% CI = 29.4, 30.1) of SAC (241 million) are estimated to have insufficient iodine intakes. Sharp regional differences persist: South-East Asia has the largest number of SAC with low iodine intakes (76 million) and there has been little progress in Africa where 39% (58 million) have inadequate iodine intakes. In summary, while iodine nutrition has been improving since 2003, global progress may be slowing. Intervention programs need to be extended to reach the nearly one-third of the global population that still has inadequate iodine intakes.

OP48

TIROKID STUDY: STATUS OF IODINE NUTRITION OF SPANISH INFANTS

Vila L[1], Donnay S[2], Arena J[3], Arrizabalaga JJ[4], Pîneda J[5], Guzmán A[6], Luengo LM[7], Villar A[8], Bandrés O[9], Muñoz Z[10], Guerrero E[11], Moll G[12], Vich F[12], Muñoz JA[13], Riestra M[14], Menéndez E[14], Beato P[7], Aguirre M[15], Santiago P[16], Aranda J[17], Torres Y[1], Gentil A[18], Serra-Prat M[19], Iodine Deficiency and Thyroid Disfunction group (SEEN)
[1]Hospital Moisès Broggi, Endocrinology and Nutrition, Sant Joan Despí, Spain, [2]Fundation Hospital Alcorcón, Endocrinology and Nutrition, Alcorcón, Spain, [3]Hospital Universitario Donostia, Neonatology, San Sebastián, Spain, [4]Hospital Txagorritxu, Endocrinology and Nutrition, Vitoria, Spain, [5]Hospital Garcia Orcoyen, Endocrinology and Nutrition, Estella, Spain, [6]Complejo Asistencial de Ávila, Endocrinology and Nutrition, Ávila, Spain, [7]Hospital Universitario Infanta Cristina, Endocrinology and Nutrition, Badajoz, Spain, [8]Hospital Clínico, Endocrinology and Nutrition, Valladolid, Spain, [9]Hospital Royo Villanova, Endocrinology and Nutrition, Zaragoza, Spain, [10]Centro de Salud Arisa, Calatayud, Spain, [11]Hospital Río Carrión, Endocrinology and Nutrition, Palencia, Spain, [12]Hospital de Inca, Endocrinology and Nutrition, Inca, Spain, [13]ICS, ABS, Seu d'Urgell, Spain, [14]Hospital Central de Asturias, Endocrinology and Nutrition, Oviedo, Spain, [15]Hospital General, Valladolid, Spain, [16]Complejo Hospitalario, Endocrinology and Nutrition, Jaén, Spain, [17]Hospital Virgen de la Luz, Cuenca, Spain, [18]Hospital Universitario Virgen de la Macarena, Endocrinology and Nutrition, Sevilla, Spain, [19]Hopital de Mataró, Research Unit, Barcelona, Spain

Introduction: Iodine deficiency (ID) is associated with psychomotor disorders and intellectual disabilities. ID has been endemic in several Spanish

regions. Studies have been conducted locally or in different regions but to date, there have been no studies which have evaluated globally the status of iodine nutrition on Spanish infants.

Objectives: 1/ To assess iodine nutrition status and 2/ To estimate thyroid dysfunction prevalence in Spanish school population.

Methods: Multicenter, observational, transversal study in Spanish school population aged 6–7 years. Multistage, stratified, random sampling according to Autonomous Regions and type of population. Urine iodine (UI) was measured using Benotti method and the TSH levels using Whatman 903 filter paper (normal range 0.4- 4.0 mcU/L).

Results: A total of 1,981 schoolchildren were evaluated (Andalusia, Aragon, Asturias, Balearic Islands, Castilla La Mancha and Castilla León, Catalonia, Madrid, Navarra, Basque Country and Extremadura). UI median was 173 mcg/L(min 5.5 - max. 605 mcg/L), < 100 mcg/L was shown in 17.9% of the population, < 50 mcg/L in 4.3% and >300 mcg/L in 10.5%. Prevalence of iodized salt (IS) consumption was 69.8%. IS and daily consumption of 2 or more glasses of milk were associated with a higher median of UI, respectively: 180.3 vs 157.7mcg/L, p< 0.001 and 181.9 vs 159.5mcg/L, p< 0.001). The prevalence of TSH < 0.4 mcU/L was 1% and the prevalence of TSH >4.0 mcU/L was 6.6%. It has not been detected any association between urine iodine concentration and TSH levels.

Conclusions: Ours results show a good iodine nutritional status within the studied population, supporting a significant change in the historical iodine deficiency in Spain. However, IS consumption does not reach the 90% recommendation. Milk consumption has contributed to these results. A high prevalence of TSH>4 mcU/L has been observed which may require further confirmation. (Supported by Merck-Serono)

OP49

BREAD FORTIFICATION WITH IODISED SALT CORRECTS IODINE DEFICIENCY IN SCHOOL-AGED CHILDREN BUT NOT IN THEIR MOTHERS: A NATIONAL SURVEY IN BELGIUM

Moreno-Reyes R[1], Mourri Bensouda A[1], Amsalkhir S[1], Avni F[2], Van Oyen H[3], Vandevijvere S[3]

[1]Hôpital Erasme, Université Libre de Bruxelles, Department of Nuclear Medicine, Brussels, Belgium, [2]Höpital Erasme, Université Libre de Bruxelles, Department of Radiology, Brussels, Belgium, [3]Scientific Institute of Public Health, Department of Public Health and Surveillance, Brussels, Belgium

Introduction: Mild iodine deficiency (MID) is a public health problem in Belgium, therefore, an agreement was signed in 2009 between the bakery sector and the Ministry of Health, to fortify bread with iodised salt. Median urinary iodine concentrations (UIC) in school-aged children is recommended for the evaluation of iodine status in the population although food habits of children may differ from those of adults.

Objective: To evaluated iodine status of Belgian school children aged 6–12 years after the introduction of bread fortification with iodised salt. In addition, we investigated whether the median UIC in school-aged children was an adequate surrogate of iodine status of their mothers.

Methods: We visited 60 schools selected from across the country in a van equipped with an ultrasound device. Thyroid volume of children was measured by ultrasound, a household salt sample and a urine sample, from the children and their mothers were collected.

Results: Median UIC in children was 113.1µg/L and 84.4 µg/L among their mothers. The median UIC in school-aged children was lower in the south than in the north of Belgium (p< 0.001) and was higher in boys than in girls (p< 0.001). The percentage of children with goitre was 7.2%. Of the 904 salt samples received, 63.2% did not contain iodine.

Conclusion: Voluntary fortification of bread with iodised salt corrects iodine deficiency in Belgian school-aged children but not in their mothers. Our findings suggest that the median UIC in school-aged children may not be an accurate surrogate of adults' iodine status. Therefore, monitoring iodine status should not be limited to school-aged children as currently recommended but should be extended to women of childbearing age.

OP50

PREDICTORS OF CHANGE IN SERUM TSH AFTER IODINE FORTIFICATION: AN 11 YR FOLLOW-UP OF THE DANTHYR STUDY

Bjergved L[1,2], Jørgensen T[2,3], Perrild H[1], Laurberg P[4,5], Ovesen L[6], Rasmussen LB[7], Knudsen N[1]

[1]Bispebjerg University Hospital, Department of Endocrinology and Gastroenterology, Copenhagen, Denmark, [2]Research Centre for Prevention and Health, The Capital region of Denmark, Glostrup, Denmark, [3]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [4]Aalborg Hospital, Aarhus University Hospital, Department of Endocrinology and Medicine, Aalborg, Denmark, [5]Faculty of Medicine, Aalborg University, Aalborg, Denmark, [6]Slagelse Hospital, Department of Gastroenterology, Slagelse, Denmark, [7]National Food Institute, Technical University of Denmark, Department of Nutrition, Søborg, Denmark

Objective: The level of iodine intake influences the occurrence and the pattern of thyroid diseases. Few data are, however, available on the effect of iodine fortification on the individual development in thyroid function in a population. The aim of the study was to evaluate changes in thyroid function after iodine fortification and to identify predictors for changes in serum thyrotropin (TSH).

Methods: A longitudinal population-based study, the DanThyr C1 cohort examined at baseline (1997–98) and re-examined 11 yr later. The nationwide mandatory program for iodization of salt was initiated in 2000. Included in the analyses were a total of 2,203 individuals, living in two areas with different levels of iodine intake at baseline, with measurement of TSH, no prior thyroid disease, and who participated in the follow-up examination.

Results: During 11 yr follow-up, mean TSH increased significantly (1.27 mU/L (95% CI,1.23–1.30) to 1.38 mU/L (CI,1.34–1.43), p< 0.001). The most pronounced increase was observed in the area with the highest iodine intake (1.30 mU/L (CI,1.25–1.35) to 1.49 mU/L (CI,1.43–1.55), p< 0.001), whereas the increase was not significant in the low iodine intake area (1.24 (CI,1.19–1.29) to 1.28 (CI,1.23–1.34), p=0.06). Change in TSH was positively associated with presence of TPO-Ab at baseline (p< 0.001), and negatively associated with baseline thyroid enlargement (p< 0.001), multiple nodules (p< 0.001) and with living in the area with the lowest iodine intake (p< 0.001). No significant association was found between change in TSH and familial disposition (p=0.93), hypoechogenicity at ultrasonography (p=0.83) or change in smoking habits (p=0.18).

Conclusions: Even small differences in the level of iodine intake between otherwise comparable populations are associated with considerable differences in TSH change at 11 yr follow-up. Multinodular goiter predicted a less pronounced TSH increase during follow-up, which may be explained by iodine-induced hyperthyroidism, and increasing degrees of autonomy in multinodular goitres.

OP8 Thyroid Cancer Basic

OP51

IDENTIFICATION OF NEW INHIBITORS OF RET RECEPTOR TYROSINE KINASE

Moccia M[1], Guida T[1], Gray N[2], Liu Q[2], Carlomagno F[1], Santoro M[1]

[1]University of Naples, Federico II, Istituto di Endocrinologia ed Oncologia Sperimentale del CNR/Dipartimento di Biologia e Patologia Cellulare e Molecolare "L. Califano", Facoltà di Medicina e Chirurgia, Naples, Italy, [2]Dana Farber Cancer Institute, Department of Cancer Biology, Harvard Medical School, Department of Biological Chemistry and Molecular Pharmacology, Boston Massachusetts, United States

Germline and somatic point mutations of RET receptor tyrosine kinase cause multiple endocrine neoplasia (MEN) type 2 syndromes and sporadic medullary thyroid carcinoma (MTC). Moreover, RET gene rearrangements are associated to papillary thyroid carcinoma (PTC). Recently Vandetanib (ZD6474), a multiple kinase inhibitor (KI) targeting RET, has been approved for MTC treatment. We tested 20 novel KIs with different structure and speci-

ficity for their ability to inhibit RET activity in NIH3T3 fibroblasts expressing RET C634R and M918T oncogenic mutants. Among them, we selected three compounds, ALW-II-41-27, HG-6-63-01 and XMD15-44, that were able to significantly reduce RET phosphorylation *in vivo* at 10 nM dose. These three compounds were able to inhibit also RET E768D, L790F, Y791F, S891A and V804M mutants, while RET alleles carrying V804L and A883F mutations were partially resistant. Consistently, ALW-II-41-27, HG-6-63-01 and XMD15-44 reduced the proliferation of RAT C634R and M918T cells with a half maximal inhibitory concentration (IC50) of less than 50 nM, while they were not effective on parental RAT1 cells (IC50 >200nM). The three compounds inhibited RET activity and signaling in human cell lines (TT, MZ-CRC-1 and TPC1) carrying oncogenic RET alleles (C634W, M918T and RET/PTC1, respectively) and were able to block the growth of TT and MZ-CRC-1 cells with an IC50 of 1–5 nM and of TPC1 cells with an IC50 of 10–50 nM. Proliferation of non tumoral human thyroid follicular cells (Nthy-ori 3-1) growth was virtually unaffected (IC50 350–1000 nM). In conclusion, ALW-II-41-27, HG-6-63-01 and XMD15-44 hold promise for the treatment of human cancers sustaining oncogenic activation of RET.

OP52

3D CULTURE OF RECONSTITUTED THYROID FOLLICLES FOR EX VIVO EVALUATION OF CANDIDATE DRUGS INTERFERING WITH CELL MIGRATION: A POTENTIAL TUMOR INVASION ASSAY

Ingeson Carlsson C[1], *Nilsson M*[1]
[1]Sahlgrenska Cancer Center, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Objectives: Three-dimensional (3D) culture systems recapitulate critical features of epithelial organ morphogenesis not possible to investigate in conventional 2D culture. Moreover, 3D-grown cancer cells are more radio- and chemoresistant than in 2D conditions. 3D culture is thus preferable for ex vivo exploration of candidate drug effects aiming to interfere with morphogenetic events as invasiveness implicated in tumor progression. To validate this further we investigated the ability of MAPK and PI3K inhibitors to block epidermal growth factor (EGF)-induced cell migration in reconstituted thyroid follicles cultured in collagen gel.

Methods: Freshly isolated porcine thyroid follicle segments were dispersed in collagen type I gel and cultured for five days. EGF was added in the presence or absence of MEK1/2 inhibitor (U0126) and/or PI3K inhibitor (LY294002) at concentrations that blocked EGF-induced phosphorylation of ERK1/2 and AKT (ser473), respectively, in the same cells. The cultures were monitored daily by light microscopy for 96 hours.

Results: EGF (10 ng/ml) induced radial migration of thyrocytes into the surrounding matrix and also antagonized follicle lumen enlargement induced by thyroid stimulating hormone (TSH, 1mU/ml). U0126 (10 μM) prevented EGF from deteriorating lumen formation however the EGF-induced cell migration was only partly inhibited. LY294002 (25 μM) paradoxically enhanced EGF-induced cell migration and in addition promoted EGF-induced destruction of follicles, an effect being substantially rescued by U0126 when both drugs were combined. Preliminary data also shows that U0126, but not LY294002, is able to induce some recovery of I^- uptake and iodination in EGF-treated cells.

Conclusions: We conclude that EGF-stimulated thyroid cell migration in ex vivo-reconstituted follicles is at least partly mediated by MEK- and PI3K-independent pathways. 3D culture offers a novel approach to dissect this mechanism further and to test new candidate drugs for identification of which drug combinations most efficiently inhibit stromal invasion i.e. of thyroid cancer cells.

OP53

CLM3, A NOVEL MULTITARGET TYROSINE KINASE INHIBITOR WITH ANTIANGIOGENIC PROPERTIES, IS ACTIVE AGAINST PRIMARY ANAPLASTIC THYROID CANCER *IN VITRO* AND *IN VIVO*

Fallahi P[1], *Ferrari SM*[1], *Bocci G*[2], *La Motta C*[3], *Mancusi C*[1], *Corrado A*[1], *Materazzi G*[4], *Danesi R*[2], *Da Settimo F*[3], *Miccoli P*[4], *Antonelli A*[1]
[1]University of Pisa, School of Medicine, Department of Internal Medicine, Pisa, Italy, [2]University of Pisa, School of Medicine, Division of Pharmacology, Pisa, Italy, [3]University of Pisa, School of Medicine, Department of Pharmaceutical Science, Pisa, Italy, [4]University of Pisa, Department of Surgery, Pisa, Italy

Objectives: The antitumor and antiangiogenic activity of a new "pyrazolo[3,4-*d*]pyrimidine" compound (CLM3), proposed for a multiple signal transduction inhibition including the RET tyrosine kinase, EGFR and VEGFR, has been studied in primary anaplastic thyroid cancer (ATC) cells *in vitro* and *in vivo*.

Methods: The new compound, CLM3, was tested in different cell lines at different concentrations:

a) in the human cell line 8305C (undifferentiated thyroid cancer) at 0.001–100 μM;
b) in ATC cells at the concentrations of 5, 10, 30, 50 μM;
c) in an ATC-cell line (AF), derived from a primary ATC culture, in CD nu/nu mice.

Results: CLM3 significantly inhibited proliferation of 8305C cells, inducing also apoptosis. A significant reduction of proliferation with CLM3 in ATC cells ($P < 0.01$, ANOVA) was shown. CLM3 increased the percentage of apoptotic ATC cells dose-dependently ($P < 0.001$, ANOVA) and inhibited migration ($P < 0.01$, Newman-Keuls test) and invasion ($P < 0.001$, Newman-Keuls test). AF-cell line was injected *sc* in CD nu/nu mice and tumor masses became detectable 25 days after. CLM3 (40 mg/kg· die) inhibited significantly tumor growth (starting 35 days after the beginning of treatment). CLM3 significantly decreased the *VEGF-A* gene expression in the AF-cell line and the VEGF-A protein and microvessel density in AF tumor tissues.

Conclusion: The antitumor and antiangiogenic activity of a new "pyrazolo[3,4-*d*]pyrimidine" compound (CLM3) has been shown in anaplastic thyroid cancer, opening the way to a future clinical evaluation.

OP54

MICRORNAS INFLUENCE THE TUMORIGENESIS OF COLD BENIGN THYROID NODULES BY ACTING ON CELL CYCLE AND APOPTOSIS

Ferraz C[1], *Lorenz S*[1], *Moll A*[1], *Paschke R*[1], *Eszlinger M*[1]
[1]Universität Leipzig, Endocrinology and Nephrology, Leipzig, Germany

Several characteristics of the cold benign thyroid nodules (CBTN) such as a disturbed hormone synthesis, oxidative stress, and an increased proliferation have been described. However, the molecular etiology of CBTN is up to now largely unknown. In previous microarray studies we defined the molecular pattern of the increased proliferation in CBTNs by a differential expression of cell cycle associated genes and microRNAs. The *in silico* integration of differentially expressed miRNAs and mRNAs showed an indirect correlation between the expression of 59 miRNAs and 133 mRNAs. The indirect correlation between cell cycle associated genes such as CDKN1C and miR-221, CCND1 and miR-31, GADD45A and miR-130b, and CDKN1A and miR-let-7f suggests a modulation of proliferation in CBTNs by miRNAs. These miRNAs were quantitatively validated and functionally characterized in cell line models.

In 20 samples of CBTN, an 11-fold down-regulation of miR-31 with a 2.6-fold up-regulation of CCND1, and a 2.6-fold up-regulation of miR-130b with a 2.3-fold down-regulation of its target GADD45A was seen in RT-qPCR when compared to its surrounding tissue. Using HTori and FTC-133 cell lines we analyzed cell cycle and apoptosis after transfection of miRNA-31 and -130b mimic and inhibitors. FACS assays indicated that the overexpression of miR-31 and the resultant down-regulation of CCND1 led to an arrest in the cell cycle-phase G1. Moreover, after 72h of overexpression of miR-130b, more apoptotic and necrotic cells and less vital cells than in the control are apparent. In conclusion, both, miR-31 by regulating cyclinD, and miR-130b have

an effect on tumorigenesis of CBTN by regulating proliferation and apoptosis mechanisms, respectively.

OP55

TRAIL CAN EFFICIENTLY KILL ANAPLASTIC THYROID CANCER (ATC) CELLS IN VITRO AND IN VIVO

Pilli T[1,2], Ranganath R[2], Carr R[2], Qin J[2], Maker AV[2,3], Li LC[2], Pacini F[1], Prabhakar BS[2]
[1]University of Siena, Department of Internal Medicine, Endocrinology&Metabolism and Biochemistry, Siena, Italy, [2]University of Illinois at Chicago, Department of Microbiology&Immunology, Chicago, United States, [3]University of Illinois at Chicago, Department of Surgery, Chicago, United States

Background: Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising anti-cancer therapy since it can induce apoptosis with little or no effect on normal cells but resistance to TRAIL is common. One such resistance factor is MADD, a splice variant of IG20 (insulinoma-glucagonoma) gene, which is overexpressed in cancer tissues and cell lines.

Objective: Therefore, we aimed to investigate the effects of TRAIL induced-apoptosis in the ATC, which has a very poor prognosis that may not be significantly altered by the current treatment regimens.

Methods: We investigated four human ATC cell lines: C643, CAL62, HTh7 and 8505C. TRAIL treatment was used in vitro, alone or in combination with IG20/MADD knockdown, as well as in a mouse xenograft model of ATC. Apoptosis was assessed by detection of activated caspase-3 by flowcytometry. A shRNA expressing lentivirus was used to selectively knockdown IG20/MADD.

Results: C643, CAL62 and HTh7 cells were sensitive to TRAIL induced-apoptosis while 8505C cells were resistant to even the highest dose of the drug (100 ng/ml). The levels of some proteins, which account for TRAIL resistance (caspase-8 and c-FLIP), were not significantly different among the cell lines; the decoy receptors 1 and 2 were low or undetectable while IG20 was overexpressed. Upon IG20/MADD knockdown in C643 we were able to induce the same percentage of apoptosis using 50 ng/ml of TRAIL as compared to 100 ng/ml. In 8505C the sensitivity to this drug improved significantly (p=0.009). Moreover, we showed that TRAIL treatment can efficiently suppress tumor growth in HTh7 xenografts in nude mice, measured by caliper and monitored through IVIS imaging system.

Conclusions: Our data suggest that the combination of TRAIL and IG20/MADD knockdown is a desirable therapeutic option since it induces significant cytotoxicity, selectively in cancer cells, and allows use of a lower dose of TRAIL.

OP56

THERAPEUTIC STRATEGY TO TARGET THE RECEPTOR TYROSINE KINASE AXL IN THYROID CANCER

Krishnamoorthy GP[1], Guida T[1], Visciano C[1], Liotti F[1], Carlomagno F[1], Melillo RM[1]
[1]University of Naples-Federico II, Dipartimento di Biologia e Patologia Cellulare e Molecolare/Istituto di Endocrinologia ed Oncologia Sperimentale del CNR "G. Salvatore", Napoli, Italy

The AXL receptor tyrosine kinase is overexpressed and active in various cancer types including thyroid carcinoma, and several preclinical studies suggest that targeting AXL is an effective therapeutic strategy in AXL-positive cancers. Heat shock protein 90 (HSP90) acts as a molecular chaperone to regulate the conformation, activation, function and stability of many cancer-related kinases. Inhibition of HSP90 by Geldanamycin and its derivative 17-Allyl-Ammino-17-demethoxygeldanamycin (17-AAG), leads to simultaneous combinatorial depletion of a wide range of its clients through the induction of their misfolding and proteasome-mediated degradation. The Quality control E3 ligase CHIP ubiquitinates misfolded proteins and favours their degradation. Here we show that treatment of AXL-expressing thyroid cancer cells with 17-AAG induces its proteasome-mediated degradation. Specifically, 17-AAG induces the down-regulation of the fully glycosylated, mature form of the receptor that is exposed on the plasma membrane and responds to ligand stimulation. Degradation is preceded by AXL ubiquitination by CHIP. Endogenous and overexpressed AXL protein co-immunoprecipitated with CHIP and HSP90, and this complex is modulated upon 17-AAG treatment. By using different AXL mutants and AXL small molecule inhibitors, we demonstrate that AXL sensitivity to 17-AAG requires AXL kinase domain, but is not dependent on AXL kinase activity. Overall our data elucidate the biological basis of AXL downregulation by HSP90 inhibition and suggest that Hsp90 inhibition could be effective in treating AXL expressing thyroid cancer.

OP57

HYPERMETHYLATION OF A NEW CPG ISLAND IS ASSOCIATED WITH REDUCED NIS GENE EXPRESSION IN THYROID TUMORS

Galrao AL[1], Sodré AK[1], Camargo RY[1], Friguglietti CU[1], Kulcsar MA[1], Lima EU[1], Moraes LS[2], Cerutti JM[2], Medeiros-Neto G[1], Rubio IG[3]
[1]University of Sao Paulo Medical School, Endocrinology - Thyroid, Sao Paulo, Brazil, [2]UNIFESP EPM, Genetics, Sao Paulo, Brazil, [3]UNIFESP, Biological Sciences, São Paulo, Brazil

Objectives: To identify and to functional characterize new CpGislands within NIS promoter region; to Investigate the methylation pattern of the new CpGisland in benign and malignant thyroid tumor(T) and in adjacent samples(NT); and to correlate the methylation degree with NISexpression.

Methods: We studied 30 pairs of cold T(10benign and 20malignant) and NT samples. New bioinformatics tools were employed to identify functional CpGislands. Methylation degree was quantified by bisulfate-sequencing. Gene reporter assays were performed to evaluate the regulatory activity of the CpGisland. Tumor cells with reduced NIS expression were treated with 5Aza demethylating agent and NISmRNA expression was evaluated by real time-PCR.

Results: We identified a new CpGisland2 in NIS promoter with 256bp, located between positions -2152/-1887(relative to ATGsite), containing 14CpG sites. We detected hypermethylation(66%) in all T(benign and malignant) when compared to NT samples(23%). The intraindividual analysis showed higher methylation degree in T than in NT in 100% of benign and 95% of malignant groups. We also identified significant inverse correlation between CpGisland2 methylation degree and NISmRNA expression. Functional studies showed that CpGisland2 may be considered a NIS enhancer. Restoration of NISmRNA expression in parallel with the reduction of the methylation degree of CpGisland2 was detected after treatment of tumor cell lines with 5Aza.

Conclusions: This is the first report that describes a second CpGisland in the 5´region of NIS gene, with enhancer activity, able to regulate gene expression by DNA methylation. This is also the first time that a NIS methylation pattern in thyroid tumors is detected. The hypermethylation of this CpGisland should be an early event in tumorigenesis and may be involved in the reduced NISexpression in benign and malignant thyroid tumors, as well as in the low uptake of iodine by the cold thyroid tumors. This new findings provides new bases for future epigenetic therapies of thyroid cancer.

OP58

IDENTIFICATION OF TARGETS OF TWIST1 TRANSCRIPTION FACTOR IN ANAPLASTIC THYROID CANCER

Di Maro G[1], Orlandella FM[1], Salerno P[1], Bencivenga TC[1], Santoro M[1], Salvatore G[2]
[1]University of Naples, Federico II, Naples, Italy, [2]University of Naples Parthenope, Naples, Italy

Objectives: Anaplastic thyroid carcinoma (ATC) is one of the most aggressive human tumors; it is characterized by chemoresistance, local invasion and distant metastases. While the prognosis of well-differentiated thyroid carcinoma is generally good, ATC is invariably fatal. Through, a cDNA microarray analysis we have isolated Twist1 as a gene upregulated in ATC. Twist1 is a basic helix-loop-helix transcription factor that plays an important role in the development and progression of human cancer. Here, we aimed to study the role of Twist1 in ATC.

Method and results: Knockdown of Twist1 by RNA interference in ATC cells reduced cell migration and invasion and increased sensitivity to apoptosis. The ectopic expression of Twist1 in thyroid carcinoma cells induced resistance to apoptosis and increased cell migration and invasion. To uncover

the molecular mechanisms underlying Twist1 biological effects, we have performed a gene expression profile of Twist1 ectopically expressing thyroid cancer TPC cells in comparison to vector control cells. We found 37 genes upregulated and 43 downregulated by more than ~ 5 fold in TPC-Twist1 transfectants compared to control cells. Twist1 gene signature was enriched for genes involved in apoptosis, migration and invasion, consistent with the biological function of Twist1. We selected for further validation 20 genes, among the top ranked up- and down-regulated genes. Expression levels of these genes was confirmed to be affected by Twist1 levels. Knockdown of HS6ST2, ID4, PDZK1, PDZK1IP, TACSTD1 Twist-upregulated target genes impaired cell viability, migration and invasion of Twist1 overexpressing cells.

Conclusions: Our data demonstrate that Twist1 plays a key role in determining malignant features of anaplastic thyroid cancer cells. These effects are mediated by a set of genes whose expression in under Twist1 control. The identified target genes are potential novel molecular determinants of ATC.

OP9 Thyroid Nodules and Cancer

OP59

TI-RADS SCORE: DIAGNOSTIC PERFORMANCE WITH AND WITHOUT ELASTOGRAPHY PROSPECTIVE STUDY ON 1305 THYROID NODULES

Russ G[1,2], Rouxel A[1,2], Bienvenu-Perrard M[1,3], Royer B[1,4], Bigorgne C[1], Leenhardt L[2]

[1]Centre de Pathologie et d'Imagerie, Paris, France, [2]Hopital La Pitié Salpétrière, Service de Médecine Nucléaire du Pr Aurengo, Paris, France, [3]Hôpital Cochin, Service de Médecine Nucléaire du Pr Richard, Paris, France, [4]Hopital Cochin, Service d'Anatomopathologie du Pr Vacher-Lavenu, Paris, France

Objectives: To evaluate the diagnostic performance of the TI-RADS score with and without elastography in differentiating benign and malignant thyroid nodules.

Materials and methods: Prospective study on 1305 thyroid nodules including 55 carcinomas in 1204 patients. First, using the TI-RADS grayscale score, each nodule was attributed a grade ranging from 1 to 5 corresponding to normal to malignant with a rising risk of malignancy. Then, US elastography with manual compression was applied and a quantitative stiffness index was calculated. A hard nodule was considered at high risk for carcinoma and therefore its score was 4B or 5. If it was soft, the grayscale score was not modified. Finally, all nodules were submitted for fine needle aspiration biopsy and the results read according to the Bethesda system. Diagnostic performances of gray-scale US alone, elastography alone and combination of both techniques were calculated and the results compared.

Results: Sensitivity, specificity, negative predictive values and accuracy of gray-scale US alone for the detection of malignancy were respectively 96%, 61%, 99.7% and 62%. For elastography alone the values were 73%, 93%, 98% and 92%. Using the combination of the two techniques the values were 99%, 48%, 99.7% and 48%. Positive predictive values for scores 2, 3, 4A, 4B and 5 without elastography were respectively 0%, 0.25%, 6%, 69%, 100% and in combination with elastography respectively 0%, 0.3%, 2%, 42%, 100%.

Conclusion: Grayscale TI-RADS has very good ability to suspect and discard malignancy. At elastography, a hard nodule should always be considered at high risk but elastography alone cannot be used, its sensitivity being too low. In combination, it raises sensitivity but decreases specificity and accuracy. More specific elastographic techniques using carotid artery pulsation or acoustic waves are needed to make elastography more accurate and useful. Meanwhile, the grayscale TI-RADS score can be used alone.

OP60

INTERSTITIAL LASER PHOTOCOAGULATION (ILP) OF BENIGN CYSTIC THYROID NODULES-A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

Døssing H[1], Bennedbæk FN[2], Hegedüs L[3]

[1]Odense University Hospital, Oto-Rhino-Laryngology and Neck Surgery, Odense, Denmark, [2]Herlev Hospital, Endocrinology, Herlev, Denmark, [3]Odense University Hospital, Endocrinology, Odense, Denmark

Aim: To evaluate remission-rate in patients with a predominately cystic benign recurrent thyroid nodule, randomized to aspiration with or without subsequent ILP.

Methods: Based on a power analysis, 44 consecutive outpatients with a recurrent cytologically benign cystic (≥ 2ml cyst- volume) thyroid nodule were randomized to a single aspiration with (N=22) or without subsequent ILP (N=22) and followed-up after 1, 3, and 6 months. ILP was performed after complete cyst aspiration and under continuous ultrasound (US) -guidance and with an output power of 2.0–3.0 W. Median treatment duration was 600 sec. (range; 153–732) and median delivered energy was 1272 J (range; 478–1800). Pressure symptoms were evaluated on a visual analogue scale (0–10cm).

Results: Remission (cyst volume ≤ 1 ml) was obtained in 15 of 22 (68%) patients in the ILP group, and 4 of 22 (18%) in the aspiration group (P=0.002). In the ILP group median cyst volume decreased from 10.8 ml (range; 2.0–52.0) to 0.5 ml (range; 0–33.0) (P=000.1); and the solid nodule volume was reduced from a median 1.8 ml to 1.0 ml (P=0.02). In the aspiration alone group neither the cyst-volume nor the solid nodule volume were significantly reduced at final evaluation. The reduction in median VAS score for pressure symptoms was significantly higher in the ILP group from (3.0 to 0.0 cm) than in the aspiration alone group (4.0 to 3.5 cm) (P=0.006, between groups). No major side effects occurred and thyroid function was unaffected throughout.

Conclusions: US-guided aspiration and subsequent ILP of benign recurrent predominantly cystic thyroid nodules is safe, feasible and significantly reduces recurrence rate, the volume of the solid nodule component, and pressure symptoms. ILP constitutes an important alternative to surgery in such patients.

OP61

MULTICENTER RANDOMIZED PROSPECTIVE TRIAL OF PERCUTANEOUS LASER ABLATION VERSUS FOLLOW-UP FOR THE TREATMENT OF COLD THYROID NODULES-TWELVE-MONTH RESULTS

Rago T[1], Papini E[2], Vitti P[1], De Feo P[3], Gambelunghe G[3], Valcavi R[4], Bizzarri G[5], Pacella CM[6]

[1]University of Pisa, Endocrinology Dept, Pisa, Italy, [2]Regina Apostolorum Hospital, Endocrinology Dept, Albano Laziale, Italy, [3]University of Perugia, Department of Internal Medicine and Endocrine and Metabolic Sciences, Perugia, Italy, [4]Arcispedale Santa Maria Nuova, Endocrine Unit &Thyroid Diseases Center, Reggio Emilia, Italy, [5]Regina Apostolorum Hospital, Radiology Dept, Albano Laziale, Italy, [6]Regina Apostolorum Hospital, Interventional Radiology, Albano Laziale, Italy

Aim of the study: To compare clinical and ultrasound (US) changes induced in cold thyroid nodules by US-guided laser ablation (LA) versus follow-up and to assess side effects and efficacy of the technique in different centers.

Patients: Two hundred consecutive patients were referred to four different thyroid centers and randomly assigned to a single LA treatment (Group 1) or follow-up (Group 2). Entry criteria: solid thyroid nodule with a volume > 5 and < 18 ml, repeated benign cytological findings, normal thyroid function, no previous thyroid gland treatment.

Methods: LA treatment was performed according to the previously described technique. Group 1: LA was performed with a 1064 nm neodymium yttrium-aluminum garnet laser with 2 fibers and an output power of 3 watts. Energy delivery was 3600 Joules for nodules up to 13 ml and 7200 in two illuminations for nodules larger than 13 ml. Volume and local symptoms changes

were evaluated one, six and twelve months after LA. Side effects and complications were registered.

Results: A significant nodule volume reduction was found at twelve months (delta volume vs baseline -56.02% ± 4.49; p = 0.0001). A reduction >50% was observed in 70,00% of cases. The mean volume reduction in the different centers was -58.18%,-66.28%,-53.66% and-46.78%. Local symptoms complain decreased from 84% to 24% of cases (p = 0.0001). The procedure was well tolerated. One case of vocal cord paresis and one case of low grade fever were reported. All complications resolved spontaneously. In Group 2 nodule volume and local symptoms significantly increase at twelve months (p = 0.001).

Conclusions: A single LA induced a significant nodule reduction and improvement of local symptoms without relevant complications. Efficacy and side effects were similar in different centers. Follow-up group presented a significant change of nodule volume and local symptoms.

OP62

ULTRASOUND-GUIDED PERCUTANEOUS ETHANOL ABLATION (UPEA) OF SELECTED NECK NODAL METASTASES (NNM) IN DIFFERENTIATED THYROID CARCINOMA (DTC): A 21-YEAR EXPERIENCE IN 161 PATIENTS

Hay I[1], *Lee R*[1], *Davidge-Pitts C*[1], *Geske J*[1], *Reading C*[1], *Charboneau W*[1]
[1]Mayo Clinic, Rochester, United States

We successfully treated with UPEA in 1991 a man with medullary thyroid cancer (MTC), who had "recurrent" NNM (JCEM 96: 2717, 2011). Over the next 21 years we treated with UPEA 160 other patients, with a limited number of biopsy-proven NNM, selected from one endocrinologist's practice. In this report, we describe details of these patients, their UPEA treatments, and their final status. Histologic patterns of 161 ablated patients were papillary (PTC) in 149 (93%), follicular (FTC) in 5, and MTC in 7. In 118 (73%), the tumor was confined to neck and UPEA was aimed at elimination (evident shrinkage and absent Doppler flow) of residual disease and curative local control. In other 43 patients (34PTC, 5FTC, 4MTC) with known distant spread, UPEA, although aimed at local control, was not expected to impact prognosis; 8/36 (22%) stage IVC dying of DTC, all seven stage II surviving at mean 5 years since UPEA. The majority (73%) of ablated patients were those 115 with localized PTC (LPTC) and stages at presentation of I, III and IVA in 89(77%), 9 and 17, respectively. In LPTC (mean age 42 years, range 19–73) we initially injected mean 0.9cc (range 0.1–4.9) of 95% ethanol into each of 171 NNM, (largest diameter mean 11mm; range 4–32). The 105 evaluated patients were followed for median 5 years (range 0.3–19). At latest follow-up, all ablated nodes were shrunken and had no Doppler flow; 47% could not be identified on sonography. In 101 autoantibody-negative patients, latest median thyroglobulin was 0.2ng/ml; 31% had thyroglobulin levels < 0.1ng/ml. Only 3 patients developed permanent hoarseness. 26/105 (25%) had successful treatment of further new NNM: 22(85%) with UPEA alone, 4 with repeat surgery. UPEA is well tolerated, considerably cheaper than neck surgery, highly effective, and should play an increasing role in LPTC patients with "recurrent" NNM.

OP63

LEPTIN AND SERUM THYROTROPIN CONCENTRATIONS IN A REPRESENTATIVE SAMPLE OF IODINE-SUFFICIENT, EUTHYROID MEDITERRANEAN POPULATION WITH DIFFERENT BODY MASS INDEX. RELATIONSHIP WITH THYROID AUTOIMMUNITY AND SMOKING HABIT

Lucas A[1], *Granada ML*[2], *Olaizola I*[1], *Castell C*[3], *Julian MT*[1], *Pellitero S*[1], *Puig-Domingo M*[1]
[1]Germans Trias i Pujol, Hospital, Endocrinologia i Nutrició, Badalona, Spain, [2]Germans Trias i Pujol, Hospital, Hormone Laboratory, Badalona, Spain, [3]General Direction of Public Health, Health Department, Generalitat of Catalonia, Barcelona, Spain

Introduction: A positive correlation between serum thyrotropin concentrations (TSH) and body mass index (BMI) has been demonstrated in some but not all studies in euthyroid subjects, or observed only if thyroid autoimmunity (TA) is present or in non-smokers individuals (NS). Leptin (Lp) could be the major link between BMI and TSH.

Design: To analyze the relationship between TSH, free thyroxin (FT4), Lp, TA (peroxidase and/or thyroglobulin antibodies) and smoking status in a representative sample of euthyroid, iodine-sufficient, non-hospitalized population of Catalonia, with different BMI. Data collected included smoking habit. Glycemia and insulinemia were measured and HOMA index, calculated.

Results: 894 adults (390 men) of 44.87±15.03 years and BMI 26.19±4.61 Kg/m^2 (17.01–52.70) with normal TSH (0.33–3.96 mIU/L) and FT4 (0.87–1.90 ng/dL), and median urine iodine concentration 150.0 mg/L were studied. Lp correlated directly with BMI in both sexes (p=0.000). There was no correlation between TSH and BMI. In men, TSH correlated directly with Lp (p=0.004) and in women, directly with Lp (p=0.002) and HOMA (p=0.031) and inversely, with FT4 (p=0.024). Only in smoker men, TSH correlated directly with Lp (p=0.010) and HOMA (p=0.024). In smoker women, TSH correlated directly with Lp (p=0.004) and in NS women, inversely with FT4 (p=0.047). Multivariate analysis showed Lp (β=0.1304, p=0.025) and age (β=-0.0051, p=0.012) to be independent predictors of TSH variations in men and Lp, the presence of TA (β=0.1168, p=0.042; β=0.2591, p=0.001) and FT4, (β=-0.1395, p=0.018) in women.

Conclusions: Leptin is a predictor factor of TSH concentration variations, in euthyroid subjects of both sexes. Other predictor factors are different in men and women. The smoking status can influence the relationship between TSH and some predictor factors. These data should be taken into account before drawing conclusions about the parameters that influence TSH concentrations in euthyroid people with different BMI.

OP64

STAGE I PAPILLARY THYROID CARCINOMAS WITH HIGH PERCENTAGE OF *BRAF*^{V600E} ALLELES HAVE A HIGH RISK OF RECURRENCE

Guerra A[1], *Fugazzola L*[2], *Rossi S*[2], *Ciriello V*[2], *Forno I*[2], *Marotta V*[3], *Cirillo M*[1], *Di Stasi V*[1], *Volpe A*[1], *Murino A*[1], *Izzo G*[1], *Vitale M*[1]
[1]University of Salerno, Department of Medicine and Surgery, Baronissi, Italy, [2]University of Milan, Milan, Italy, [3]University of Naples "Federico II', Naples, Italy

Context: An association of *BRAF*^{V600E} with a more advanced disease and with a worst prognosis in papillary thyroid carcinoma (PTC) has been reported in many studies. We recently demonstrated that: a) clonal *BRAF*^{V600E} is a rare occurrence in PTC, whilst frequently this cancer consists of a mixture of tumor cells with wild-type and mutant *BRAF*; b) PTCs with high percentage of cells harbouring *BRAF*^{V600E} have higher recurrence rate. Recurrence in stage I PTC is rare and unpredictable and the need for a stringent follow-up is controversial. In this study we examined the association of percentage of *BRAF*^{V600E} alleles with clinicopathologic parameters at diagnosis and disease recurrence in a series of stage I PTC.

Study design: Tumour genotyping for *BRAF*^{V600E} was performed by pyrosequencing in 132 patients with stage I PTC. Then, we determined the association between clinicopathologic characteristics including disease recur-

rence at follow-up (median = 5.2 years) and the percentage of *BRAF* mutant alleles.

Results: Tumors positive for $BRAF^{V600E}$ were 55.3%. In the PTC positive for $BRAF^{V600E}$, the percentage of mutant alleles ranged 5.3%-45.0% of total *BRAF* alleles, with a median of 20.8%. The presence or the percentage of $BRAF^{V600E}$ alleles did not correlate significantly with, gender, multicentricity, lymph node metastasis, age at diagnosis and tumour volume. The percentage of $BRAF^{V600E}$ alleles predicted the recurrence of lymph node metastasis. The odds ratio of recurrence in PTC with $BRAF^{V600E}$ alleles ≥35% was a 15.5-fold higher (P = 0.0004, 95% CI = 2.4 to 98.6) in comparison with PTC with $BRAF^{V600E}$ alleles < 35%.

Conclusions: High percentage of $BRAF^{V600E}$ alleles defines a PTC molecular subtype with a shorter post-surgery disease-free survival. Stage I PTC with high percentage of $BRAF^{V600E}$ alleles have a high risk of recurrence and require a more careful follow up.

OP65

QUALITY OF LIFE AND DEPRESSION IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

Molinaro E[1], *Lippi C*[1], *Piaggi P*[2], *Agate L*[1], *Passannanti P*[1], *Valeria B*[1], *Biagini A*[1], *Santini F*[1], *Vitti P*[1], *Pinchera A*[1], *Elisei R*[1]
[1]Department of Endocrinology, University of Pisa, Pisa, Italy, [2]Department of Energy and Systems Engineering, University of Pisa, Pisa, Italy

Background: Patients with differentiated thyroid cancer (DTC) have an excellent outcome and a long-term survival. However, there is limited information on long-term health-related quality-of-life (HRQOL) after initial therapy. The primary objective of this study was to evaluate the HRQOL and the depression status in patients with DTC during their follow up. As secondary objective we evaluated the determinants of HRQOL.

Methods: This is a cross-sectional study in which consecutive DTC-patients (571) were interviewed during one of their clinical and biochemical controls. They were distinguished into 3 groups according with the clinical status: cured, not cured, uncertain cured. Two validated questionnaire, the Short Form-36 (SF-36) test to assess generic HRQL and The Beck Depression Inventory (BDI) to measure depressive symptoms, were used. Data from a large population based survey of the Italian general population were used as control.

Results: The response rate for the questionnaires was 86% (489/571). When analysed all together with the SF-36, DTC-patients showed a decreased HRQOL in 6/8 functional domains (i.e. physical role, general health, vitality, emotional role, social functioning and mental health) compared with controls ($p< 0.05$). Conversely, no significant differences were found for physical functioning and bodily pain. BDI depression scores also showed greater distress in DTC than in controls ($p< 0.05$). When the analysis was restricted to the cured DTC (n=221), still physical role, vitality and social functioning remained significantly lower than in general population while an improvement of mental and general health and emotional role was observed with respect to not cured and uncertain cured DTC-patients.

Conclusions: Surviving DTC-patients experience a significantly decreased HRQOL and a greater depression status than normal controls. When considering the subgroup of cured patients, some improvements were observed. Supportive psychological care is warranted for all DTC-patients but mostly for not cured and uncertain cured groups.

OP66

OBESITY AND OVERWEIGHT ARE MAJOR RISK FACTORS OF RECURRENCE AFTER THYROIDECTOMY FOR MACROSCOPIC PAPILLARY CANCER

Tresallet C[1], *Noullet S*[1], *Godiris-Petit G*[1], *Hoang C*[2], *Leenhardt L*[3], *Menegaux F*[1]
[1]APHP, Université Pierre et Marie Curie, Paris 6, Endocrine Surgery, Paris, France, [2]APHP, Université Pierre et Marie Curie, Paris 6, Pathology Departement, Paris, France, [3]APHP, Université Pierre et Marie Curie, Paris 6, Nuclear Medicine, Paris, France

The impact of excess bodyweight on prognosis of papillary thyroid carcinoma (PTC) remains unknown. We aimed to evaluate the relation between PTC and overweight in a population who had surgery for thyroid disease.

Patients and methods: Patients were classified into categories of body size as follows: BMI of < 25 kg/m^2 (normal weight), BMI of 25–29.9 (overweight) and BMI≥30 (obese). From June 2002 to December 2009, 6597 patients were included, 1217 patients with PTC were identified. Events considered as recurrences were loco-regional recurrence or distant metastases. The median follow-up of 0.9 years (0.2–6.4)

Results: The risk of PTC was not associated with BMI since PTC occurred in 696/3698 patients with a BMI < 25 (18.8%), 349/1927 patients with a BMI of 25.0–29.9 (18%),172/946 patients with a BMI≥30 (18%) (NS). Recurrence occurred in 80 patients (7%), 62/536 macro-PTC >10mm (12%) and 18/681 micro-PTC ≤10mm (3%). BMI was not associated with the risk of recurrence in micro-PTC but in macro-PTC the recurrence rate rose from 11% if BMI < 25 and 9% if BMI 25–29.9 to 20% if BMI≥30 (p=0.04). Other risk factors of recurrence in macro-PTC were lymph node (LNM) metastases, LNM in the lateral compartment, multifocality, bilaterality and an extra-thyroidal extension of the PTC. In a multivariate analysis, LN metastases (OR=9.1 95% CI [3.8–22]) and BMI (OR=5.0 95% CI [1.6–16] for BMI of 25–29.9, and OR=7.2 95% CI [1.9–27.4] for BMI≥30 when compared with BMI < 25) were the only independent factors that were significantly associated with macro-PTC recurrence.

Conclusion: BMI was not associated with the risk of PTC. Overweight and obesity were strongly associated with the risk of recurrence after surgery for macro-PTC, along with LNM. PTC patients with excess bodyweight should therefore benefit from a close follow-up to detect and treat a possible recurrence at an early stage.

OP10 Thyroid Basic 1

OP67

THE THYROID HORMONE RECEPTOR-COACTIVATOR INTERFACE MEDIATES NEGATIVE FEEDBACK REGULATION OF THE HUMAN PITUITARY THYROID AXIS

Agostini M[1], *Moran C*[1], *Schoenmakers E*[1], *Mitchell C*[1], *Gregory J*[2], *Gurnell M*[1], *Chatterjee K*[1]
[1]University of Cambridge, Institute of Metabolic Science, Cambridge, United Kingdom, [2]University Hospital Wales, Department of Child Health, Cardiff, United Kingdom

Corepressors and coactivators of thyroid hormone receptor action mediate repression and transactivation of positively-regulated target genes respectively, but their role in negative regulation is not understood.

We have identified two individuals (Proband 1 (P1) age 11 yrs; Proband 2 (P2) age 39 yrs), with raised circulating free thyroid hormones, non-suppressed TSH levels and recognised clinical features of Resistance to Thyroid Hormone.

The probands are heterozygous for mutations (P1; E457Q, P2; E457D) in the TRβ gene, involving a highly conserved residue located in its carboxyterminal transactivation domain. Although the mutant receptors bind T3 normally (WT/E457Q Ka ratio = 1.02; WT/E457D Ka Ratio =0.81), hormone-

Table 1. Proband phenotype (for Abstract 0P67).

Mutation	Proband 1	Proband 2
TSH mU/L, Ref range 0.4–4.0	3.34	2.02
FT4 pmol/L, Ref range 9–20	54.8	41.3
FT3 pmol/L, Ref range 3.0–7.5	19.9	13.9
Clinical Features	growth retardation, frequent ear infections, learning difficulties, hearing deficit, hyperactivity and anxiety	tremor, palpitations, osteopaenia, hearing deficit, hyperactivity and anxiety

dependent negative regulation by E457Q (TRH, TSHα promoters) and E457D TRβ (TSHα promoter) is markedly impaired.

When coexpressed, E457Q and E457D TRβ are strong dominant negative inhibitors of WT receptor function. In protein-protein interaction assays, E457Q and E457D TRβ bind and dissociate from corepressors (NCoR, SMRT); however, the mutant receptors bind coactivators differently, being either globally (E457Q) or selectively (E457D) impaired for coactivator (e.g TRAP 220, SRC-1, RIPI40, LCoR) recruitment. Crystallographic modelling indicates that substitution of glutamine or aspartic acid for glutamic acid at codon 457 impairs receptor-coactivator interactions.

Elevated thyroid hormones with non-suppressed TSH in the Probands indicate impaired negative feedback in the pituitary-thyroid axis *in vivo*, consistent with impaired function of E457Q and E457D TRb when tested with negatively-regulated promoters (TRH, TSHa). Together, these observations suggest that proteins recruited to the thyroid receptor-coactivator interface mediate negative transcriptional regulation of target genes in the human pituitary-thyroid axis.

OP68

ROLE OF CYSTEINE RESIDUES IN THE MCT8 THYROID HORMONE TRANSPORTER

Lima de Souza EC[1], *Groeneweg S*[1], *Visser EW*[1], *Peeters RP*[1], *Visser TJ*[1]
[1]Eramus University Medical Center, Internal Medicine, Rotterdam, Netherlands

Cysteines are reactive amino acid residues involved in different processes such as disulfide formation, protein folding, substrate recognition and catalysis. The objective of this research is to study the role of the Cys residues in the MCT8 function.

JEG-3 cells were transiently transfected with empty vector (pcDNA3), human wild-type (wt) MCT8 or the Cys>Ala mutants C184A, C231A, C244A, C281A, C283A, C436A, C481A, C491A, C497A, and C546A. The transfected cells were treated for 5–15 min at 37°C with 10–100 µM p-chloromercurybenzene sulfonate (pCMBS), a specific, membrane-impermeable reagent for modification of the free SH group of Cys residues. After washing, T3 uptake was determined during 10 min at 37°C. Antibody against MCT8 was used for western blotting and confocal microscopy. Pretreatment of JEG-3 cells, expressing MCT8, with pCMBS resulted in a dose- and time-dependent inhibition of subsequent T3 uptake. As cysteines can form disulfide bonds we treated the cells with DTT before incubation with pCMBS, but no effect was observed. However, DTT reversed inhibition of MCT8 by pCMBS. In order to discover which cysteines are involved in this inhibition we introduced into MCT8 single Cys mutations. Most Cys>Ala mutations had little effect on MCT8 protein expression and T3 uptake. However, the single mutations C244A and C281A resulted in a significant increase in T3 uptake, associated with an increased MCT8 protein expression. The C491A mutant showed a large reduction in T3 uptake and a slight decrease in protein expression. Furthermore, the C491A mutant was properly expressed at the cell membrane. The mutants C481A and C497A were less sensitive to pCMBS than wt MCT8 suggesting modification of these Cys residues by pCMBS.

Therefore some cysteines are important for MCT8 function. However there is no evidence for disulfide bond formation, but the free SH groups play a role in the function of the transporter.

OP69

UNCOUPLING PROTEIN-3 (UCP3) IS INVOLVED IN METABOLIC ADAPTATION INDUCED BY TRIIODOTHYRONINE.

Lombardi A[1], *Busiello RA*[1], *Senese R*[2], *Cioffi F*[3], *Goglia F*[3]
[1]University of Naples 'Federico II', Biological Science, Napoli, Italy, [2]Second Univesity of Naples (SUN), Caserta, Italy, [3]Sannio University, Benevento, Italy

Objective: Triiodothyronine (T3) influences calorigenesis and lipid metabolism, however the molecular determinants underlying its effects are partially known. It has been reported that T3 enhances the levels of UCP3, a mitochondrial protein proposed to play a role both in thermogenesis and fatty acid oxidation, and we suggested that UCP3 is a molecular determinant of the metabolic effects exerted by T3. A debate about the effective role of UCP3 exists, and new data should be obtained to confirm its role in the metabolic effects elicited by T3.

Methods: To this aim above we used wild-type (WT) and UCP3-null (KO) mice maintained at thermoneutrality, and we detected: -thermogenesis and fatty acid oxidation rate in isolated skeletal muscle mitochondria -whole animal Resting Metabolic Rate (RMR), Heat Production (HP) and Respiratory Quotient (RQ). To evaluate the role of UCP3 in T3-induced metabolic adaptation, we injected a single dose of T3 (25microgr/100g bw) in both WT and KO hypothyroid mice and measured their RMR, HP and QR.

Results: Mitochondria from KO mice showed lower (-50%) fatty acid-induced proton-conductance (index of mitochondrial thermogenesis) and fatty acid oxidation rate (-25%) compared to WT ones. KO mice showed significantly lower RMR (-20%) and HP (-23%), and higher RQ (+ 5%) compared to WT. T3 administration into hypothyroid mice induced an increase in RMR and HP and a reduction in RQ. However, in WT mice the time course and the extent of the T3-induced variations were more prolonged and higher than those observed in KO ones. Indeed, 48h after T3 administration the increase in HP was +20% and +7% in WT and KO mice, respectively, while a significant decrease in RQ (-6%) was observed exclusively in WT mice.

Conclusion: As a whole, these evidences support a role for UCP3 as a molecular determinant in T3-induced metabolic adaptations.

OP70

ABSENCE OF TYPE 3 DEIODINASE LEADS TO RESTRICTIVE CARDIOMYOPATHY AND AGGRAVATES CARDIAC HYPERTROPHY IN MICE

Olivares EL[1], *Ueta CB*[2], *Oskouei BN*[3], *Pinto JR*[4], *Correa MM*[2], *Simovic G*[2], *Simonides WS*[5], *Hare JM*[3], *Bianco AC*[2]
[1]Federal Rural University of Rio de Janeiro, Physiological Sciences, Seropedica, Brazil, [2]University of Miami Miller School of Medicine, Division of Endocrinology, Diabetes and Metabolism, Miami, United States, [3]University of Miami Miller School of Medicine, Interdisciplinary Stem Cell Institute, Miami, United States, [4]University of Miami Miller School of Medicine, Department of Molecular and Cellular Pharmacology, Miami, United States, [5]University Medical Center, Institute for Cardiovascular Research, Amsterdam, Netherlands

Objectives: Cardiac injury induces myocardial expression of the thyroid hormone inactivating deiodinase (D3), which in turn dampens local thyroid hormone signaling. Here we investigated the role of D3 in newborns hearts and in cardiac remodeling/function of hypertrophied adult mice hearts.

Methods and results: Experiments were conducted in newborns (P1) or 4-month-old 129/Sv/C57 Black/6J male mice. Animals heterozygous for the D3

mutation (HtzD3KO) and wild type littermates were studied. Cardiac hypertrophy was induced by subcutaneous injections of D-L isoproterenol(ISO) for 10 days and 0.9% saline solution as control (n=10/group). Cardiac function was assessed by echocardiography and hemodynamic evaluation at baseline and at the end of the treatment period. Mice were euthanized by CO2 asphyxiation. Serum levels of TSH, T4 and T3 were measured and RT-PCR for gene expression study and D3 activity by HPLC were assessed in the hearts and brain of all animals. Skinned papillary muscles were prepared from the left ventricle of WT or HtzD3KO mice hearts. Results showed that myocardium of 1-day old HtzD3KO pups is normal but, as a result of the lifelong cardiac increase in thyroid hormone signaling, 4-month old animals exhibit a unique phenotype of restrictive cardiomyopathy that includes myocardial fibrosis, impaired myocardial contractility and diastolic dysfunction. ISO worsened this phenotype, caused congestive heart failure and doubled the mortality rate. In sharp contrast, WT siblings were able to potently reactivate myocardial D3 and cardiac remodeling took place with LV dilatation.

Conclusions: The heart's ability to reactivate D3 in response to injury is a critical component of a successful remodeling process. In its absence there is restrictive cardiomyopathy that is further accentuated in response to an adrenergic overdrive.

OP71

THE INTRACELLULAR INACTIVATION OF THYROID HORMONE SIGNALING IN MUSCLE STEM CELLS IS REQUIRED FOR SUCCESSFUL MUSCLE REGENERATION

Dentice M[1], *Ambrosio R*[1], *Sibilio A*[1], *Luongo C*[1], *Damiano V*[1], *Bonelli C*[1], *De Stefano A*[1], *Fenzi G*[1], *Larsen PR*[2], *Salvatore D*[1]
[1]University of Naples "Federico II', Department of Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]Brigham and Women's Hospital and Harvard Medical School, Thyroid Section, Division of Endocrinology, Diabetes and Hypertension, Boston, United States

Intracellular thyroid hormone (TH) concentration is determined by a balance between activating and inactivating deiodinases. In functional combinations, these regulatory enzymes provide the ability to fine-tune TH action at cell level. D1 and D2 activate TH, whereas D3, by inactivating T3 and T4, terminates or prevents TH action.

TH has long been known to have important effects on skeletal muscle physiology. We recently demonstrated that D2-induced local T3 production is essential for normal myogenesis and muscle regeneration. D3 − the TH inactivating enzyme− is an oncofetal protein frequently re-expressed in adult life in proliferating tissues. D3 can also be reactivated in response to tissue injury, including myocardial infarction, liver regeneration and neural injury. In this study, we explored the role of D3 in muscle precursor cells and in muscle regeneration.

We analyzed D3 expression in muscle at different phases of muscle differentiation. As working models, we used in vitro primary cultures of muscle satellite cells (pp6 cells) and immortalized myoblast progenitors (C2C12). We found that D3 is highly expressed in proliferating pp6 and C2C12 cells but its expression declines with differentiation. Soon after cardiotoxin injury of TA muscle, D3 mRNA, protein and activity increase markedly peaking in the in the early phases of regeneration, at a time at which satellite cells are actively proliferating. Later, D3 falls as the expression of D2 increases. Preliminary data in muscle specific D3KO mice indicate that muscle regeneration is severely hampered by the absence of D3.

In conclusion, our data demonstrate that the D2 and D3 are sequentially expressed in myoblasts during differentiation and muscle regeneration. We postulate that the changes in intracellular T3 resulting from this highly coordinated expression of these two deiodinases produce the biphasic changes of intracellular T3 essential for the proper development and repair of injured skeletal muscle.

OP72

FUNCTIONAL ANALYSIS OF NEWLY DISCOVERED MUTATIONS IN THE SECIS ELEMENT OF THE THYROID HORMONE ACTIVATING TYPE 2 DEIODINASE

Zevenbergen C[1], *Visser WE*[1], *Visser TJ*[1]
[1]Erasmus Medical Center, Internal Medicine, Rotterdam, Netherlands

Thyroid hormone is important for the development of the brain. Type 2 deiodinase (D2) is highly expressed in brain and converts T4 to T3. Deiodinases contain an essential selenocysteine residue and its incorporation requires a selenocysteine insertion sequence (SECIS) element in the 3' UTR of the mRNA. We were the first to identify three mutations in the SECIS element in subjects with mental retardation. The present study aims to evaluate the functional consequences of these mutations. SECIS mutants (5703C>T, 5730A>T and 5858T>G) and a mutation known to inactivate the SECIS element (5679G>A) were created using site-directed mutagenesis. COS-1 cells were cultured in medium without or with selenium (100 nM) and transiently transfected with D2 WT or mutant cDNA. D2 activity was assayed by measuring the conversion of [125I]T4 to [125I]T3. In lysates from cells cultured with 100 nM added selenium, the 5703C>T, 5730A>T, 5858T>G and 5679G>A mutants, display an activity relative to D2 of 95±11%, 89±2%, 102±0.5% and 0%, respectively. Without selenium, WT D2 and mutants show a similar decrease in deiodinase activity of approximately 60%. Intact cell metabolism with100 nM added selenium shows an activity of 93±2%, 94±10%, 106±2% and 5±0.1% in mutants compared to WT D2. Without selenium, WT D2 and mutants show a decrease of approximately 25%.

Our data show no significant difference in activity between D2 and SECIS mutants in lysates and intact cells. Probably, these mutations are not localized in the crucial part of the SECIS element, in contrast to the 5679 mutant, which was used as a negative control. Selenium deficiency did not affect the results. In conclusion, although these mutations in the SECIS element of D2 are rare variants, they do not appear to have functional effects.

OP73

ALTERNATIVE SPLICING OF TYPE 1 IODOTHYRONINE DEIODINASE IN PITUITARY ADENOMA IS REGULATED BY PROTO-ONCOGENIC SPLICING FACTOR SF2/ASF

Kedzierska H[1], *Poplawski P*[1], *Maksymowicz M*[2], *Grajkowska W*[3,4], *Matyja E*[3,5], *Bonicki W*[6], *Nauman P*[6], *Piekielko-Witkowska A*[1]
[1]The Medical Centre of Postgraduate Education, Department of Biochemistry, Warsaw, Poland, [2]M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Department of Pathology, Warsaw, Poland, [3]M. Mossakowski Medical Research Centre, Polish Academy of Sciences, Department of Experimental and Clinical Neuropathology, Warsaw, Poland, [4]The Children's Memorial Health Institute, Department of Pathology, Warsaw, Poland, [5]M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Department of Neurosurgery, Warsaw, Poland, [6]Institut of Psychiatry and Neurology, Department of Neurosurgery, Warsaw, Poland

Objectives: Type 1 iodothyronine deiodinase (D1) participates in activation and inactivation of thyroid hormones. Pituitary tumors belong to the most common intracranial neoplasms. Previous studies revealed variable expression of D1 in pituitary tumors and normal cells. D1 mRNA expression and activity do not correlate in pituitary tumors, suggesting possible posttranscriptional regulation.

SF2/ASF is a splicing regulator encoded by protooncogene SFRS1. The aim of this study was to analyze alternative splicing of D1 in pituitary tumors.

Material: 30 pituitary tumors, 5 control non-neoplastic pituitary samples, rat pituitary tumor GH3 cell line.

Methods: RNA isolation, reverse transcription, cloning into pGEM-Teasy vector, real-time PCR, silencing of SF2/ASF using siRNA, *in silico* analysis using SFmap software.

Results: Cloning of D1 splice isoforms from pituitary tumor samples revealed six known splice variants and four new ones, not previously reported. In most of the nontumorous pituitary samples no D1 transcripts were found. Among ten cloned different splice variants, five were devoid of exon 3. Analysis of the whole sequence of D1 primary transcript using SFmap revealed multiple binding sites for splicing factor SF2/ASF. The predicted binding sites

with the highest score were located in exon 3. Silencing of SF2/ASF in pituitary GH3 cells resulted in change of ratio between D1 isoforms lacking and possessing exon 3, favoring the expression of variants with missing exon 3. The expression of SF2/ASF in pituitary tumors was increased when compared with nontumorous control samples.

Conclusions: In comparison with nonneoplastic glands, pituitary adenomas express multiple splice variants of D1. The alternative splicing of D1 is regulated by SF2/ASF whose expression is disturbed in pituitary tumors.

The work supported by the National Science Centre grant NN401532140.

OP74

A CONTRIBUTING ROLE FOR HEPATIC SIRTUINS IN THE PREVENTION OF DIET-INDUCED ADIPOSITY BY 3,5-DIIODO-L-THYRONINE (T2)

de Lange P[1], Senese R[1], Cioffi F[2], de Matteis R[3], Ziello A[1], Goglia F[2], Lanni A[1]
[1]Second Univesity of Naples (SUN), Caserta, Italy, [2]University of Sannio, Benevento, Italy, [3]Università degli Studi di Urbino 'Carlo Bo', Urbino, Italy

Objectives: The metabolic syndrome and related complications such as type 2 diabetes mellitus are becoming ever increasing worldwide problems. This has created a strong demand for the development of pharmaceutical compounds which counteract adiposity while at the same time ameliorating systemic insulin resistance. Thyroid hormone metabolites may be interesting candidates in this context. 3,5-diiodo-L-thyronine (T2) prevents adiposity and insulin resistance, and concomitantly increases hepatic fatty acid oxidation in rats receiving a high-fat diet. These effects are correlated with a direct activation of sirtuin 1 (SIRT1) by T2. Here we studied to what extent in vivo activation of hepatic SIRT1 and SIRT3 target proteins by T2 is involved.

Methods: Male Wistar rats subjected to a high fat diet for 4 weeks were contemporarily treated with T2. Acetylation of hepatic sirtuin target proteins was measured by immunoprecipitation, and target gene expression was assessed by real time PCR.

Results: In the liver T2 caused deacetylation of the SIRT1 targets PGC-1a and SREBP-1c, increased expression of PGC-1a target genes involved in fatty acid oxidation and reduced expression of SREBP-1c target genes involved in lipogenesis, respectively. Furthermore, the expression of genes involved in gluconeogenesis was reduced. In addition, mitochondrial proteins were deacetylated among which we identified the SIRT3 target long-chain acyl-CoA dehydrogenase (LCAD), associated with increased mitochondrial oxidative activity. In this manner, T2, by activating nuclear and mitochondrial sirtuin activity in the liver, prevents adiposity. Whether sirtuins are activated in white adipose tissue, and to what extent this has consequences for the activity of this tissue is currently under study.

Conclusions: Thus, activation of hepatic sirtuins by T2 contributes to the amelioration of obesity-related parameters such as adiposity and insulin resistance by contemporarily increasing fatty acid oxidation and decreasing lipogenesis, respectively.

OP11 Thyroid Cancer

OP75

LONG TERM EFFICACY AND TOLERABILITY OF SORAFENIB IN DIFFERENTIATED THYROID CARCINOMA: FINAL RESULTS OF A PHASE II TRIAL

Schneider T[1], Abdulrahman R[1], Kapiteijn E[1], Smit JW[1]
[1]Leiden University Medical Center, Leiden, Netherlands

Purpose: Based on the knowledge that the multikinase inhibitor sorafenib targets BRAF, RET and VEGF, we conducted a prospective phaseII clinical trial to determine the efficacy of sorafenib in patients with advanced differentiated thyroid cancer (DTC).

Patients and methods: 31 patients with progressive metastatic or locally advanced radioactive iodine 131-I ablation (RaI) refractory DTC received sorafenib 400mg orally twice daily. The study end points included response rate (RR), progression free survival (PFS), overall survival (OS), best response by Response Evaluation Criteria in Solid Tumors (RECIST) and toxicity.

Results: The study completed enrollment in October 2008 and was closed for follow-up in Februari 2011. Median PFS was 18 months (95% CI: 7–29) and median OS was 34.5 months (95% CI: 19–50). Eight patients (31%) achieved PR and 11 patients (42%) showed SD. At a median follow-up of 25 months (range 3.5- 39) 4 patients (15%) had an ongoing partial response (PR) and 3 patients (12%) had stable disease (SD). Toxicity was consistent with other sorafenib trials and included hand foot syndrome (HFS), weight loss, diarrhoea and rash.

Conclusion: Sorafenib has clinically relevant antitumor activity in patients with progressive metastatic or locally advanced RaI refractory DTC. The toxicity profile is acceptable. Sorafenib can nowadays be considered as standard option in the treatment of advanced RAI-refractory DTC patients.

OP76

CLINICOPATHOLOGIC CHARACTERISTICS OF PAPILLARY THYROID CARCINOMA BASED ON AGE GROUPS

Park YS[1], Jung SP[1], Lee J[1], Kim J[1], Choi MY[1], Lee SK[1], Kil WH[1], Lee JE[1], Nam SJ[1], Choe JH[1], Kim JH[1], Kim JS[1]
[1]Sungkyunkwan Univ., School of Medicine, Department of Surgery, Seoul, Korea, Republic of

Purpose: This study compared and analyzed the clinicopathologic characteristics of papillary thyroid carcinoma based on the following age groups: < 25 years; 25–44 years; 45–64 years; and > 64 years.

Methods: The medical records of 4,491 patients diagnosed with papillary thyroid carcinoma and underwent thyroidectomies were retrospectively reviewed. Patients were divided to four groups : group I (< 25 years, n = 116), group II (25–44 years, n = 1,849), group III (45–64 years, n = 2,198), group IV (>64 years, n = 328).

Results: The proportion of men was significantly lower in groups I and II than in groups III and IV (P< 0.001). The rate of modified radical neck dissections was significantly higher in group I than the others (P< 0.001). The rate of papillary microcarcinomas was significantly lower in group I than the others (P=0.023), extrathyroidal extension significantly lower in group II than the others, multifocality significantly lower in groups I and II than groups III and IV, number of patients with T3 stage significantly higher in groups I and IV than groups II and III, and lymph node metastasis significantly higher in group I than the others. The rate of lymph node metastasis within the same T stage was significantly higher in group I than the others. The rate of distant metastasis was significantly higher in groups I and IV than groups II and III. The recurrence rate was significantly higher in group I than the others. The disease-free survival rate was significantly lower in group I than the others.

Conclusion: This study showed that patients < 25 years of age, in comparison to the other age groups, had the lowest rate of papillary microcarcinoma, the highest rate of lymph node metastasis and recurrence, and a higher rate of extrathyroidal extension and distant metastasis.

OP77

PAPILLARY THYROID CANCER GENE PROFILE MODIFICATION OVER THE LAST 15 YEARS

Romei C[1], Fugazzola L[2], Puxeddu E[3], Frasca F[4], Viola D[1], Muzza M[2], Moretti S[3], Nicolosi ML[4], Giani C[1], Cirello V[2], Avenia N[5], Rossi S[6], Vitti P[1], Pinchera A[1], Elisei R[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy, [2]University of Milano, Department of Medical Sciences, Milano, Italy, [3]University of Perugia, Department of Medicine, Perugia, Italy, [4]University of Catania, Department of Clinical and Molecula Biomedicine, Catania, Italy, [5]University of Perugia, Department of Surgical, Radiological and Odontostomatologic Sciences, Perugia, Italy, [6]AO San Paolo, Department of Anatomic Pathology, Milano, Italy

Objectives: Evidences of an increased prevalence of $BRAF^{V600E}$ mutations and a decreased prevalence of *RET/PTC* rearrangements have been recently doc-

umented. The aim of our study was to evaluate the prevalence of both *RET/PTC* rearrangements and *BRAF*^{V600E} mutations in an Italian cohort of PTC patients followed at the Endocrine Units of Pisa, Milano and Perugia from 1996–2010.

Methods: 401 PTC patients were examined for the presence of *BRAF*^{V600E} mutations and RET/PTC rearrangements. They were grouped according to the time of surgery: group-1, 1996 and 2000; group-2, 2001 and 2005 and group-3, 2006 and 2010. Clinical and epidemiological data were analyzed. In parallel, the molecular characteristics of 459 PTCs from Sicily were studied.

Results: The prevalence of genetic alterations in the 3 groups was significantly different ($p< 0.0001$). In particular, the frequency of RET/PTC rearrangements was decreased over the time: 33% (33/100) in group-1, 17% (26/148) in group-2 and 9.8% (15/153) in group-3. In parallel, the prevalence of *BRAF*^{V600E} mutation was increased during the same period, with a frequency of 28% (28/100) in group-1, 48.9% (73/148) in group-2 and 58.1% (89/153) in group-3. The three groups were homogeneous for gender, lymph-node and distant metastases, histologic variants and history of irradiation in the neck region. A statistically significant increase in the mean age at diagnosis and a decrease in tumor size over the study period was observed. A consistent increase in *BRAF*^{V600E} prevalence was observed in the Sicilian group ($p< 0.0001$). Interestingly, in these samples rearrangements RET/PTC were virtually absent (2 cases out of 459).

Conclusions: The genetic profile of PTC changed over the last 15 years, with a significant decrease in the prevalence of *RET/PTC* rearrangements and an increase in *BRAF*^{V600E} mutations. In addition, the mean age at diagnosis increased and tumor size decreased over the study period.

OP78

THE MAJOR IMPORTANCE OF AGE AT EXPOSURE AND LATENCY ON THE NUMBER AND PROPORTION OF THYROID CARCINOMAS IN BELARUS DUE TO CHERNOBYL, A 25 YEAR STUDY

Demidchik Y[1], *Williams D*[2]
[1]Belarussian State Medical University, Minsk, Belarus, [2]Cambridge University, Cambridge, United Kingdom

Analysis of all 5093 thyroid carcinomas that have occurred in Belarus from1986 to 2010 by age at the accident (ATA) shows that the highest incidence occurs in those under 1 ATA, falling by almost half by 3–4 years of age ATA. No obvious increase is seen >13 ATA.

Interval analysis finds the incidence at age 15–19 ATA is below US SEER rates (among the highest worldwide) at all time points from 1990 to 2010. Using a rate adjusted for this and matched for age and year of operation, the table shows numbers of thyroid cancers after Chernobyl and the estimated% due to exposure (AF) (* $p< 0.05$)

Those aged 0–4 ATA showed significantly raised incidence rates throughout ($p =0.002749$ in 2010); the attributable fraction (% of cases due to exposure) falls from 99% to 34%. Those aged 10–14 ATA showed variable small non-significant increases at 5, 10, and 15 years, but none at 20 and 25 year latency. Additional analysis shows the importance of dose, the major role of dietary iodide in modifying risk, and the importance of ascertainment.

These findings show the very marked age related sensitivity to thyroid carcinogenesis after exposure to fallout, and that the risk, although diminished, is still present 25 years after the accident in those < 5 at exposure. Past studies of 'Chernobyl-related' tumours may well have investigated largely sporadic thyroid carcinomas if no attention was paid to age at both exposure and operation

Table for Abstract OP 78.

Year of operation	1990		1995		2000		2005		2010	
Age at accident	no	AF	no	AF	no	AF	no	AF	no	AF
0–4	20	99%*	83	98%*	89	83%*	78	58%*	95	39%*
5–9	10	90%	33	79%	40	25%	67	24%	82	7%
10–14	4	50%	22	9%	57	14%	67	0%	90	0%
15–19	5	0%	29	0%	57	0%	81	0%	91	0%

OP79

IS THE GENETIC PREDISPOSITION TO PAPILLARY MICROCANCER THE SAME AS FOR CLINICALLY EVIDENT PTC?

Kalemba M[1], *Handkiewicz-Junak D*[1], *Kula D*[1], *Oczko-Wojciechowska M*[1], *Kowal M*[1], *Tyszkiewicz T*[1], *Zebracka-Gala J*[1], *Polańska J*[2], *Jarzab B*[1]
[1]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Dept. of Nuclear Medicine and Endocrine Oncology, Gliwice, Poland, [2]Silesian University of Technology, Institute of Automatic Control, Gliwice, Poland

Objectives: The genetic background of papillary thyroid cancer (PTC) is still not sufficiently understood. Recently, a gene on chromosome 9q22, FOXE1, was found to be associated with PTC. However, no relation with tumor size was analyzed, an aspect potentially important as the majority of microPTC (stage T1a) are considered incidental findings, while more advanced PTC (clinically evident, macroPTC) show more aggressive behaviour. In the present study we address the question, whether some clinical PTC features: stage T1a and age of diagnosis are associated with 9q22 locus single nucleotide polymorphisms (SNP)

Methods: We analysed 902 PTC patients (116 with microPTC (14%) and 786 of macro PTC (>pT1aN0). They were compared to 900 healthy controls with thyroid disease excluded by ultrasound. Median age of PTC diagnosis was 53 years. Nine chr. 9q22 SNPs were investigated by allele discrimination. Association analysis by multivariate regression was carried out.

Results: Two FOXE1 gene SNPs (rs186727, rs144344) were significantly different between PTCs and controls, as described previously. At the dominant model of inheritance, the third SNP from this locus (rs1098370) showed an association, at recessive model, two other SNPs were significant (rs1877431, rs965513). Some of these SNPs showed significant association depending on patient age (prominent for rs1867277) - difference was noted mainly in patients aged between 39 and 55 years at diagnosis. When microPTC cases were considered, both rs1867277 and rs1443434 showed the trend to difference ($p=0.08$ and $p=0.06$, resp.) in relation to macroPTC and were not significantly different from healthy controls, with similar genotype frequencies in microPTC and controls.

Conclusion: Only cases of clinically evident PTC exhibit association with chr.9q22 SNPs, with significant impact of PTC onset age. Micro PTC does not show an association with these loci.

Research supported by grants N N402 193740 and N N519 579938

OP80

THE PREVALENCE OF RAS MUTATIONS IN AN ITALIAN MEDULLARY THYROID CANCER SERIES AND A META-ANALYSIS OF PUBLISHED STUDIES

Ciampi R[1], *Mian C*[2], *Fugazzola L*[3], *Cosci B*[1], *Romei C*[1], *Barollo S*[2], *Cirello V*[3], *Bottici V*[1], *Marconcini G*[1], *Pelizzo MR*[4], *Borrello MG*[5], *Basolo F*[6], *Ugolini C*[6], *Materazzi G*[6], *Pinchera A*[1], *Elisei R*[1]
[1]Università di Pisa, Department of Endocrinology and Metabolism, Pisa, Italy, [2]Università di Padova, Department of Medicine-DIMED, Padova, Italy, [3]Fondazione IRCCS Ca' Granda, Endocrine Unit, Milano, Italy, [4]Università di Padova, Department of Surgical, Oncological and Gastroenterological Sciences- DISCOG, Padova, Italy, [5]Fondazione IRCCS Istituto Nazionale dei Tumori, Experimental Oncology Department-U.O. Molecular Mechanisms, Milano, Italy, [6]Università di Pisa, Department of Surgery, Pisa, Italy

Objectives: Approximately 60% of sporadic Medullary Thyroid Carcinomas (sMTC) remain orphan of a recognized genetic cause. Recently, a high percent-

age of *RAS* point mutations has been described in *RET*-negative sMTC. In this study, we analyzed a large series of hereditary and sporadic MTC for H-, K- and N-*RAS* point mutations that were collected in four Italian Centers.

Methods: We studied codons 12, 13 and 61 of H-, K- and N-*RAS* genes in 188 MTC samples by PCR and direct sequencing. We performed *in silico* analysis of the mutations and correlation between the *RAS* mutational status and the clinical-pathological features of MTC patients was made, as well as a meta-analysis of all published data until now.

Results: The prevalence of *RAS* mutations in sMTC was 10.1%, and 17.6% when considering only *RET*-negative cases. A novel mutation in codon 72 (M72I) was found, but it had a low or null transforming potential. No association was found between the presence of *RAS* mutations and the clinical-pathological features of the patients. The meta-analysis showed a prevalence of 11.3% for *RAS* mutations in sMTC.

Conclusions: The prevalence of *RAS* mutations in our MTC series was relatively low and corresponded to what emerged from the meta-analysis. We found that *RAS* mutations were only present in *RET*-negative sMTC thus confirming their mutual exclusivity. *RAS* mutations were found in MTC tumoral tissue, but not in peripheral blood indicating their somatic origin. Likely, MTC that harbour a *RAS* mutation identify a subgroup of tumors with a less aggressive behavior. To our knowledge, this is the largest series of MTC studied for the presence of mutations in the three *RAS* genes and the first meta-analysis on this specific topic.

OP81

DIAGNOSTIC IMPACT OF THE DETECTION OF POINT MUTATIONS AND REARRANGEMENTS IN 320 ROUTINE AIR DRIED FINE NEEDLE ASPIRATION (FNA) SMEARS

Eszlinger M[1], *Muenz S*[1], *Ferraz C*[1], *Rehfeld C*[1], *Krogdahl A*[2], *Jensen E*[2], *Boesenberg E*[1], *Hegedus L*[3], *Paschke R*[1]
[1]University of Leipzig, Divisions of Endocrinology and Nephrology, Leipzig, Germany, [2]Odense University Hospital, Department of Pathology, Odense, Denmark, [3]Odense University Hospital, Department of Endocrinology and Metabolism, Odense, Denmark

Fine needle aspiration (FNA) is the most sensitive method to select suspicious thyroid nodules for surgery. However, this method has some inherent limitations, e.g. "indeterminate" samples. As rearrangements (*PAX8/PPARG, RET/PTC)* and point mutations (*BRAF, NRAS, HRAS, KRAS*) have been detected in follicular carcinomas (FTC) and papillary carcinomas (PTC), their detection in FNA smears could improve the diagnosis. However, rearrangements have up to date only been detected in fresh FNA material.

RNA and DNA was extracted from 320 routine air-dried FNA smears (163 indeterminate, 54 malignant, 16 non-diagnostic, 87 non-neoplastic) and corresponding formalin-fixed paraffin-embedded tissue (FFPE) samples (160 follicular adenomas, 32 FTCs, 50 PTCs, 78 goiters). *PAX8/PPARG* and *RET/PTC1* and *3* rearrangements were detected by qPCR, while *BRAF* and *RAS* point mutations were detected by high resolution melting (HRM)-PCR and by pyrosequencing. Less than one percent of extracted FFPE samples did not allow DNA based analysis of point mutations, in comparison to 8.5% of routine FNA samples. In total and for the 163 indeterminate samples, *BRAF* mutations could be detected in 23/0 FNA samples and 34/1 FFPE samples, respectively. *NRAS* mutations were present in 14/11 FNA samples and in 30/21 FFPE samples, respectively. *HRAS* mutations were found in 3/3 FNA samples compared to 9/7 *HRAS* mutations in the FFPE samples. A *KRAS* mutation could be detected in one/0 FNA sample. *PAX8/PPARG* rearrangements were detected in 5/4 FNA and in 8/6 FFPE samples, while *RET/PTC* rearrangements were detected in one/0 FNA and in 1/0 FFPE samples. In summary, these data show that molecular screening for point mutations and also for rearrangements is feasible in routine air dried FNA smears and suggest to analyse this panel of point mutations and rearrangements especially in indeterminate routine air-dried FNA smears in everyday practice to reduce the number of diagnostic thyroid surgeries.

OP82

EXPRESSION PATTERNS IN PAPILLARY THYROID CARCINOMAS WITH BRAF V600E OR RET/PTC SUGGESTS ACTIVATION OF DIFFERENT PATHWAYS

Bastos AU[1], *Oler G*[1], *Cerutti JM*[1]
[1]Genetic Bases of Thyroid Tumors Laboratory, Universidade Federal de São Paulo, Department of Morphology and Genetics, São Paulo, Brazil

Background: Papillary Thyroid Carcinoma (PTC) is the most common subtype of thyroid cancers. Activating point mutations of *RAS* and *BRAF* or rearrangements of *RET* oncogene, effectors along the MAPK pathway, are central for its malignant transformation. Although these genes convey signals along the same pathway, recently studies shows that these BRAF V600E or RET/PTC rearrangements have distinct downstream targets.

Objectives: To identify genes that are potentially modulated by BRAF V600E or RET/PTC rearrangements.

Methods: In a cohort of 118 PTCs, we determined BRAF V600E mutation by direct sequencing. The most common RET/PTC isoforms were determined by nested-RT-PCR. The expression of *NIS, TPO, PDS, TG, TSHR, CST6, CXCL14, DHRS3, SPP1, AFAP1L2, VAV3* and *AREG* was determined by qPCR. The mutational status was correlated with clinical pathological features. Kruskall-Wallis test was performed to detect the differences between expression levels in the subgroups.

Results: BRAF V600E modulated the expression of *NIS, TPO, PDS, TG, CST6, CXCL14* and *DHRS3* expression while RET/PTC-positive tumors did not. Additionally, *CST6* and *CXCL14* expression was correlated with the presence of lymph node metastasis.

Conclusion: Our findings suggests that BRAF V600E and RET/PTC are able to signal through alternative pathways, which may explain the different biological features observed in BRAFV600E or RET/PTC-positive tumors. Determination of pathways associated with the different mutational status could lead to better strategies in patient's management.

OP12 Thyroid Basic 2

OP83

DOSE DEPENDENT EFFECTS OF A BLOCKING TYPE MONOCLONAL AUTOANTIBODY (K1-70) IN HYPERTHYROID RATS

Furmaniak J[1], *Sanders J*[1], *Young S*[1], *Kabelis K*[1], *Sanders P*[1], *Evans M*[1], *Clark J*[1], *Wilmot J*[1], *Rees Smith B*[1]
[1]FIRS Laboratories, RSR Ltd, Cardiff, United Kingdom

Human monoclonal TSHR autoantibodies (MAbs) M22 and K1-70 have high binding affinity for the TSH receptor (TSHR). M22 is a potent stimulator of thyroid hormone secretion *in vivo* in rats while K1-70 is a potent inhibitor of M22 or TSH thyroid stimulating activity *in vivo*. In this study dose dependent effects of K1-70 IgG on M22 stimulated thyroid hormone levels were carried out in T3 suppressed rats. Animals were injected intramuscularly at time zero with M22 IgG (4µg/animal) followed by K1-70 IgG (4, 10, 50, 100 or 200µg/animal) at 24 hours (h). Serum levels of total T4, free T4 and MAbs were measured at 24h, 36h, 48h and 60h. The peak rat serum total T4 level was 79nmol/L 24h after injection of 4µg M22 IgG and decreased slowly over time to 50nmol/L at 36h, 47nmol/L at 48h and 33nmol/L at 60h. After administration of 200µg or 100µg of K1-70 IgG the levels of total T4 at 36h decreased to below the detection limit of the assay in all five rats (< 26nmol/L). Furthermore, injection of 50µg of K1-70 reduced the total T4 to below the detection limit in 4/5 rats and to 45nmol/L in 1/5 rats. However lower doses of K1-70 (10µg and 4µg per animal) had no effect on the total T4 levels. K1-70 (at the doses studied) had a similar effect on serum free T4 levels in rats stimulated with M22. In conclusion, K1-70 has the ability to rapidly (within 12 hours) decrease elevated thyroid hormone levels stimulated by M22 *in vivo*. This potent *in vivo* activity of K1-70 emphasises its potential use to block the effects of stimulating type TSHR autoantibodies in patients with Graves´ disease.

OP84

MOLECULAR SAMPLING OF TSH RECEPTOR ALLOSTERIC BINDING POCKET: SWITCHING AGONISM TO ANTAGONISM AND REVERSE

Hoyer I[1], Haas A-K[1], Furkert J[1], Rutz C[1], Schülein R[1], Krause G[1]
[1]Leibniz-Institut für Molekulare Pharmakologie (FMP), Berlin, Germany

The therapeutic gap for treatment of Graves` orbitopathy is apparent. A potential approach could be suppression of the pathogenic auto-antibody`s activation directly on the thyrotropin receptor (TSHR) by drug like small molecule ligands (SMLs). In contrast to the activating antibodies that bind like thyrotropin to the TSHR extracellular region, synthetic SMLs bind downstream allosterically into a binding pocket within the transmembrane domain. For our long term goal of a selective interference by high affinity antagonists, the knowledge about molecular details within this pocket is instrumental. Modelling driven mutagenesis led to distinct silencing mutations and constitutively activating mutations (CAM) and change TSHR conformation to an inactive or active state. Mapping these residues onto a structural model of TSHR indicate locations where in the pocket a SML may interact and also switch the receptor to an inactive or active conformation respectively. Here we report the effects of SMLs on these signalling-sensitive amino acids at TSHR. The antagonistic effect of SML c52 was surprisingly reversed to an agonistic effect, if tested at the silencing TSHR mutant M572A. Such a reversing effect of c52 was also observed at the CAM Y667A. In the molecular model c52 is wedged between these two residues. Either of these two mutations lead to a relocation of c52 similar to position of the agonist. c52 differs from the partial agonist org41841 only by an enlarged substituent, which in the model coincide with a cluster of residues showing silencing mutations. Our modifications are switching agonism to antagonism and reverse by changing either small molecule ligand or by mutation of residues covering the binding pocket. Detailed knowledge about discriminative pharmacophores on both counterparts, ligand and receptor, prepares the basis for rational optimization of further high affinity antagonists having the potential to interfere with pathogenic activation of the TSHR.

OP85

THYROTROPIN RECEPTOR (TSHR) ACTIVATION ENHANCES SUBCUTANEOUS ADIPOGENESIS, FAVOURING BROWN ADIPOSE TISSUE (BAT) FORMATION, A ROLE FOR HYALURONAN?

Zhang L[1], Grennan-Jones F[1], Dayan CM[1], Rees DA[1], Ludgate M[1]
[1]Cardiff University, School of Medicine, Cardiff, United Kingdom

Objectives: TSHR expression increases during lineage-specific differentiation of mesenchymal stem cells (MSC). Our previous studies demonstrated that TSHR activation (TSHR*) increases but adipogenesis decreases subcutaneous hyaluronan (HA) production. We hypothesise that TSHR* (and HA) influence MSC differentiation.

Methods: Human primary subcutaneous preadipocytes (n=10) were obtained with appropriate approvals/consent. They were cultured in complete (CM) or adipogenic medium (AM) and experienced TSHR* by gain-of-function mutant L629F (introduced using retroviral vectors) or monoclonal thyroid stimulating antibody (TSAB). Adipogenesis was compared in cells with/without TSHR* using oil red O (ORO) staining, counting adipogenic foci and QPCR measurement of differentiation (LPL) and BAT (PRDM16, PGC-1α & UCP-1) markers. The effect of HA on adipogenesis was evaluated by treatment with 0.1mM 4-Methylumbelliferone (4MU, inhibitor of hyaluronan synthesis), siRNA knockdown of HA synthase (HAS) 1 and HAS2 or overexpression (conditioned medium from HAS1/HAS2 transfected HEK 293 cells). PPARγ and p-Akt were analyzed by Western-blot.

Results: Preliminary microarrays revealed that TSHR* preadipocytes had significantly increased SFRP4 (Wnt signalling) but decreased osteoprotogerin transcripts compared with control, suggesting adipogenesis was favoured. TSHR* cells cultured in AM (20 days) displayed 8.6±1.8 (foci), 5.5±1.6 (LPL transcripts) and 1.4±0.07 (ORO) fold increases compared with controls. The TSHR* cells also displayed significantly increased (2–4 fold) transcripts for PRDM16, PGC-1α and UCP-1; PGC-1α transcription was significantly increased by TSAB. HA decreases during subcutaneous adipogenesis; to investigate further preadipocytes were cultured in AM+4MU and found to display significantly enhanced adipogenesis with fold increases of 4.1±0.63 (foci), 2.6±0.21 (LPL transcripts) and 1.52±0.18 (ORO) compared with AM alone. Levels of pAkt and PPARγ protein were increased 20% (p=0.04) and 40% (p=0.01) respectively by 4MU whilst HAS2 siRNA or overexpression produced 16% increase/ 30% decrease in PPARγ transcripts respectively.

Conclusions: TSHR activation and reduced HA (products of HAS2?) promote subcutaneous MSC adipogenesis and favour BAT formation.

OP86

EFFECTS OF IN VIVO 3-IODOTHYRONAMINE ADMINISTRATION ON GENE EXPRESSION IN ADIPOSE TISSUE, LIVER AND HEART

Righi M[1], Iofrida C[1], Melissari E[1], Mariotti V[1], Di Russo M[1], Pellegrini S[1], Zucchi R[1]
[1]Università di Pisa, Pisa, Italy

Objectives: 3-Iodothyronamine (T1AM) is an endogenous relative of thyroid hormone, which produces significant functional effects, including modulation of energy metabolism and of cardiac function, and therefore has been proposed to be a proper hormone. T1AM does not interact with thyroid hormone receptors, but rather with specific G protein-coupled receptors, and it is unclear whether it may produce transcriptional effects. In the present investigation we determined the effects of in vivo T1AM administration on gene expression in rat adipose tissue, liver, and heart.

Methods: Eight Wistar rats were treated with T1AM for five days (10 mg/Kg twice a day by intraperitoneal injection). The rats were sacrificed by guillotine and tissue samples were immediately removed and frozen in liquid nitrogen. Gene expression was investigated by two-colour microarray analysis, using the Whole Rat Genome G4131F microarrays (Agilent Technologies, Palo Alto, CA, USA).

Results: Chronic T1AM administration induced significant changes in gene expression. In adipose tissue we detected 374 differentially expressed genes (DEGs), 265 up-regulated and 109 down-regulated; in liver there were 114 DEGs (63 up-regulated and 51 down-regulated), and in heart 129 DEGs (49 up-regulated and 80 down-regulated). Functional analysis of microarray results revealed interesting interplays among DEGs. In adipose tissue pathway analysis provided evidence of decreased adipogenesis and with increased lipolysis and fatty acid catabolism; in liver changes consistent with increased cholesterol uptake and increased gluconeogenesis were observed; in heart T1AM modulated the expression of genes involved in the regulation of adrenergic signaling and cardiac contraction, and its expected effects include reduced sensitivity to catecholamines and to hypertrophic stimuli.

Conclusions: In vivo T1AM administration produced significant transcriptional effects, which might contribute to some of its reported functional effects, particularly reduced fatty mass and increased lipid catabolism. The molecular mechanisms underlying modulation of gene expression by T1AM require further investigation.

OP87

METABOLOME DYNAMICS OF T1AM, AN ENDOGENOUS THYROID HORMONE DERIVATIVE: EFFECTS ON LIPID METABOLISM, WEIGHT LOSS, AND APPETITE IN MICE

Assadi-Porter F[1], Reiland H[1], Butz D[1], Tonelli M[1], Ghelardoni S[2], Scanlan T[3], Zucchi R[2], Chiellini G[2]
[1]UWMadison, Biochemistry, Madison, United States, [2]University of Pisa, Scienze dell'Uomo e dell'Ambiente, Pisa, Italy, [3]OHSU Portland, Oregon, Portland, United States

Objectives: T1AM is an endogenous natural compound that has opposing physiological effects to those of thyroid hormone. T1AM is thought to switch metabolism from carbohydrate to lipid. Due to its recent discovery, detailed actions of T1AM on affected metabolic pathways are still unknown. In a previous pilot study, we observed that subchronic low doses of T1AM could significantly increase lipolysis in mice. The present work is focused on studying the effects of T1AM on carbohydrate and lipid metabolism in obese mice using Nuclear Magnetic Resonance (NMR) spectroscopy by dynamic metabolomics. This novel way of monitoring all serum metabolites simultaneously in individual animals in response to T1AM could potentially identify pathways through which T1AM acts.

Methods: To distinguish carbohydrate from lipid pathways, we used ^{13}C-glucose labeling in three groups of spontaneously overweight mice: Group1: five obese control mice injected with saline once daily for seven days; Group 2: five obese mice injected with T1AM (10 mg/kg/day) once daily for seven days; Group 3: same as in Group 2 but using an higher dose of T1AM (25 m/kg/day). The mice were monitored prior to and after the week of injections. In particular we examined small molecules intermediates in carbohydrate and lipid metabolism, appetite through food intake, and weight measurements over the course of four weeks.

Results: We observed that exogenous T1AM administration was associated with a body weight loss trend. After T1AM withdrawal, mice regained only part of lost weight in the following 2 weeks, indicating long-lasting effects of this natural molecule. No difference in food intake was observed at any time. NMR metabolic profiling experiments are currently underway to better identify key changes in fuel and energy metabolism.

Conclusions: T1AM produced beneficial effects in obese mice and might become an effective human weight-loss drug.

OP88

3,5-DIIODOTHYRONINE ADMINISTRATION IMPROVES CHOLESTEROL METABOLISM IN LDL RECEPTOR KNOCK-OUT MICE (LDLR $^{-/-}$) BY MODIFYING HEPATIC PROTEOMIC PROFILE

Moreno M[1], Silvestri E[1], Glinni D[1], Goldberg IJ[2], Ehrenkranz J[3], Scanlan TS[4], Goglia F[1]

[1]University of Sannio, Benevento, Italy, [2]Columbia U. College of Physicians and Surgeons, New York, United States, [3]Intermountain Healthcare, Murray, United States, [4]Oregon Health Sciences University, Portland, United States

Objectives: Thyroid hormones (THs) lower plasma levels of LDL-cholesterol, by increasing hepatic expression of the LDL receptor. However, clinical use of THs has been hampered mainly by their cardiotoxic effects. 3,5-diiodo-L-thyronine (T2) lowers plasma cholesterol both in rats and in humans without inducing thyreotoxic effects. Very recently, we have shown that administering T2 led to significant (~70%) reductions in circulating cholesterol in Ldlr $^{-/-}$ mice. This was associated with a reduction in both apoB100- and apoB48- containing lipoproteins, in VLDL and LDL. Here, we aimed to further characterize T2 effects on cholesterol metabolism in Ldlr $^{-/-}$ mice to uncover new molecular/biochemical pathways affected by T2 and identify novel putative strategies in the treatment of hypercholesterolemia which do not involve the LDL receptor pathway. Comparative studies using T3 were performed.

Methods: Ldlr $^{-/-}$ mice were placed on a western diet one week prior to receive 12.5 mg/kg T2 or 0.75 mg/kg T3, by oral gavages for 1 week. A proteomic analysis on liver expression pattern [(2D-E, nHPLC-MS/MS, and ingenuity pathways analysis (IPA)] was performed.

Results: Attending to their molecular function, the identified hepatic proteins individually affected by either T2 or T3 were involved in 3 major categories: substrate metabolism, energy expenditure, and oxidative stress. APOA1 protein levels were down-regulated by T3 but not affected by T2 while APOE protein levels were down-regulated by T2 but not by T3. IPA network analysis identified HFN4a and PPARa as the highest-scoring nodes involved in the hypocholesterolemic effect of T2 and T3. HFN4a directly interacts with focus proteins influenced by T2 such as ALDH2, APOE, MDH1, FABP2. PPARa directly interacts with focus proteins influenced by T3 such as APOA1, ALDH2, PRDX6, GPD.

Conclusions: The obtained functional interrelations add new insight into the differential mechanisms involved in T2 and T3 hypocholesterolemic effects in Ldlr $^{-/-}$ mice.

OP89

THE ROLE OF CONSERVED CHARGED AMINO ACIDS IN TRANSMEMBRANE DOMAINS OF THE THYROID HORMONE TRANSPORTER MCT8

Groeneweg S[1], Friesema ECH[1], Visser TJ[1]

[1]Erasmus MC, Internal Medicine, Rotterdam, Netherlands

Background: The thyroid hormone transporter MCT8 facilitates cellular influx and efflux of T4 and T3. Mutations in MCT8 lead to severe psychomotor retardation known as the Allan-Herndon-Dudley syndrome. The MCT8 protein is predicted to have 12 transmembrane domains (TMDs) with an intracellular C-terminus and N-terminus. Here, we studied the importance of the conserved charged amino acids Arg445 in TMD8 and Asp498 in TMD10 for substrate recognition and helix interactions. This was done by studying the effects of different single and double mutations of these residues on TH transport in transfected cells. The R445C and D498N mutations have been identified in patients.

Methods: We introduced the following mutations into human MCT8 cDNA: R445A, R445C, R445D, R445K, D498A, D498E, D498N, D498R, R445A+D498A, R445D+D498R, and R445K+D498E. COS1 and JEG3 cells were transiently transfected with these mutants or wild-type MCT8, and analyzed for T3 and T4 uptake capacity. Cellular localization was studied by confocal microscopy. Protein expression, dimerization capacity and protein stability were analyzed by Western blotting.

Results: Mutations in R445 or D498 resulting in a change of local charge resulted in a near complete loss of TH uptake capacity, while the expression, stability and localization of these mutant MCT8 proteins was not markedly affected. Upon exchanging R445 and D498, significant residual uptake of especially T4 was retained. Mutations R445K and D498E leading to incorporation of equally charged residues resulted in TH uptake levels comparable to WT.

Conclusion: The presence of two oppositely charged amino acid residues predicted in close structural proximity at position R445 and D498 within TMD8 and TMD10 of MCT8 is crucial for efficient TH uptake. This might be indicative for the presence of an, at least transient, salt-bridge between R445 and D498, which is essential during substrate translocation.

OP90

MUTATIONS OF MCT8 IN PATIENTS WITH ALLAN-HERNDON-DUDLEY SYNDROME AFFECT ITS CELLULAR DISTRIBUTION

Kersseboom S[1], Friesema ECH[1], Visser WE[1], Klootwijk W[1], Visser TJ[1]

[1]Eramus University Medical Center, Internal Medicine, Rotterdam, Netherlands

Introduction: Mutations in the *SLC16A2* gene coding for the thyroid hormone (TH) transporter MCT8 are associated with the Allan-Herndon-Dudley Syndrome (AHDS). This syndrome is characterized by severe psychomotor retardation and a specific TH profile - high T3, low-normal T4, and normal TSH - in serum. Over 35 single amino acid mutations have been identified in AHDS patients, but their exact pathogenic mechanism is still unclear. Therefore, we explored the subcellular location and transport capacity of such mutations identified in 7 AHDS patients.

Methods: We used two cell models: 1) COS1 and JEG3 cells transiently transfected with wild-type or mutant MCT8 or MCT8-CFP fusion protein, and 2) Flp-in 293 cells stably transfected with wild-type or mutant MCT8-CFP fusion protein. MCT8 protein expression was studied by TH uptake assays, immunoblotting and confocal microscopy.

Results: In all 3 cell lines, the 7 mutants were expressed at the protein level. TH transport studies showed significant ($p < 0.05$) cell-type-dependent residual transport of T3 and T4 by 3 mutants (G282C, P537L, G558D) in COS1 and Flp-in 293 cells. All mutants were inactive in JEG3 cells. Confocal microscopy showed a plasma membrane location of 4 mutants (G221R, P321L, D453V, P537L). The other mutants (insV236, G282C, G558D) were localized mainly in the endoplasmic-reticulum.

Conclusion: Our results support the idea of two main pathogenic mechanisms: (1) loss-of-function by partial or complete loss of substrate recognition (i.e. G221R, P321L, D453V, P537L), and (2) mutations that mainly result in protein expression and trafficking defects (i.e. insV236, G282C, G558D). Overall, impaired TH uptake in (neuronal) target cells by mutated MCT8 explains the psychomotor retardation in AHDS patients.

European
Thyroid Journal

Full posters are available online from September 7 to December 31 at www.karger.com/etj

PO1 Medullary Thyroid Cancer Basic/Translational

P1

SIGNIFICANT DIFFERENCIES IN FREQUENCIES OF *RET* POLYMORPHISMS IN HIRSCHSPRUNG'S DISEASE PATIENTS AND ITS ASSOCIATION WITH MEDULLARY THYROID CARCINOMA

Vaclavikova E[1,2], *Dvorakova S*[1], *Sykorova V*[1], *Vcelak J*[1], *Halkova T*[1], *Skaba R*[3], *Vlcek P*[4], *Bendlova B*[1]
[1]Institute of Endocrinology, Department of Molecular Endocrinology, Prague, Czech Republic, [2]Faculty of Science, Charles University, Department of Biochemistry, Prague, Czech Republic, [3]2nd Faculty of Medicine, Charles University and Hospital Motol, Department of Pediatric Surgery, Prague, Czech Republic, [4]2nd Faculty of Medicine, Charles University and Hospital Motol, Department of Nuclear Medicine and Endocrinology, Prague, Czech Republic

Objectives: Hirschsprung´s disease (HSCR) is a congenital aganglionosis of the colon myenteric and submucosal plexuses. The main genetic cause is inactivating mutations in the *RET* proto-oncogene. In rare cases, HSCR could be associated with medullary thyroid carcinoma (MTC), caused by activating *RET* mutations. Besides *RET* mutations, influence of some *RET* polymorphisms on development of both diseases is considered.

Methods: DNAs of 162 patients with HSCR, 302 patients with sporadic MTC and 205 healthy controls were isolated from peripheral leukocytes. HSCR and MTC patients were routinely tested for *RET* mutations by sequencing of risk exons 10, 11, 13, 14, 15 and 16. Genotyping of 11 polymorphisms was performed using TaqMan probes and SSCP method.

Results: Germline *RET* mutations were detected in 16 HSCR patients (10%). In 2 families mutations in exon 10 with dual character (activating and inactivating) was found and patients underwent prophylactic TTE (2 confirmed MTC, 1 C-cell hyperplasia). Mutations associated mainly with MTC so far (exon 11, 13) were found in 8 HSCR cases. Four novel mutations with unknown pathogenicity were also detected. Statistical evaluation of studied SNPs revealed significant differencies in frequencies of polymorphic variants between patient cohorts and controls: for patients with sporadic MTC vs. controls only intronic polymorphism IVS14-24G/A was significant (p=0,003); HSCR patients vs. controls significantly differed for IVS1+2846G/T (p=2.7E-33), IVS1+9277C/T (p=2.2E-32), Ala45Ala (p=1.9E-32), Ala432Ala (p=0,018), Gly691Ser (p=1.2E-7), Leu769Leu (p=3.3E-10), Ser904Ser (p=2.4E-7), IVS19-627C/T (p=8.2E-11) and g.57317T/C (p=0,028). Distribution of generated haplotypes by Haploview programme also significantly differed between patients and controls.

Conclusions: Considering the detection of *RET* mutations with MTC risk in HSCR patients, they should be systematically tested for more risk exons, not only for exon 10. Some *RET* polymorphisms seem to have a function of genetic modifiers.

Supported by the grant projects GAUK 411611 and IGA MH CR NT13901-4.

P2

PRAZOSIN INDUCES APOPTOSIS IN MEDULLARY THYROID CARCINOMA CELLS BY TARGETING MULTIPLE ORGANELLES

Fuchs R[1], *Schwach G*[1], *Rinner B*[2], *Stracke A*[1], *Allard N*[1], *Kueznik T*[2], *Froehlich E*[2], *Birner-Gruenberger R*[2], *Sadjak A*[1], *Roswitha P*[1]
[1]Medical University of Graz, Institute of Pathophysiology and Immunology, Graz, Austria, [2]Medical University of Graz, Center for Medical Research, Graz, Austria

Objectives: Previous studies have shown that the adrenergic antagonist Prazosin induces apoptosis in Medullary Thyroid Carcinoma (MTC) cell lines through non-adrenergic mechanisms. Since MTC exhibits high resistance against chemotherapy and radiotherapy, we wanted to characterize the pro-apoptotic mechanism of Prazosin to disclose possible new therapeutic strategies.

Methods: Proliferation of MTC-SK cells was quantified using an electronic cell counter. Ongoing cell death and DNA content were analyzed by flow cytometry using Annexin V/7-AAD, respectively propidium iodide. Specific inhibitors of signal transduction were combined with Prazosin to characterize pro-apoptotic pathways. For identification of the target-organelle of Prazosin, we used the fluorescent Prazosin derivate BODIPY® FL Prazosin (QAPB) and organelle-specific vital dyes.

Results: Prazosin inhibited growth and induced apoptosis in MTC-SK cells. Surviving cells exhibited an enlarged cell size in comparison to untreated cells and manifested tetraploidy and an arrest of the G2/M phase of the cell cycle. Finally, also tetraploid cells died. LY 294,002, an inhibitor of PI3K, and SB 203580, an inhibitor of the p38-MAPK did not restore growth of Prazosin-treated cells but inhibited the formation of huge cells. Using QAPB and confocal microscopy, we could observe colocalization of QAPB and LysoTracker®Red, a dye which specifically accumulates in lysosomes. Pretreatment of cells with chloroquine, which affects the mass and pH of lysosomes, protected MTC-SK cells against the toxity of Prazosin.

Conclusion: In addition to the previous observation that Prazosin induces endoplasmatic reticulum (ER) stress in MTC cells, we show here that also the lysosomes are involved in the cytotoxic reaction of Prazosin. Lysosomes may act as a protective buffer against Prazosin. Surviving cells undergo endomitosis instead of mitosis, but finally these cells are going to die too. Summarizing, Prazosin treatment affects several organelles, including the ER, lysosomes and the nucleus.

P3

IDENTIFICATION OF NOVEL VARIANTS OF RET ONCOGENE POTENTIALLY LINKED TO THE PATHOGENESIS OF PHEOCHROMOCYTOMA AND MEDULLARY THYROID CARCINOMA

Bim LV[1], *Delcelo R*[2], *Lima Jr. JV*[3,4], *Dias da Silva MR*[4], *Maciel RM*[4], *Cerutti JM*[1]
[1]Universidade Federal de São Paulo, Genetic Bases of Thyroid Tumor Laboratory, Department of Morfology and Genetics, São Paulo, Brazil, [2]Universidade Federal de São Paulo, Department of Pathology, São Paulo, Brazil, [3]Hospital Santa Casa de São Paulo, Department of Endocrinology, São Paulo, Brazil, [4]Universidade Federal de São Paulo, Department of Endocrinology, São Paulo, Brazil

Aim: Germline activating mutations of RET oncogene are associated with an autosomal dominant hereditary syndrome called multiple endocrine neoplasia type 2 (MEN 2), which can be classified into three subtypes: familial medullary thyroid carcinoma (FMTC), MEN 2A and MEN 2B. MEN 2A

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/etj

is characterized by the presence of medullary thyroid carcinoma (MTC), Pheochromocytoma (PHEO) and hyperparathyroidism (HPT). FMTC is characterized by the presence of MTC as the only clinical feature. Our group described a novel heterozygous mutation in exon 8 of *RET* gene associated with FMTC, which leads to a p.G533C substitution. Later, a member of this family was diagnosed with PHEO. Interestingly, in addition to the RET mutation p.G533C, two novel variants within RET oncogene were found in the DNA isolated from PHEO, which were not detected in the DNA extracted from the blood of the patient. Whether this event is associated with the pathogenesis of hereditary or sporadic PHEO is still unclear. We here investigated the prevalence of these new variants in the *RET* gene exon 8 (p.G548V) and exon 9 (p.S556T) in sporadic and hereditary PHEO and MTC.

Methods: A set of sporadic and MEN 2-associated PHEO (*n*=24) and MTC (*n*=39) were selected from the Department of Pathology at the Federal University of Sao Paulo, Brazil. Detection of RET variants in paraffin-embedded specimens or frozen samples was performed by direct sequencing of PCR products. Primers for exons 8 and 9 of the *RET* gene were designed using primer3 program.

Results and discussion: Here we report for the *first time* the RET p.G548V variant in DNA isolated from PHEO and MTC samples, while it was not found in the matched-DNA isolated from peripheral blood. Further functional studies are needed to demonstrate whether the p.G548V variant may play a role in the pathogenesis and/or progression of PHEO and MTC.

P4

ANGIOGENESIS-RELATED GENE EXPRESSION PROFILE ASSOCIATED WITH *RET* MUTATIONS IN MEDULLARY THYROID CANCER PATIENTS

Durante C[1], *Sponziello M*[1], *Checquolo S*[2], *Boichard A*[3], *Dima M*[1], *Verrienti A*[1], *Tamburrano G*[1], *Russo D*[4], *Schlumberger M*[5], *Bidart J-M*[3], *Filetti S*[1]

[1]University of Rome Sapienza, Department of Internal Medicine and Medical Specialties, Rome, Italy, [2]University of Rome Sapienza, Department of Experimental Medicine, Rome, Italy, [3]Institut de Cancérologie Gustave Roussy, Laboratoire de Recherche Translationnelle, Villejuif, France, [4]University of Catanzaro Magna Graecia, Department of Pharmacobiological Sciences, Catanzaro, Italy, [5]Institut de Cancérologie Gustave Roussy, Départment de médecine nucléaire et de carcinologie endocrinienne, Villejuif, France

Aims: Targeted molecular therapies that inhibit RET and other tyrosine kinase receptors known to be involved in angiogenesis are showing promising therapeutic results in the treatment of metastatic medullary thyroid cancer (MTC). Our objective was to identify an angiogenesis-related gene expression profile in medullary thyroid cancer patients in order to identify novel molecular targets.

Methods: A large series of 57 MTC patients were analyzed for the expression level of major proangiogenic factors. They included 13 familial MTCs, all hosting a RET mutation, and 44 sporadic forms, 21 of which with a RET somatic mutation. Quantitative real-time PCR with TaqMan Low Density Array (TLDA) was used to measure mRNA levels for vascular endothelial growth factors and VEGF receptor family; platelet derived growth factors and their receptors; angiopoietins; Matrix Metalloproteinases and their inhibitors. Moreover expression levels of Notch signaling pathway related-genes were assessed.

Results: mRNA levels for most of proangiogenic factors were significantly higher in patients carrying the *RET* mutation (both somatic and germinal) than in wild-type cases. Namely, the presence of RET mutations was associated to a significant over-expression of gene involved in Notch- (*NOTCH1-4* receptors; *JAGGED1-2* ligands; *TCF3*, *TLE1*, *RBPJ* and *MALM* regulators; *HEY1*, *HEY2*, *HEYL* effectors; *NUMB* repressor), VEGF- (*VEGF-A* ligand, and *VEGFR-1*, *VEGFR-2*, *VEGFR-3* receptors) and PDGF- (*PDGF-A* and *PDGF-B* ligands; *PDGFR-α*, *PDGFR-β* receptors) pathway and to a light significant increase of Angiopoietin2 gene. Metalloproteinases genes (MMPs) involved in matrix remodelling showed very low expression, while their inhibitors (TIMP genes) displayed higher mRNA expression level. Moreover the more aggressive diseases (N1, M1) showed an increase of *DLL3*, *JAGGED1-2*, *HEY1, HEYL*; *PDGFR-α, PDGFR-β;* Angiopoietin2 and *MMP2* gene expression.

Conclusions: These preliminary data demonstrate that altered expression of elements of angiogenic pathways is associate with the presence of the oncogenic RET activation in MTCs.

P5

DIFFERENTIAL *HES1* METHYLATION PROFILE IN FAMILIAL AND SPORADIC MEDULLARY THYROID CANCER

Cardoso MG[1], *Kizys MML*[2], *Harada MY*[2], *Ierardi DF*[3], *Molognoni F*[3], *Lindsey SC*[2], *Valente FOF*[2], *Delcelo R*[4], *Martins JRM*[2], *Maciel RMB*[2], *Jasiulionis MG*[3], *Dias da Silva MR*[2]

[1]Universidade Federal de Sao Paulo, Biochemistry, Sao Paulo, Brazil, [2]Universidade Federal de Sao Paulo, Medicine, Sao Paulo, Brazil, [3]Universidade Federal de Sao Paulo, Pharmacology, Sao Paulo, Brazil, [4]Universidade Federal de Sao Paulo, Pathology, Sao Paulo, Brazil

Introduction: Abnormal methylation seems to play an important role in differentiated thyroid carcinomas, in which several of the tumor suppressor genes are epigenetically silenced. Little is known about the methylation profile of genes related to medullary thyroid carcinoma (MTC). It has been observed aberrant Notch signaling in MTC that results in downregulation of *HES1* and up-regulation of *ASCL1* genes, following by higher expression of chromogranin A and calcitonin.

Objective: Therefore, we investigated if a downregulation of *HES1* tumor-suppressor could occur by hypermethylation of its regulatory region, and how its expression is correlated to the different clinical outcome observed in patients with MTC.

Methods: Paraffin-tumor tissue DNA extraction was collected from three familial (same kindred) and three sporadic MTC patients. DNA was treated with sodium bisulfite, purified and performed BSP-PCR amplification, thus submitted to bisulfite-genomic sequencing.

Results: Our data obtained from familial MTC and TT has shown hypomethylation of *HES1* promoter. However, it was observed hypermethylation in patients with sporadic MTC pattern. As Notch signaling has two faces depending on the cellular context and crosstalk with other signal-transduction pathways; one that promotes and the other that suppress tumorigenesis, our results might be related with the primary constitutive activation of the MAPK signaling pathway in familial cases, leading to hypomethylation of HES1, and as a second hit in sporadic ones, where HES1 can be hypermethylated. Such methylation-mediated silencing of tumor suppressor genes can act as one of the two hits advocated in Knudson´s hypothesis. In addition, our results suggest a strong correlation between the patterns of differential methylation with different clinical outcome observed in these patients.

Conclusion: Therefore, Notch pathway signaling can play a role in the progression and differentiation of MTC by hypermethylation of *HES1* tumor suppressor gene, comprising the simultaneous presence of both epigenetic and genetic alterations in MTC.

P6

EXPRESSION PATTERN OF MATRIX METALLOPROTEASES IN HUMAN MEDULLARY THYROID CARCINOMA CELL LINES

Ghaffari Tabrizi N[1], *Haas HS*[1], *Fuchs R*[1], *Schwach G*[1,2], *Allard N*[1], *Webersinke G*[3], *Sadjak A*[1], *Pfragner R*[1]

[1]Medical University of Graz, Institute of Pathophysiology and Immunology, Graz, Austria, [2]Yale School of Surgery, Department of Surgery, New Haven, United States, [3]Hospital Barmherzige Schwestern, Department of Internal Medicine, Laboratory for Molecular Biology and Tumorcytogenetics, Linz, Austria

Objectives: Medullary carcinoma of the thyroid (MTC) is a rare thyroid carcinoma that originates in the parafollicular C cells of the thyroid gland having a high metastasis potential. Over the last decade, several findings indicate that matrix metalloproteases (MMPs) are involved in tumourigenesis and metastasis. Their expression is related to the progression of several types of cancer. However the impact of MMPs in the formation and metastasis of MTC is not investigated.

Materials and methods: In this study we verified the expression pattern of the 23 MMPs, presently known in humans, in well characterized human medullary carcinoma cell lines. In total, 9 MTC-cell lines (BOJO, GRS-IV, GRS-V, MTC-SK, RARE, SHER-1, SINJ, OEE-III and TT) were examined. The expression of matrix metalloproteases was analyzed by RT-PCR. Western blot analyses were performed on selected MMPs.

Results and conclusion: All MTC cell lines constitutively express a wide variety of MMPs at mRNA and protein levels. In our study MMP-12, -20, -25,- 26 and -27 have not been detected at mRNA levels in any of the 9 cell lines analyzed, but MMP-2, -9 and -14 in most of them. Some of MMPs had a rather diverse expression pattern. We conclude that MTC cell lines can serve as promising candidates for future investigation dealing with the role of MMPs in processes of tumourigenesis and metastasis of medullary thyroid carcinoma.

P7

MICRORNA PROFILES IN FAMILIAL AND SPORADIC MEDULLARY THYROID CARCINOMA: PRELIMINARY RELATIONSHIPS WITH RET STATUS AND OUTCOME

Mian C[1], *Pennelli G*[1], *Fassan M*[1], *Balistreri M*[1], *Barollo S*[1], *Cavedon E*[1], *Galuppini F*[1], *Pizzi M*[1], *Vianello F*[2], *Pelizzo MR*[1], *Girelli ME*[1], *Opocher G*[2], *Rugge M*[1]
[1]University of Padua, Padua, Italy, [2]Veneto Institute of Oncology -IRCCS, Padua, Italy

Aim: microRNAs (miRNAs) are involved in the pathogenesis of human cancers, including medullary thyroid carcinomas (MTC). Here, we investigated miRNA dysregulation in familial and sporadic MTC, correlating miRNA expression with *RET* status and patients' prognosis.

Methods: We analyzed the expression of nine miRNAs (miR-21, miR-127, miR-154, miR-224, miR-323, miR-370, miR-9*, miR-183 and miR-375) by quantitative RT-PCR in 40 MTCs and 2 cases of C cell hyperplasia (CCH). Sporadic MTCs were genotyped for somatic *RET* and RAS mutations. Disease status was defined on the basis of the concentration of serum calcitonin at the latest follow-up.

Results: MTC and CCH are both characterized by a significant overexpression of the whole set of miRNAs (the increase being 4.2-fold for miR-21, 6.7-fold for miR-127, 8.8-fold for miR-154, 6.6-fold for miR-224, 5.8-fold for miR-323 and 6.1-fold for miR-370, 13-fold for miR-9*, 6.7-fold for miR-183 and 10.1 for miR-375, $p< 0.0001$). In sporadic MTCs carrying somatic *RET* mutations, the up-regulation of miR-127 is significant less pronounced than in cases without mutations. In sporadic and familial MTC, the up-regulation miR-224 correlated with the absence of node metastases and lower stages at diagnosis, and with biochemical cure during follow-up.

Conclusions: miRNAs are significantly dysregulated in MTCs, and this dysregulation is probably an early event in C cell carcinogenesis. Our preliminary findings suggest that at least the miR-224 up-regulation could represent a favorable prognostic indicator.

P8

SUNITIB REDUCES CELL VIABILITY IN PRIMARY CULTURES AND IN A CELL LINE OF MEDULLARY THYROID CARCINOMA

Rossi M[1], *Gentilin E*[1,2], *Minoia M*[1], *Tagliati F*[1], *degli Uberti E*[1,2], *Zatelli MC*[1,2]
[1]University of Ferrara, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy, [2]LTTA, University of Ferrara, Ferrara, Italy

RET constitutive activation is crucial for medullary thyroid carcinoma (MTC) pathogenesis and represents a pharmacological target for compounds targeting tyrosine kinases. Sunitinib (SU11248) is a multi-kinase inhibitor with both antiangiogenetic and antiproliferative activities, that also inhibits Vescular Endothelial Growth Factor (VEGF) and RET receptors. Sunitinib has been emèployed in clinical trials in the attempt to medically treat progressive MTC. We here investigate the possible mechanisms implicated in the antiproliferative effects of Sunitinib. We evaluated cell viability in a MTC cell line (TT cells) and in MTC primary cultures. MTC-derived cells were treated over 3 days with increasing Sunitinib concentrations (from 0.05 to 10 μM) or vehicle control. Sunitinib significantly reduced cell viability and VEGF secretion (~ 20%; $p< 0.01$) after 48 h at concentrations ≥ 7 μM. On the contrary, VEGF 10 ng/ml significantly promoted MTC-derived cell viability (+ 20%; $p< 0.05$), an effect completely counteracted by Sunitinib. These data indicate that Sunitinib reduces MTC cell viability with a mechanism involving VEGF, supporting its employment in the medical treatment for persistent/recurrent MTC.

P9

MTOR INHIBITORS HAMPERS CELL VIABILITY IN SELECTED HUMAN MEDULLARY THYROID CARCINOMA PRIMARY CULTURES

Minoia M[1], *Rossi M*[1], *Tagliati F*[1], *Rossi R*[1], *degli Uberti E*[1,2], *Zatelli MC*[2,3]
[1]University of Ferrara, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy, [2]LTTA, University of Ferrara, Ferrara, Italy, [3]University of Ferrara, Section of Endocrinology, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy

It has been demonstrated that mTOR inhibitors have potent anti-proliferative effects in a human Medullary Thyroid Carcinoma (MTC) cell line. We here explore the possible role of mTOR inhibitors, Everolimus and BEZ235 (which also inhibits the PI3K pathway) on the effects of Insulin-like Growth Factor-1 (IGF-1) in human MTC primary cultures. To this purpose, 20 MTC primary cultures, were treated without or with 1 mM Everolimus, 10 nM BEZ235, and/or 50 nM IGF-1. Cell viability and apoptosis were evaluated after 48 h. Everolimus and Bez235 significantly reduced MTC cell viability by 30% and 40%, respectively, while IGF-1 enhanced cell viability, an effect completely blocked by mTOR inhibitors. Co-incubation with an IGF-1R blocking antibody enhanced the antiproliferative effects of mTOR inhibitors. Phosphorylation of p70S6K, a down-stream effector of mTOR, was as well enhanced by IGF-1 and reduced by Everolimus and BEZ235. In conclusion, mTOR inhibitors reduced MTC cell viability by inducing apoptosis, with a mechanism likely involving IGF-1 signalling, suggesting that it might represent a possible medical treatment for persistent/recurrent MTCs.

P10

HIGH PREVALENCE OF *RAS* MUTATIONS IN SPORADIC MEDULLARY THYROID CARCINOMA

Sykorova V[1], *Dvorakova S*[1], *Vaclavikova E*[1,2], *Halkova T*[1,2], *Ryska A*[3], *Kodet R*[4], *Kodetova D*[4], *Astl J*[5], *Betka J*[5], *Duskova J*[6], *Vlcek P*[7], *Novak Z*[8], *Bendlova B*[1]
[1]Institute of Endocrinology, Department of Molecular Endocrinology, Prague, Czech Republic, [2]Charles University, Faculty of Science, Department of Biochemistry, Prague, Czech Republic, [3]Charles University Faculty of Medicine and University Hospital, The Fingerland Department of Pathology, Hradec Kralove, Czech Republic, [4]2nd Faculty of Medicine and Faculty Hospital Motol, Department of Pathology and Molecular Medicine, Prague, Czech Republic, [5]1st Faculty of Medicine and Faculty Hospital Motol, Charles University, Department of Otorhinolaryngology and Head and Neck Surgery, Prague, Czech Republic, [6]Institute of Pathology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [7]2nd Faculty of Medicine, Charles University and Hospital Motol, Department of Nuclear Medicine and Endocrinology, Prague, Czech Republic, [8]Institute of Endocrinology, Department of Clinical Endocrinology, Prague, Czech Republic

Objectives: Medullary thyroid carcinoma (MTC) occurs as a sporadic disease (70–85%) or less commonly as an autosomal dominant inherited form which comprises multiple endocrine neoplasia (MEN) type 2A and 2B syndromes and familial MTC (FMTC). The genetic cause of MTC are germline or somatic mutations in the *RET* proto-oncogene. Recently, the role of *RAS* mutations in the pathogenesis of sporadic *RET*-negative MTCs has been suggested. In our cohort of sporadic MTC, somatic activating mutations in *RET* proto-oncogene were detected in 39.5% of cases. The aim of our study was to determine the rate of *RAS* mutations in our cohort of sporadic *RET*-negative MTCs.

Methods: The presence of *RAS* mutations in exons 1 and 2 of the *H-RAS* and exon 2 of the *K-RAS* gene were determined in 33 sporadic *RET*-negative MTC samples (17 fresh frozen thyroid samples and 16 paraffin-embedded formalin-fixed samples) by direct sequencing.

Results: In the *H-RAS* gene we detected the mutation in codon 13 (p.Gly13Arg) in three of 33 MTC patients (9.1%) and the mutation in codon 61

(p.Gln61Arg) in five of 22 MTC patients (22.7%). In *K-RAS* gene we detected the mutation in codon 61 (p.Gln61Leu) in one of 33 MTC patients (3%).

Conclusion: In our cohort of 33 sporadic MTCs without *RET* mutation, we detected *RAS* mutations overall in 27.3% of cases. It seems that not only *RET* but also *RAS* gene plays a very important role in the development of sporadic MTC.

Supported by IGA MH CR NT 13901-4.

P11

COMPARISON OF THE FREQUENCY OF VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS) IN RET ONCOGENE BETWEEN PATIENTS WITH MEDULLARY THYROID CANCER (MTC) AND AN UNAFFECTED CONTROL POPULATION

Lindsey SC[1], *Germano Neto F*[1], *Kunii IS*[1], *Sittoni MY*[1], *Camacho CP*[1], *Valente FOF*[1], *Yang JH*[1], *Signorini PS*[1], *Maciel RMB*[1], *Dias da Silva MR*[1]
[1]Federal University of São Paulo, Medicine, São Paulo, Brazil

RET sequencing allows the identification of familial cases of MTC and early diagnosis or prophylactic thyroidectomy in affected relatives.

Several mutations have been described so far, along with a great number of synonymous and non-synonymous polymorphisms (SNPs). Many of the non-synonymous SNPs are considered VUS and this constitutes a common problem in clinical practice, as in all types of genetic testing, especially when it could lead to unnecessary thyroidectomy.

To analyze the frequency of VUS in RET in patients with MTC and to compare it to the frequency described for the general population. We analyzed the entire coding region of RET in 50 patients (100 chromosomes) with sporadic MTC for the presence of VUS. We then compared VUS allelic frequency to that of an unaffected control population from the USA obtained from the NHLBI Exome Sequencing Project (comprising over 4550 chromosomes) available at the Allele Frequency Database.

We observed the presence of three VUS: p.Gly691Ser, p.Gly550Glu and p.Arg982Cys. The frequency of p.Gly691Ser (rs1799939) was similar to that described in a group of 2275 individuals (ss342296549). The variant p.Tyr791Phe, which is subject of clinical controversy regarding its pathogenic role, was not observed. The variant p.Arg982Cys (rs17158558) was seen in one patient, similar to the frequency in a group of 2276 subjects (ss342296569). As for p.Gly550Glu, which affects a splicing region and has not been previously reported, we evaluated the patient's relatives; the mother and one sister were tested positive for this variant, but had undetectable serum calcitonin and no thyroid nodule at ultrasound examination.

Conclusions: Both VUS p.Gly691Ser and p.Arg982Cys are unlikely to be deleterious. As for the variant p.Gly550Glu, although it is unlikely damaging, due to its rarity and location at a splice site, the patient and her relatives must be monitored for signs and symptoms of MTC or MEN.

PO2 Thyroid Cancer Diagnostics Clinical 1

P12

THE COMBINATION OF AUTOIMMUNE TIREODIT AND MALIGNANT LESIONS OF THYROID TISSUE

Ryabchenko E[1]
[1]Krasnodar Municipal Medicinal - Diagnostic Association, Department of Endocrinologycal Surgery, Krasnodar, Russian Federation

Diagnosis of thyroid nodules (thyroid) in the presence of autoimmune tireodit (AIT) before surgical intervention is often very difficult.

The aim is to determine the effect of AIT as an underlying disease on the formation and development of various forms of nodular transformation of the thyroid gland and the accuracy of the results of cytological and histological examination of thyroid nodules on the background of Hashimoto´s thyroiditis.

Retrospective analysis of the results subjected to examination and treatment of 250 patients in the department of endocrine surgery after fine-needle biopsy (FNA) and surgical treatment. Histological examination of the drug, along with remote sites had morphological features of AIT in the form of lymphocytic infiltration of thyroid tissue. According to our data, in most cases the indication for surgical intervention in patients with nodes on the background of Hashimoto´s thyroiditis getting the results of cytological studies of nodes. Cytological diagnosis of "follicular neoplasm" was established in 164 cases, "papillary carcinoma" - 37 "follicular carcinoma" - 4 "follicular papillary carcinoma in 3." In 17 (54.8%) of 31 cases of colloid nodules on the background of Hashimoto´s thyroiditis after cytology defined indications for surgery: the presence of follicular tumors - 8, papillary carcinoma - 2, B-cell tumors - 1, follicular cancer - and 4-medullary two. In addition to cytology results in patients with Hashimoto´s thyroiditis, and there were clinical indications for surgical intervention. This is primarily the size of the site, its location behind the breastbone, or signs of compression of the surrounding host organs (magistrall vessels, respiratory tract). Thus, the AIT is often the background disease in patients undergoing surgical interventions on the thyroid gland at the junction of its transformation, and in most of our observations were true thyroid nodules on the background of Hashimoto´s thyroiditis.

P13

CONVENTIONAL PAPILLARY THYROID CARCINOMA IN CHILDREN AND ADOLESCENTS

Frydman M[1], *Mankovskaya S*[1], *Savva N*[2], *Krasko O*[3], *Schmid KW*[4], *Demidchik Y*[5]
[1]Republic Centre of Thyroid Tumors, Pathology, Minsk, Belarus, [2]Republic Scientific and Practical Centre for Childhood Tumors and Hematology, Childhood Cancer SubRegistry of the Republic of Belarus, Minsk, Belarus, [3]United Institute of Informatics Problems, Biomedical Statistic, Minsk, Belarus, [4]University Hospital of Essen, University of Duisburg-Essen, Institute of Pathology and Neuropathology, Essen, Germany, [5]Republic Centre of Thyroid Tumors, Surgery, Minsk, Belarus

Aims: To present wide-ranging clinical and pathological data of papillary thyroid cancer in patients less than 19 years old at the time of surgery. The entire series included 169 consecutive surgically treated patients, counting 23 (13.6%) children and adolescents who have the history of irradiation and 146 (86.4%) sporadic cases.

Material and methods: Retrospective analysis based on morphological reclassification.

Results: The mean age of patents was 14.4 years (range, 4.7–18.9 years). It was 126 girls and 43 boys (sex ratio, 2.9:1) In the majority of patients the carcinoma had already broke through the organ's capsule and afflicted lymph nodes of both paratracheal (level VI) and parajugular (level II-IV, in a few cases level V too) zones (pT3bN1bM0, n=52; 34.9%). Median tumor size was 12 mm (range, 1–100 mm). Classical variant of papillary thyroid carcinoma was the commonest subtype (n=67; 39.6%) follow by follicular (n=33; 19.5%) and tall cell (n=23; 13.6%) variants. Incidence of lymph node metastases at presentation was 76.3% (N1a - 21.3%, N1b - 55.0%). Classical architectonic ($p< 0.01$), nodular type of lymphoid infiltration ($p< 0.01$), lymph vessels invasion ($p< 0.001$) and infiltrative growth or diffuse (diffuse sclerosing or diffuse sclerosing-like) involvement were associated ($p< 0.01$) with lymph node metastases.

Conclusion: Usually tumours were >10mm in size (n=100; 59.2%). Extrathyroidal infiltration (n=68; 40.2%) and intrathyroid lymphatic vessels penetration by tumor complexes and psammoma bodies (n=139; 82.2%) was common. It is also typical that the tumor undergoes secondary scarring located mostly in central parts (massive fibrosis involves 30–70% of neoplasm volume observed in 48 cases; 28.4%). The tumors spread regionally. Finally, autoimmune thyroiditis appears to play a role in the background pathology (n=40; 23.7%).

P14

UNDETECTABLE PRE-ABLATION THYROGLOBULIN LEVELS IN PATIENTS WITH DIFFERENTIATED THYROID CANCER: NOT ALWAYS WHAT IT SEEMS

Pitoia F[1], Bueno F[1], Abelleira E[1], Salvai ME[1], Niepomniszcze H[1]
[1]Hospital de Clinicas - University of Buenos Aires, Buenos Aires, Argentina

Undetectable pre-ablation stimulated Tg (U Tg) is a very rare condition, that might be indicating: a complete surgery, secretion of non immunoreactive Tg or presence of non-measurable Tg-Ab.

Objetive: To establish the frequency of U Tg in patients with Tg-Ab negative, measured by IMA technology, and to evaluate the outcome of these patients in the follow-up.

Methods: We retrospectively reviewed 535 patients' records. Twenty eight patients (5.3%) had U Tg. Mean age was 48±14 years old, TNM Stages (*AJCC):* E I: n=17, EII: n= 2, EIII: n= 5, E IV: n=4. Risk of Recurrence: very low, n=2; low n=16; high n=10 (*LATS guidelines*). Finding of thyroiditis in pathology: 11/28 (39%). Mean radioiodine ablative dose: 123±40 mCi 131-I, follow-up: 42±38 months. All included subjects had received a total thyroidectomy, lymph node dissection had been performed in 18 patients (64%). Tg levels were measured 4 weeks after surgery and Tg-Ab levels were assessed by IMA technology in different laboratories. Free of disease (DF) status was defined as undetectable stimulated Tg + negative Tg-Ab and/or negative WBS, together with normal imaging studies.

Results: Seventeen patients (60%) were considered FD. Four patients (14%) had persistent disease (mediatinum, n=1, lung n=2, unknown n=1), and 7 (25%) had Tg-Ab detection by other methodology in their follow-up. Three of these 7 patients were finally considered FD (undetectable Tg with negative Tg-Ab in follow-up), and 4 of them still persist with detectable Tg-Ab.

Conclusions: Undetectable pre- ablation Tg levels usually indicate a complete surgery. However in a low percentage of patients, this situation may be related to the non-detectable Tg-Ab. When thyroiditis is found in pathology, or when initial TNM Stages and discordant pre-ablation Tg level is found, it is imperative to measure Tg-Ab with different laboratory kits, to avoid considering erroneously a patient as FD.

P15

INTRINSIC FACTORS AFFECTING ADEQUACY IN THYROID NODULE FINE-NEEDLE ASPIRATION CYTOLOGY

Grani G[1], Calvanese A[1], Carbotta G[1], D'Alessandri M[1], Nesca A[1], Bianchini M[1], Del Sordo M[1], Fumarola A[1]
[1]Sapienza University of Rome, Dept. of Experimental Medicine, Rome, Italy

Objectives: Fine-needle aspiration (FNA) is a safe and cost-effective method for the characterization of thyroid nodules. Inadequacy is common and can be ascribable to several factors. The aim of this study was to indagate demographic characteristics, as well as US features, that may identify patients at risk for nondiagnostic FNAC results.

Methods: Between May 2005 and April 2011, 3279 ultrasonography-assisted FNACs were carried out and features of nodules prospectively recorded. Univariate logistic regression analyses were performed to estimate the association between non-diagnostic cytology and variables such as age, gender, single nodule, maximum nodule diameter, and estimated volume.

Results: Inadequate or non-diagnostic samples were reported in 1195 FNACs. All diameters were found to be predictors of non-diagnostic cytology; estimated nodule volume, on the other hand, was not. Nodules with a diameter < 10 mm are more frequently non-diagnostic (OR 1.65, 95% CI 1.40–1.94, p< 0.001). Neither the micro- nor macro-calcifications increase risk of inadequacy. On the contrary, mixed lesions are more frequently diagnostic (OR 0.68, 95% CI 0.85–0.80, p< 0.001). Solid nodule aspiration is performed more easily on isoechogenic nodules (OR 0.64, 95% CI 0.54–0.77, p>0.001); this same procedure is more cumbersome on hypoechogenic lesions (OR 1.87, 95% CI 1.62–2.16, p>0.001). Increased vascularization does not cause a significant increase of non-diagnostic results. Blurred margins increase inadequacy rate (OR 1.45, 95% CI 1.24–1.69, p< 0.001), while hypoechogenic halo decreases it (OR 0.67, 95% CI 0.54–0.82, p< 0.001).

Conclusions: Some ultrasonographic features suggestive of malignancy may be predictive of inadequate cytology. Patients must be notified that the FNA report may be non-diagnostic and that this represents a limitation of the technique related to the structure of lesions.

P16

DETECTION OF RESIDUAL THYROID TISSUE AFTER TOTAL THYROIDECTOMY FOR DIFFERENTIATED THYROID CARCINOMA

Nabawi A[1], Al-Wagih H[1], Zakarya SED[1], El serfay M[2], Arafat W[3], Mansour F[1]
[1]Alexandria University, Faculty of Medicine, Surgery, Alexandria, Egypt, [2]Alexandria University, Faculty of Medicine, Radiology, Alexandria, Egypt, [3]Alexandria University, Faculty of Medicine, Clinical Oncology, Alexandria, Egypt

Objectives: The aim of this work is to study the validity of Radioactive Iodine Scanning (RAIS) versus Ultrasonography (US) and Computed Tomography (CT) in the detection of residual thyroid tissue after total thyroidectomy for patients with differentiated thyroid carcinoma (DTC).

Methods: Thirty patients with DTC were treated by total thyroidectomy and the appropriate type of neck dissection when indicated. One month postoperatively they were all adjuvantly treated with radioactive iodine. All patients were followed up postoperatively by the following: 1- (RAIS), (CT), and (US) within two weeks. 2- Serum Thyroglobulin after Radioactive Iodine ablation after one month. 3- (RAIS), (CT), and (US) within two months.

Results: After two weeks; (US) was 90% accurate followed by (CT) 83.33% then (RAIS) 46.67%. After two months; (US) accuracy reached 100%, (CT) 96.6%, and (RAIS) 90%.

Conclusions: Neck (US) is highly specific for detection of residual thyroid tumors at the surgical bed compared to (RAIS) although it is an operator dependent technique. (CT) follows (US) as regards specificity for detection of residual tumor but it is less sensitive. Serum Thyroglobulin has the highest sensitivity and specificity for detecting recurrent disease after total thyroidectomy and Radioactive Iodine ablation of any microscopic residual thyroid cells.

P17

THE UTILITY OF BONE SCINTIGRAPHY AND THORAX CT BEFORE RAI TREATMENT FOR DETECT BONE AND LUNG METASTASES

Ozkaya M[1], Elboga U[2], Kalender E[2], Celen YZ[2]
[1]University of Gaziantep, Endocrinology, Gaziantep, Turkey, [2]University of Gaziantep, Nuclear Medicine, Gaziantep, Turkey

Objective: Differentiated thyroid carcinomas are usually treatable malignancies with good prognosis. However in some cases distant metastases may occur. The aim of this study is to determine the success of the bone scintigraphy and thorax CT which were identified before RAI treatment to detection bone and lung metastases.

Methods: Twenty eight patients with lung metastases who were identified thorax CTs before RAI treatment and 10 patients with bone metastases who were identified bone scintigraphy before the RAI treatment included in this study. We evaluated the findings of thorax CT, bone scintigraphy and whole body I-131 scanning which was identified after RAI treatment of these patients.

Results: Bone metastases were detected with bone scintigraphy which were identified before RAI treatment in 80% of patients with bone metastases and lung metastases were detected with thorax CT which were identified before RAI treatment in 79% of patients with lung metastases.

Conclusion: Bone scintigraphy and thorax CT are useful imaging methods to detecting bone and lung metastases before RAI treatment in the patients diagnosed with differentiated thyroid carcinoma who have high risk characteristics and thyroglobulin levels higher than expected. In these patients correlation of bone scintigraphy and thorax CT findings with findings of whole body I-131 scanning which is identified after RAI treatment have very high spesicifity and sensitivity in determining lung and bone metastases.

P18

UNDERUSE OF DIAGNOSTIC POSSIBILITIES IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMAS

Lincke T[1], Dörnfelder M[2], Paschke R[3], Sabri O[1]
[1]Uniklinik für Nuklearmedizin, Leipzig, Germany, [2]Uniklinik, Leipzig, Germany, [3]Uniklinik für Endokrinologie, Leipzig, Germany

At an early stage thyroid carcinomas are often asymptomatic and are therefore mostly detected by a standardized diagnostic approach to thyroid nodules. The aim of this study was to examine which diagnostic tools were applied, finally leading to the diagnosis of thyroid cancer. We retrospectively screened the charts of 256 patients with a history of differentiated thyroid carcinoma at the Leipzig University Hospital. Missing data were retrieved from referring physicians and the patients were interviewed in a standardized manner. Preexisting thyroid diseases like goiter or thyroid nodules were present in 23% and 27%. Palpable nodules or nodule growth were noted by 37% and 15% of the patients. Nodules with diameter of more than 3 cm were noticed significantly more frequent than smaller ones. As a diagnostic procedure thyroid scintigraphy was performed most often in 78,5%. The scintigraphic appearance of carcinomas >10mm was isocaptant in 28%, warm in 2% and cold in 70%. Ultrasound results were available for 251 patients. No comment on the echogenicity was found in 54%, hypoechogenicity in 32% hyperechogenicity in 2%, echocomplexity in 8%, isodensity in 2% and cysts in 2%. Fine needle aspiration biopsy was performed for sonographically >10 mm nodules in 10%. It was non diagnostic in 26%, benign in 15% and malignant in 59%. Patients with a malignant FNAC underwent primary thyroidectomy significantly more often (65%) than patients without(50%). Only 16% of the patients were operated because of a preoperative suspicion of malignancy. Our data demonstrate that most patients later diagnosed with a thyroid carcinoma underwent primary thyroid surgery without a specific suspicion of malignancy. This could most likely mainly be due to the very infrequent use of preoperative FNAC, a high rate of non diagnostic FNACs and a lack of malignancy risk stratification by ultrasound criteria.

P19

MULTIFOCAL PAPILLARY THYROID CARCINIOMA ASSESSMENT IN PATIENTS WITH HASHIMOTO THYROIDITIS AFTER POSSIBLE RADIATION EXPOSURE

Zaplatnikov K[1], Soukhov V[2]
[1]Clinic for Nuclearmedicine Nuernberg, Nuclearmedicine, Nuernberg, Germany, [2]Militar Medical Academy St. Petersburg, Nuclermedicine, St. Petersburg, Russian Federation

Papillary thyroid carcinoma (PTC) sometimes develops within background of Hashimoto´s thyroiditis (HT). It is often difficult to differentiate between benign and malignant nodules due to vast variety of ultrasonographic HT representation. The aim of our work was to characterize the US and scintigraphic features of PTC in patients with HT and studied relatives of patients with HT and PTC. We prospectively studied 42 first-grade relatives (f30; m12; median age, 59 +/-14 yrs) of patiets with HT/ PTC. 38 of 42 studied patients (90%) were residents of North-eastern regions of Kazakhstan near from Nucleartestregion, prior to their repatriation to Germany. Initial investigation included clinical examination, sonography, ^{99m}Tc scan, thyroid hormone levels as well as anti-TPO and anti-Tg antibodies detection. Every case of PTC was confirmed by pathohistological examination. All pts had HT with high levels of thyroid Ab (TgAb, TPOAb). 17 of 33 autoantibody positive pts with suspicious multifocal non-uniform thyroid nodules (hypoechogeneic, with calcifications, presenting cold lesion in ^{99m}Tc scan and highly vascular) underwent thyreoidectomy. In 58%- 10/17 pts in this Group had multifocal PTC (up to pT3). US signs of calcifications in these pts have been revealed significantly frequently (P=0.05) than in Group without PTC, but al other features assumed as diagnostic parameters (size of nodules, shape, location in the gland,, tracer uptake) did not show any particular statistically difference between HT and PTC Groups.

A high prevalence (100%) of HT and multifocal PTC (25%) might be related to the fact, that a majority of pts were previously residents of Regions of Kazakhstan (probability of extensive radiation exposure). Indeed, a high incidence of HT/PTC, adjacent to the Semipalatinsk nuclear test site was reported. Our results justify a neccessity of screening for HT/PTC in this population group. Calcifications can be a useful indicator of enhanced PTC risk.

P20

POORLY DIFFERENTIATED FORMS OF THYROID CARCINOMA ARE OVER REPRESENTED IN CANCER DIAGNOSED AT AN ADVANCED STAGE. PRELIMINARY ANALYSIS OF A FRENCH PROSPECTIVE COHORT IN THE FRAME OF TUTHYREF NETWORK

Bournaud C[1], Decaussin M[2], Cimarelli S[3], de la Fouchardière C[3], Nejjari Z[4], Sassolas G[4], Bringuier PP[2], Mognetti T[3], Masson S[1], Borson Chazot F[1,4], Schlumberger M[5], TUTHYREF network
[1]Groupement Hospitalier Lyon-Est, Federation d'Endocrinologie et CMN, Bron Cedex, France, [2]Groupement Hospitalier Lyon-Sud, Service de Chirurgie et Anapathologie, Lyon, France, [3]CLCC Léon Bérard, Lyon, France, [4]CRCL Inserm U1052, Université Lyon 1, Lyon, France, [5]Institut Gustave Roussy, Service de Médecine Nucléaire et Endocrinologie, Paris, France

It is generally estimated that 5% of patients with thyroid cancer will develop distant metastases, and most of them had an advanced stage of the disease at presentation. Thirty per cent of them are resistant to radio iodine therapy and are called "refractory". Their long term survival is estimated to be less than 10%.

From a retrospective study of 45 patients with refractory thyroid cancer, we found that 90% of them were discovered at an advanced stage (pT3 > 2 cm, pT4 or M1). In collaboration with the Thyroid Cancer Registry of the Rhône-Alpes *region (TCRRA)* - a population-based collection of histologically proven incident cases - a prospective study was undertaken to identify the factors associated with poor outcome in a cohort of 400 patients with advanced thyroid cancer followed during 5 years. Anaplastic and medullary thyroid carcinomas were excluded. One hundred and sixty patients referred for iodine therapy after surgery, were prospectively included in 2010 and 2011. They corresponded to 12% of thyroid cancers annually diagnosed in the *TCRRA*. Preliminary analysis of the 119 first cases (female 67%, age 56; range 19–89 years) showed at diagnosis 104 pT3, 11 pT4 and 9 patients metastatic. As for histology, 88% were well differentiated thyroid carcinomas (papillary n= 95, follicular n= 9), and 12% (n=14) were poorly differentiated mainly from the insular subtype.

By comparison with the *TCRRA* population (n=5367 cases), there was a higher proportion of poorly differentiated thyroid cancer (3% vs 12%, $p<.001$) among patients with cancer diagnosed at an advanced stage.

P21

ULTRASONOGRAPHIC FEATURES OF PAPILLARY CARCINOMA: FIVE-YEAR EXPERIENCE IN THYROID REFFERAL CENTER

Sisko Markos I[1], Franceschi M[1], Roncevic S[1], Gladic Nenadic V[1], Matesa N[1], Kusic Z[1]
[1]University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia

Objective: To evaluate the ultrasonographic (US) features of thyroid nodules diagnosed by FNA (fine-needle aspiration) as papillary carcinoma (PC).

Methods: Thyroid US of patients (pts) with PC was retrospectively analysed from a 5-year period (2007–2012). Basic demographic data, thyroid mass, location and size of the nodules, US features: a) echogenicity (hypo-, iso-, hyper-, complex); b) vascularisation (yes/no); c) microcalcifications (yes/no) d) borders (regular/irregular) were evaluated. Neck US ability to detect lymph node metastasis in lateral neck compartments was also assessed.

Results: 122 PC nodules in 115 pts were detected. Mean age of pts was 48 years (range 13y to 80y), and the female/male ratio was 9:1. The PC nodules were located mostly in the lower third of right lobe of thyroid gland - 39 (29%), and the least common location was in the middle third of left lobe - 11 (8%). Nodules ranged in size from 5 mm to 29 mm, with mean 12.6 mm. Mean thyroid mass was 26 gr. 52% of nodules were hypoechogenic, 39% were isoechogenic, 2.5% were hyperechogenic and 6.5% were complex. Microcalcifications were present in 50% of the nodules, increased nodal vascularity was detected in 11.5% nodules and 20% of the nodules had irregular

borders. 31% of pts with PC had Hashimoto's thyroiditis as well. Ipsilateral lymph node metastases were detected in 5.2% pts.

Conclusions: The most common US features of PC nodules are hypoechogenicity and microcalcifications. Location of the nodule can be used to identify the pts with increased risk of PC. Irregular borders and increased nodal vascularity are present only in every fifth and ninth PC nodule, respectively. Our pts with nodules and Hashimoto's thyroiditis have increased risk of PC.

P22

FEASIBILITY OF REAL-TIME PCR TESTING FOR BRAF V600E MUTATIONS IN FINE-NEEDLE ASPIRATES OF THYROID TISSUE

Lozano MD[1], *Labiano T*[1], *Montanana M*[1], *Echeveste JI*[1], *Lawrence HJ*[2], *Shieh F*[2], *Algarra SM*[1]

[1]Universidad de Navarra, Department of Oncology, Pamplona, Spain, [2]Roche Molecular Systems, Genomics and Oncology, Pleasanton, United States

Objectives: BRAF mutations are common in papillary thyroid cancer (PTC). Those thyroid cancers with BRAF mutations are generally more aggressive that their counterparts without the mutation. Moreover BRAF mutation testing is helpful in the cytological preoperative diagnosis of suspicious/indeterminate thyroid nodules. Thyroid nodules are typically assessed with FNAs, which provide little DNA for molecular testing.

Methods: The performance of the **cobas**® 4800 BRAF V600 Mutation Test was assessed in FNA thyroid specimens. This test is a CE-marked, FDA-approved assay for detecting BRAF mutations in formalin-fixed paraffin-embedded tissue (FFPET) specimens of melanoma and thyroid. The assay can be performed in < 8 hours; analysis and result reporting is fully automated.

Results: 31 thyroid FNAs were tested with the cobas BRAF test, including 27 specimens of PTC, 1 case of nodular hyperplasia, and 3 cervical lymph node metastases of PTC. In 30 cases (97%), DNA was isolated from stained smears. All FNAs used in the study were fixed in 96º ethanol and stained with Papanicolau. DNA was isolated in duplicate using the cobas DNA isolation kit and Nucleospin DNA extraction kit. Although < 5 ng/ul of DNA was isolated in 11/31 samples using the cobas kit, and in 16/31 using the Nucleospin kit, valid test results were achieved for all 31 specimens using cobas DNA isolation kit and in 29 using the Nucleospin kit. V600E mutations were detected in 22/31 (71%) specimens. Sanger sequencing was performed on 16/31 specimens and yielded concordant results with the cobas test in all cases.

Conclusions: Despite the low DNA yields, it is feasible to use the **cobas** test to detect BRAF mutations in FNAs of thyroid nodules. Although the cobas reagents are designed to work with FFPET, DNA yields from cytological stained smears using the cobas DNA isolation kit were adequate for mutation testing.

P23

FIRST UK THYROID CANCER AWARENESS CAMPAIGN

Farnell K[1], *Perros P*[1], *Bliss R*[1], *Mallick UK*[1]

[1]Freeman Hospital, Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom

Introduction: Thyroid cancer is potentially curable, yet late presentations still occur. Current guidelines recommend that newly discovered palpable thyroid nodules should be investigated.

Objectives: To promote public awareness of thyroid lumps and thyroid cancer.

Methods: Butterfly Thyroid Cancer Trust in partnership with the Newcastle Thyroid Cancer clinical team hosted an awareness event. A professionally produced video was shown via the Butterfly website, YouTube and on local TV. A dedicated website to promote the event was launched (www.neckcheck2011.org.uk). The event took place in a busy shopping mall on a Saturday morning in September 2011. Several volunteers including twelve thyroid experts took part. A seating area for fifty was provided in front of a screen, which projected educational material on thyroid cancer. Members of the public who thought they had thyroid lumps had the opportunity to be examined by a member the medical team.

Results: Members of the public began arriving at 8.30am. By 10am the queue was three hundred deep. Admission to the event had to close at 5 pm. The medical team examined one thousand necks. Average waiting time was ninety minutes. Forty people were identified as requiring further investigation. A fast track clinic was arranged in advance in anticipation of this. Pathology has confirmed two new thyroid cancers. Feedback from the public was positive and many asked for this event to be repeated annually.

Conclusion: There is a great demand by the public to learn about thyroid lumps and thyroid cancer. Wide advertising, appropriate choice of venue and joint hosting by a patient led organisation and thyroid experts appear to be important factors in making the event attractive. The yield of thyroid cancer among people who think they may have thyroid lumps or thyroid cancer is very low. This experience will be valuable in planning further awareness events.

P24

RATE, TIME AND RISK FACTORS FOR RECURRENCE IN PATIENTS AFFECTED WITH DIFFERENTIATED THYROID CANCER (DTC): A 10 YEAR PROSPECTIVE STUDY

Pieruzzi L[1], *Molinaro E*[1], *Giani C*[1], *Marconcini G*[1], *Viola D*[1], *Valerio L*[1], *Biagini A*[1], *Bianchi F*[1], *Brozzi F*[1], *Taddei D*[1], *Nencetti C*[1], *Pinchera A*[1], *Vitti P*[1], *Elisei R*[1]

[1]University of Pisa, Department of Endocrinology, Pisa, Italy

Background: It is known that 10–15% of DTC will recur during the 30–40 years after their clinical remission but it is still not well defined which are the prognostic factors of recurrences. Aim of this study was to evaluate the recurrence rate, the time of recurrence and the prognostic factors in a series of DTC patients who were declared free-of-disease between 1999 and 2001 and then prospectively followed up for more than 10 years.

Methods: We analyzed 138 DTC patients: 126(91.3%) with a papillary histotype(PTC) and 12(8%) with a follicular histotype(FTC). Patients were followed with annual clinical and biochemical controls. The evidence of detectable levels of serum thyroglobulin(Tg) or the identification of lymph-node at neck ultrasound suggested the recurrence. Clinical and pathological features were reported in a database.

Results: During a follow-up of 10 years, we observed 11/138(7.97%) recurrences, 6 of whom (6/11, 54.5%) happened within the first five years from the clinical remission. Among the several possible prognostic factors that we analyzed only an advanced stage at diagnosis ($p< 0.02$), a more aggressive variant ($p< 0.01$) and an older age at diagnosis ($p< 0.04$) were significantly correlated with the recurrence rate. Conversely, sex, intra or extrathyroidal extension, presence of lymph-node or distant metastases *per se* and the ATA risk level did not correlate with the recurrence rate.

Conclusions: About 8% of recurrences were observed in a series of DTC, who were defined in clinical remission according with the most recently defined criteria, and prospectively followed-up for at least 10 years after the definition of their cure. More than 50% of recurrences were found within the first five years from the remission. Among several, the significant poor prognostic factors for the recurrence were the most aggressive histological variant, the advanced stage and an older age at diagnosis.

PO3 Thyroid Cancer Pathogenesis Basic

P25

FREQUENT INCIDENCE OF *BRAF* MUTATION IN POST-CHORNOBYL PAPILLARY THYROID CARCINOMA

Dinets A[1,2], *Hulchiy M*[2], *Sofiadis A*[1], *Ghaderi M*[3], *Höög A*[3], *Larsson C*[1], *Zedenius J*[1]

[1]Karolinska Institutet, Molecular Medicine and Surgery, Stockholm, Sweden, [2]Kyiv City Teaching Endocrinlogical Center, Endocrine Surgery, Kyiv, Ukraine, [3]Karolinska University Hospital, Pathology-Cytology, Stockholm, Sweden

Papillary thyroid carcinoma (PTC) is a most common endocrine malignancy. PTCs commonly demonstrate a *BRAF* mutation resulting in thymine-

to-adenine transversion at position 1799 in exon 15. Although, the most patients with PTC have an excellent prognosis, the *BRAF* mutation is reported to be a factor of worse outcome.

Objectives: To investigate and correlate the *BRAF* mutation in a cohort of adult patients with PTC who, during their childhood were exposed to radioactivity from the Chornobyl accident in 1986.

Methods: Seventy patients (61 females, 9 males), with a mean age of 30.5 (range 19–39 years) operated on for PTC during 2004–2008 were identified for the study. Those patients were younger than 18 years of age at the time of the Chornobyl accident, but diagnosed for PTC in their adolescence. Two groups were established according to diagnosis. Patients with classical PTC comprised PTC group (n = 54), whereas PTC accompanied by chronic lymphocytic thyroiditis (PTC/CLT) comprised the second group (n = 16). Pyrosequencing was performed to determine *BRAF* mutation status. The clinical data and Pyrosequencing findings were used for statistical analyses.

Results: Incidence of *BRAF* mutation was 3.5 times higher in the PTC group (24/54, 44%) as compared to PTC/CLT (2/16, 12%), p = 0.02. The mean tumor size was slightly higher in PTC (2 cm) as compared to PTC/CLT (1.8 cm) group. The mean age at diagnosis (30 years) and age at the Chornobyl accident (10 years) were not significant between the groups.

Conclusions: The clinical features of this cohort of adult PTC patients exposed to the radioactive fallout from the Chornobyl accident seem to be no different than other PTC cohorts. Our results suggest that *BRAF* mutation is associated with more aggressive PTC, while the presence of CLT in PTC seems to lead to a better prognosis.

P26

HIGHER EXPRESSION OF AMPK AND PHOSPHO-THR172-AMPK IN PAPILLARY THYROID CANCER

Andrade B[1], *Vidal AP*[2], *Vaisman F*[3], *Cazarin J*[1], *Caroli-Bottino A*[2], *Corbo R*[4], *Vaisman M*[2], *Carvalho D*[1]

[1]Federal University of Rio de Janeiro, IBCCF, Rio de Janeiro, Brazil, [2]Federal University of Rio de Janeiro, Clementino Fraga Filho University Hospital-UFRJ, Rio de Janeiro, Brazil, [3]Federal University of Rio de Janeiro/ National Institute of Cancer, Endocrine Service - Clementino Fraga Filho University Hospital-UFRJ, Rio de Janeiro, Brazil, [4]National Institute of Cancer, Rio de Janeiro, Brazil

Introduction: Although the role of AMP-activated protein kinase (AMPK) in cancer cells is poorly understood, at least 2 antagonist actions have been described for this kinase: (1) survival of cells during metabolic "stress conditions"; (2) decrease in cell proliferation rate. Recently, we described that AMPK activation decreases iodide and increases glucose uptake in rat thyrocytes. However, the participation of AMPK in thyroid cancer development and progression is not known.

Objective: To evaluate the expression and phosphorylation of AMPK in papillary thyroid carcinomas.

Methods: We examined AMPK-a and phospho-Thr172-AMPK by immunohistochemistry using one block of tissue microarray (TMA) composed of tissues from 57 patients with papillary thyroid carcinomas (PAP CA) accompanied at the Clementino Fraga Filho University Hospital-UFRJ. The expression was compared with non-neoplastic tissue (NNT) from the same patient. Two different pathologists following previously established scores of intensity and proportion of staining analyzed the samples. We calculated the overall staining score by multiplying the values of intensity and proportion.

Results: When paired samples were compared analyzing the expression of AMPK-a and phospho-Thr172-AMPK, a significant increased was found in the overall score of PAP CA in relation to NNT (AMPK-a - 15.9± 0.39; 14.0± 0.62, and AMPK-a-phospho Thr172 - 12.1± 0.72; 7.8± 0.67, respectively). Specifically, the increased overall score was predominantly due to an increase in the number of cells stained with the highest score (proportion), comparing PAP CA spots and NNT for both AMPK-a (96 vs 46% of total samples, respectively) and phosphor-Thr172-AMPK-a (67 vs 9%, of total samples, respectively).

Conclusion: Our results show an increase in the number of cells expressing a higher content of total and phosphorylated AMPK in PAP CA in relation to their NNT counterpart. However, more studies are necessary to understand the pathophysiological role of AMPK in this thyroid tumor subtype.

P27

CHARACTERISTICS OF ADULT-ONSET PAPILLARY THYROID CANCER WITH REARRANGED *ALK* GENE IN ATOMIC BOMB SURVIVORS

Hamatani K[1], *Mukai M*[1], *Takahashi K*[1], *Hayashi Y*[2], *Nakachi K*[1], *Kusunoki Y*[1]

[1]Radiation Effects Research Foundation, Radiobiology/Molecular Epidemiology, Hiroshima, Japan, [2]Geriatric Health Service Facility Hidamari, Hiroshima, Japan

Thyroid cancer is one of the malignancies most strongly associated with ionizing radiation in humans. RERF epidemiology studies of atomic bomb (A-bomb) survivors have indicated that excess relative risk of papillary thyroid cancer (PTC) per Gy was remarkably high in the survivors.

We therefore aim to clarify mechanisms linking A-bomb radiation exposure and development of PTC, and use such information for the prevention, diagnosis and treatment of thyroid cancer. Toward this end, we intend to clarify characteristics of gene alterations occurring in radiation-associated adult-onset PTC from the Life Span Study cohort of A-bomb survivors. We have thus far found that with increased radiation dose, relative frequency of PTC cases with chromosomal rearrangements (mainly *RET/PTC* rearrangements) significantly increased and those with point mutations (mainly $BRAF^{V600E}$) significantly decreased. Relative frequency of PTC cases with non-detected gene alterations that carried no mutations in *RET*, *NTRK1*, *BRAF* or *RAS* genes tended to increase with increased radiation dose, and significantly decreased with time elapsed since exposure, suggesting that some of these PTC cases were associated with radiation exposure. Through analysis of 25 PTC cases with non-detected gene alterations, we found rearranged anaplastic lymphoma kinase (*ALK*) gene for the first time in 10 of 19 radiation-exposed PTC cases but none in 6 non-exposed cases. Solid/ trabecular-like architectures were observed in 6 of 10 PTC cases with *ALK* rearrangements. In addition, these 6 PTC cases with *ALK* rearrangements and solid/ trabecular-like architectures were significantly associated with increased radiation dose and decreased age at atomic bombings, compared with the other 19 PTC cases. These findings imply that not only *RET/PTC* rearrangements but also *ALK* rearrangements may be closely associated with the development of radiation-associated adult-onset PTC.

P28

GENETIC PREDISPOSITION TO THE DIFFERENTIATED THYROID CANCER

Köhler A[1,2], *Chen B*[1], *Gemignani F*[3], *Elisei R*[4], *Romei C*[4], *Kalemba M*[2], *Kula D*[2], *Broderick P*[5], *Houlston R*[5], *Jarząb B*[2], *Hemminki K*[1,6], *Landi S*[3], *Försti A*[1,6]

[1]German Cancer Research Center (DKFZ), Molecular Genetic Epidemiology, Heidelberg, Germany, [2]Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Department of Nuclear Medicine and Endocrine Oncology, Gliwice, Poland, [3]University of Pisa, Department of Biology, Pisa, Italy, [4]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy, [5]Institute of Cancer Research, Section of Cancer Genetics, Sutton, United Kingdom, [6]Lund University, Center for Primary Health Care Research, Clinical Research Center, Malmö, Sweden

Differentiated thyroid cancer (DTC) is the most common endocrinological malignancy. Apart from medullary thyroid cancer, also DTC can have familial background, although the inheritance pattern is not so clear. It is presumed that it can be caused by multiple low- and moderate-penetrance DNA changes, which together can lead to increased susceptibility to DTC. Few genome-wide association studies (GWASs) followed by replication studies have shown that genetic variants in the *FOXE1* and *NKX2-1* region as well as in *NRG1* and *DIRC3* genes have association with the disease. Still, they don't explain all the possible causes. The aim of our study was to search for possible thyroid cancer risk variants other than the already well described *FOXE1*. For initial GWAS, 694 Italian DTC samples and 498 controls were used. The analysis was conducted on Omni_Quad 1M platform (cases) and Omni_Express 730K (controls). Based on the results of the GWAS and a linkage disequilibrium analysis of polymorphisms with minor allele frequency >0.05, Hardy-Weinberg equilibrium >0.00005 and genotype call rate >0.95, we initially

selected 32 polymorphisms in different loci for replication (p-values between $1,1 \times 10^{-3}$ and $1,4 \times 10^{-6}$); eight polymorphisms in *FOXE1* were among the best 50 and were not considered further. The polymorphisms were replicated in three different populations: Italian (1557 cases and 1712 controls), Polish (468 cases and 470 controls) and UK (509 cases and 1118 controls). The combined analysis revealed association of two loci with thyroid cancer: 2q35 (*DIRC3*, p-value $1,1 \times 10^{-8}$) and 7q35 (p-value $1,2 \times 10^{-6}$). Additionally, in the Italian population, two other loci, 3q25.32 and 9q34.3, showed an association at a lower significance level (p-values $3,2 \times 10^{-3}$ and $5,2 \times 10^{-4}$, respectively). Our results confirmed the recently described *FOXE1* and *DIRC3* genes as possible DTC susceptibility genes and suggested an involvement of three other predisposing variants.

P29

EXPRESSION OF THE RING LIGASE PRAJA2 IN THYROID CANCER

Cantara S[1], *D'Angeli F*[1], *Toti P*[2], *Castagna MG*[1], *Capuano S*[1], *Feliciello A*[3], *Pacini F*[1]
[1]University of Siena, Department of Internal Medicine, Endocrinology & Metabolism and Biochemistry, Siena, Italy, [2]University of Siena, Department of Human Pathology and Oncology, Siena, Italy, [3]University of Naples, Federico II, Department of Biology and Molecular and Cellular Pathology "L. Califano, Naples, Italy

Introduction: Praja2 is a RING ligase which degrades regulatory subunits of PKA thus controlling the strength and duration of PKA signal in response to cAMP. TSH, through activation of its receptor, increases cAMP inside the cells, sustaining tyrocytes growth and hormone production. Differentiated thyroid cancer (DTC) is a TSH-dependent tumor and its function is modulating by TSH levels.

Aim: We aimed to analyse PRAJA2 expression in a group of 36 DTC, 14 benign nodules and 6 anaplastic thyroid cancers (ATC).

Methods: To this purpose, we measured mRNA levels by real time RT-PCR and protein by western blot and immunohistochemestry. Possible association between PRAJA2 mRNA and presence of known mutations was evaluated.

Results: We found a statistical significant ($p < 0.001$) increase of mRNA levels in PTC compared to benign nodules and ATC. In particular, the expression was maximal in well differentiated histological variants and decreased progressively with loss of differentiation. Western blot revealed that PRAJA2 mRNA was translated into a protein with OD arbitrary units for PTCs significantly higher ($p < 0.001$) compared to the benign nodules without data overlapping. By immunohistochemestry we observed a marked cytoplasmatic localization of PRAJA2 in PTCs which decreased in the less differentiated variants and completely disappeared in the ATC. We, then, measured mRNA levels in three different cell lines stable expressing BRAFV600E mutation, RET/PTC1 and RET/PTC3 rearrangements. We observed a significant ($p < 0.01$) increase in mRNA expression in RET/PTC1 positive cells compared to RET/PTC3 but not against BRAF positive cells. Similar results were obtain with cancer tissues with the same mutations. Analysis of the clinical data showed that protein expression was not associated with outcome, TNM, tumor diameter.

Conclusions: PRAJA2 is markedly overexpress in DTC and its protein expression decrease together with tumor de-differentiation. The expression might be linked to the mutational status of the tumor.

P30

HUMAN MAST CELL-DERIVED MEDIATORS INDUCE EPITHELIAL-TO MESENCHYMAL TRANSITION IN THYROID CANCER CELLS

Visciano C[1], *Liotti F*[1], *Prevete N*[2], *Sabetta RL*[1], *de Paulis A*[2], *Marone G*[2], *Santoro M*[1], *Melillo RM*[1]
[1]University of Naples, Federico II, Dipartimento di Biologia e Patologia Cellulare e Molecol, Naples, Italy, [2]University of Naples, Federico II, Divisione di Immunologia Clinica ed Allergologia e Centro Interdipartimentale di Ricerca in Scienze Immunologiche di Base e Cliniche, Naples, Italy

Mast cells derive from bone marrow precursors and are typically involved in many innate and adaptive immune responses. Mast cells play also a key role in the remodeling of tumor microenvironment, in tumor angiogenesis and in tumor growth. Recently, we have demonstrated that human papillary thyroid carcinomas (PTCs) display a mast cell infiltrate, whose density correlates with tumor invasiveness. Mast cells were mainly found at the invasive front (the tumor-host interface) of human PTCs, where they may facilitate tumor cell migration and extracellular matrix degradation. The increased motility and invasiveness of tumor cells are reminiscent of epithelial-to mesenchymal transition (EMT), which is characteristic of embryonic development, tissue remodeling, wound healing and cancer invasion. During EMT, epithelial cells acquire fibroblast-like morphology and properties and show reduced intercellular adhesion and increased motility by activating a transcriptional program characteristic of mesenchymal cells. Here we show that, upon 24h incubation with mast cell line-derived conditioned media (MC CM) or with 10ng/ml TGF-β, a known EMT inducer, normal and cancerous human thyroid cell lines acquired a fibroblast-like morphology. We show that thyroid cancer cell lines treated with MC CM dramatically increased their ability to invade matrigel and migrate in the scratch wound healing assay. The expression levels of several EMT markers, such as vimentin, β-catenin, Snail, Slug and ZEB1, increased upon 24h MC CM treatment. Other typical epithelial markers, such as claudin 1 and cytokeratins were instead decreased by MC CM. We also identified mast cell-derived IL-6, IL-8, TNF-α as the strongest inducers of EMT in thyroid cancer cells. Our data indicate that inflammatory mediators secreted by tumor resident mast cells have a pivotal role in inducing thyroid cancer invasiveness by activating EMT. Our results also suggest that therapeutic targeting of mast cell-derived mediators may have favourable outcome in thyroid cancer.

P31

LOSS OF HETEROZYGOSITY OF TUMOR SUPRESSOR GENES(FHIT, P16, RB, E-CADHERIN, P53) IN THYROID TUMORS

Kim JH[1], *Rho YS*[2], *Lee DJ*[1], *Park IS*[3], *Jung EJ*[2]
[1]Hallym University Kangnam Sacred Heart Hospital, Otorhinolaryngology-Head and Neck Surgery, Seoul, Korea, Republic of, [2]Hallym University Kangdong Sacred Heart Hospital, Otorhinolaryngology-Head and Neck Surgery, Seoul, Korea, Republic of, [3]Hallym University Hankang Sacred Heart Hospital, Otorhinolaryngology-Head and Neck Surgery, Seoul, Korea, Republic of

Objective: To investigate the LOH of 5 tumor suppressor genes(FHIT, p16, Rb, E-cadherin, p53) in thyroid tumors and to correlate their results with various clinicopathological factors.

Material and method: Eighty thyroid tumor cases (50 papillary carcinomas, 10 follicular carcinomas, 20 follicular adenomas), treated by surgery alone, have been analyzed for the presence of LOH for FHIT, p16, Rb, E-cadherin and p53 genes, using microsatellite markers and DNA obtained from formalin-fixed paraffin-embedded archival tumor and noraml tissues. LOH was examined at ten microsatellite loci including D3S1300, D3S1067, D9S162, D9S104, D13S118, D13S153, D16S419, D16S3106, TP53, D17S796.

Results: There was rare detected LOH in follicular adenoma. LOH on Fhit gene was found in 10.5%, 33.3% and 30.4% of follicular adenoma, follicular carcinoma and papillary carcinoma, respectively. LOH on p16 gene was found in 6%, 44.4% and 47.8%, respectively. LOH on Rb gene was found in 5.3%, 20.0% and 35.4%, respectively. LOH on E-cadherin gene was found in 5.3%, 22.2% and 43.8%, respectively. LOH on 17p13 was found in 0%, 40% and 45.8%, respectively. LOH results of all five suppressor genes showed statistical discrimination between benign tumor and malignant tumor. LOH results of p16, E-cadherin and p53 genes well correlated with poorly differentiated grade. LOH results of Fhit, E-cadherin and p53 genes were more frequently detected in papillary carcinoma showing metastasis and extratyroidal tumor invasion, but not statistically significant.

Conclusion: These results suggest that microsatellite alterations on various tumor suppressor genes may contribute to the malignant transformation of follicular cells and malignant thyroid tumor progression, independently. Also combined use of various LOH markers may help in deciding prognosis of thyroid tumor patients.

P32

THYROID CANCER AND ACROMEGALY: INCIDENTAL ASSOCIATION?

Achir S[1], Hasbellaoui F[2], Ziani K[2], Khalifa A[2], Semrouni M[2]
[1]Medical University of Algiers, Endocrinology, Algiers, Algeria, [2]Medical University of Algiers, Algiers, Algeria

Acromegaly is a chronic disease with excess of GH and IGF1 secretion, it is associated frequently with high risk of developing cancers. the risk of thyroid cancer in acromegaly remain controversial.

Our cases are retrospective: 4 patients aged respectively 34, 39, 51 and 40 years; diabetes was found in 3/ 4 patients.

Cervical ultrasonography performed in all acromegalic patients.

Biological tests of thyroid function (TSHus and FT4).

Fine needle aspiration cytology was performed in all patients (4).

TCT performed before thyroid surgery.

All patients had a total thyroidectomy, papillary cancer was found in 3 /4 patients.

Insuline resistance syndrome was found in 75%.

Even if this associaion: acromegaly and thyroid cancer remains controversial, thyroid needs to be tested in acromegalic patients, and thyroid nodules have to be analyzed by FNAC.

P33

MAPPING OF GENE EXPRESSION PATTERNS OF EPH RECEPTORS AND EPHRIN LIGANDS IN HUMAN THYROID CANCERS

Liang S[1], Javadi A[1], Hussein Z[1], Ingeson C[1], Nilsson M[1]
[1]Sahlgrenska Cancer Center, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Objectives: Eph receptors are the largest receptor tyrosine kinase family of cell membrane bound receptors. Together with their cognate ligands, the ephrins, Eph/ephrins are emerging as novel regulators of cell-cell interaction in tissues and their relevance is increasingly recognized in several diseases including cancer. EphA2 is the most widely expressed Eph receptor in various cancers. Currently, there is limited literature on Eph/ephrin expression and its function in human thyroid cancers. This study provides a mapping of Eph and ephrin gene expression patterns in two anaplastic thyroid cancer (ATC) cell lines (C643 and SW1736), two papillary thyroid cancer (PTC) cell lines (BCPAP and TPC1) and a medullary thyroid cancer (MTC) cell line (TT).

Methods: RT-PCR was used to analyse gene expression pattern of EphA and B receptors along with Ephrin-A and -B ligands in various human thyroid cancer cell lines.

Results: RT-PCR analysis of class A and B Eph receptors and Ephrin-A and -B ligands from human ATC, PTC and MTC cell lines revealed considerable variation in levels of mRNA expression. Eph receptors and ephrin ligands show distinctively higher expression in differentiated and medullary thyroid cancer cell lines compared to undifferentiated cell lines. For instance, EphA6, A7, A8, B1 and ephrin-B3 exhibit elevated expression levels. Additionally, EphA2, B4, Ephrins-A1, -A5 and -B1 were all highly expressed in all cell lines investigated, which suggests their functional significance in different subtypes of thyroid cancer.

Conclusion: We see significant variations in expression levels of different Eph/ephrins in the various cell lines investigated. This suggests a trend of increasing Eph/ephrin gene expression in differentiated and medullary thyroid cancer cell lines when compared to undifferentiated cell lines. Moreover, several Eph/ephrins had elevated expression across all cell lines, thereby suggesting their functional relevance in human thyroid cancers.

P34

EXPRESSION OF PODOLANIN AND TRANSCRIPTION FACTOR PROX 1 IN THYROID CANCER CELLS

Sikorska J[1], Rudzińska M[1], Strzyżewska-Jówko I[1], Czerwińska J[2], Kiedrowski M[3], Olszewski W[3], Górnicka B[4], Sowiński J[5], Czarnocka B[1]
[1]Medical Center of Postgraduate Education, Department of Biochemistry and Molecular Biology, Warsaw, Poland, [2]Medical Center of Postgraduate Education, Department of Pathology, Warsaw, Poland, [3]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Department of Pathology, Warsaw, Poland, [4]Medical University of Warsaw, Department of Pathology, Warsaw, Poland, [5]Poznan University of Medical Sciences, Department of Endocrynology, Poznań, Poland

Objectives: Primary tumor cells spreading is a key step during invasion of malignant cancer. The most common routs are hematogenous and lymphogenous metastases. Dissemination of thyroid cancers FTC and PTC differs and its molecular mechanism at present is poorly understood. Thus, we examined the expression of key molecular regulators of lymphangiogenesis: podoplanin (PDPN) and Prox1 in cell lines and differentiated thyroid tumors (DTC).

Methods: PDPN and Prox1 expression was assessed in PTC and FTC derived cell lines and series of DTC using Q-RT-PCR, Western blot and immunochemical (IHC, ICF) methods.

Results: High podoplanin mRNA and protein localized to the cytoplasm was found in BCPAP and TPC1, whereas the majority of FTC derived cell lines were PDPN negative. Unexpectedly, FTC236 derived from lymph node and FTC238 from lung metastasis highly expressed podoplanin in contrast to FTC133 line established from the same patient. Cell lines with high PDPN showed low or undetectable expression of Prox1 transcript, while PDPN negative cell lines expressed high Prox1 mRNA level. However, the protein level was not proportionate to the mRNA level, and showed nucleocytoplasmic pattern. Immunohistochemically the majority (72/120) of PTC and all FTC were PDPN negative, however 40% of PTC cases displayed podoplanin in tumor cells. Podoplanin neoexpression was positively correlated with patients' age. Normal thyroid (NT) and normal peritumoral tissues (NPT) with intensively stained lymphatics were used as internal controls. Prox1 was strongly expressed in cytoplasm, weakly in some nuclei of PDPN positive PTCs and negatively expressed in other tissues.

Conclusions: The difference in the expression of pro-lymphangiogenic molecules podoplanin and Prox1 in PTC and FTC suggest the distinct ways of their invasion. Moreover our results show that FTC133 considered as originating from lymph node may originate from primary tumor. Further on-going studies will clarify the role of lymphangiogenesis in DTCs dissemination.

CMKP 501-1-25-01-11.

P35

XRCC1 POLYMORPHISMS AND THE RISK OF PAPILLARY THYROID CANCER IN THE CZECH COHORT

Halkova T[1,2], Vaclavikova E[1], Sykorova V[1], Dvorakova S[1], Vcelak J[1], Kodetova D[3], Kodet R[3], Astl J[4], Betka J[4], Vlcek P[5], Bendlova B[1]
[1]Institute of Endocrinology, Department of Molecular Endocrinology, Prague, Czech Republic, [2]Charles University, Faculty of Science, Department of Biochemistry, Prague, Czech Republic, [3]2nd Faculty of Medicine and Faculty Hospital Motol, Department of Pathology and Molecular Medicine, Prague, Czech Republic, [4]1st Faculty of Medicine and Faculty Hospital Motol, Charles University, Department of Otorhinolaryngology and Head and Neck Surgery, Prague, Czech Republic, [5]2nd Faculty of Medicine, Charles University, Department of Nuclear Medicine and Endocrinology, Prague, Czech Republic

Introduction: Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer. Beside causal somatic changes involving rearrangements of *RET* and *NTRK1* and *BRAF* mutations, the influence of single nucleotide polymorphisms (SNPs) in low-penetrance genes is suggested. One of the promising is the *XRCC1* gene (X-ray repair cross-complementing group 1). This case-control study is focused on possible association of SNPs Arg399Gln and -77T/C in *XRCC1* with PTC risk.

Methods: DNAs of 188 PTC patients were isolated from fresh frozen tissues, DNAs of 188 healthy controls from peripheral leukocytes. The SNPs Arg399Gln (rs25487, C/T) and -77T/C (rs3213245) were assessed by TaqMan probes and statistically analyzed by Chi-square test and Mann-Whitney test. The association of these genetic variants with gender and age at diagnosis was also examined.

Results: The allelic frequencies of Arg399Gln did not differ between PTC patients and healthy controls (T allele: 32.8% vs. 34.6%). Overall, Arg399Gln was not associated with PTC risk, gender and age at diagnosis. We found no significant difference in -77T/C allelic frequencies between PTC patients and controls (C allele: 45.9% vs. 43.3%) and no association with age at diagnosis. Nevertheless, the allelic distribution significantly differs in PTC patients related to gender (C allele male vs. female: 60.0% vs. 42.3%; p=0.012; OR=2.05; CI 95%: 1.2–3.5). Moreover, in the PTC cohort, the frequency of CC-homozygots in males is 2.7 times higher than in females (χ^2=13.5; p=0.0012). In males, CC-homozygozity increases the risk of PTC almost 4 times (p=0.0030; OR=3.81; CI 95%: 1.63–8.9).

Conclusion: We found out that Arg399Gln is not associated with the risk of PTC in the Czech population. However, our results indicate for the first time that -77T/C is a potential genetic risk modifier of PTC in males, especially CC homozygozity significantly increases the risk of PTC.

Supported by IGA MH CR NT/13901-4.

PO4 Thyroid Cancer Therapeutics Clinical 1

P36

SALIVARY GLAND DYSFUNCTION AFTER RADIOIODINE ABLATION IN A MURINE MODEL

Choi J-S[1], Lim J-Y[1], Kim S-K[2], Kim Y-M[1]
[1]Department of Otorhinolaryngology, Inha University College of Medicine, Incheon, Korea, Republic of, [2]Department of Nuclear Medicine, National Cancer Center, Goyang, Korea, Republic of

Objectives: Ablation of the thyroid remnants using radioiodine (RI) after surgical treatment of differentiated thyroid cancer could induce radiation-related salivary gland (SG) dysfunction. We tried to evaluate the morphological and functional changes in murine salivary glands after RI exposure.

Materials and methods: Sixty C57BL/6 mice were divided into untreated control group (n=30) and a group that received RI orally (n=30, 0.01 mCi/g ^{131}I / body weight). At 1, 2, 3, 6 and 12 months after RI exposure, salivary functions were evaluated by measuring salivary flow rates (SFR) and lag time of salivation after stimulation as well as by a single-photon emission computed tomography (SPECT). Histological evaluations and TUNEL assay were performed in RI-exposed SGs.

Results: Body weights and glandular weights in RI-exposed mice weighted significantly less than those of controls. Salivary flow rate significantly decreased in RI-exposed mice than in the control group and lag time of salivation in the RI-exposed mice significantly increased than in the control group. Histology of RI-exposed SGs showed pale cytoplasm, atypical ductal configuration, septa widening, cytoplasmic vacuolization with pleomorphism, lymphocyte infiltration, and increased fibrosis. More TUNEL-positive cells were observed in RI-exposed acini and ducts. The pattern of 99m Tc pertechnetate uptake and excretion in RI-exposed mice were quite different from normal control mice at 1 and 12 months post-treatment.

Conclusion: RI exposure to SGs may lead to morphological and functional deteriorations in murine SGs and this animal model could be useful for studies on mechanism and treatment of salivary gland dysfunction after RI ablation therapy.

P37

POST-THYROIDECTOMY CHYLOUS FISTULA. PLEASE GIVE YOUR PATIENT A CHANCE

Abdelrahman TEF[1], Hassanein KM[2], Amer I[2], Gaber M A[1]
[1]Sohag University, Head and Neck Surgery Unit, Department of Surgery, Sohag, Egypt, [2]Sohag University, Maxillofacial, Head and Neck Surgery, Sohag, Egypt

Chyle leakage is an uncommon complication after thyroidectomy either when done alone or when associated with Neck dissection. We are reporting seven cases suffered from post-thyroidectomy chyle leakage, Intraoperative chyle leakage was not found in any of those patients. the amount of leakage varied from 200 to 580 ml/ day. and the duration of leakage varied from 8 days to 15 days. All these patients were treated with pressure dressings and a medium-chain triglyceride diet All chyle leakages stopped after conservative management without surgical intervention, the conservative measures included pressure dressings and a medium-chain triglyceride diet. We concluded that chyle leakage one of life threatening complication could occur after thyroidectomy and conservative measure could achieve good results without need for surgery. This report will aid in the recognition and treatment of this uncommon complication during the early postoperative period.

P38

MULTIPLICITY AS A PROGNOSTIC FACTOR OF PAPILLARY THYROID CARCINOMA

Kim JM[1], Won JC[1], Ko KS[1], Rhee BD[1]
[1]Sanggye Paik Hospital, Inje University College of Medicine, Department of Internal Medicine, Seoul, Korea, Republic of

Backgrounds: Mutiplicity of PTC are not an unusual finding, although the origin of these foci is unclear. Either intraglandular metastases from a single dominant tumor or unrelated neoplastic clones were definitively proven as the means by which multicentric PTC form. In addition, there is insufficient clinical information concerning multicentric PTC presentation, prognosis, and long-term follow-up studies after treatment. Multiplicity of papillary thyroid carcinoma (PTC) has not been considered as an independent prognostic factor from a variety of tumor staging systems.

Aims: To evaluate whether that the presence of mulciplicity would be associated with tumor recurrence in PTC patients.

Methods: A total 249 PTC patients at a single institution who underwent total thyroidectomy and node dissection were retrospectively reviewed; the mean follow-up period was 2.8 years. Postoperative radioactive iodide ablation for thyroid remnant was performed after surgery for most patients.

Results: Of all the PTC cases reviewed, 85 cases (34%) were categorized as multicentric PTC. Compared with patients with unifocal PTC, multicentric PTC patients demonstrated higher cervical lymph node metastasis and tumor recurrence. Multiplicity was also significantly associated with tumor recurrence; 6% vs. 1% with and without multiplicity, respectively (P = 0.022 by log-rank test). However, this association was lost on multivariate analysis adjusting for conventional clinicopathological predictors of recurrence.

Conclusions: In patients with PTC, multiplicity is associated with tumor recurrence.

P39

DOES HÜRTHLE CELL CARCINOMA OF THE THYROID HAVE A POORER PROGNOSIS THAN ORDINARY FOLLICULAR THYROID CARCINOMA?

Sugino K[1], Kameyama K[2], Ito K[1], Nagahama M[1], Kitagawa W[1], Shibuya H[1], Okuwa K[1], Yano Y[1], Uruno T[1], Suzuki A[1], Masaki C[1], Ito K[1]
[1]Ito Hospital, Surgery, Tokyo, Japan, [2]Keio University Hospital, Pathology, Tokyo, Japan

Objective: Hürthle cell carcinoma (HCC) of the thyroid is a rare type of thyroid carcinoma and is considered to be a variant of follicular thyroid carcinoma. However, little is known about its biological characteristics or clinical behavior. We attempted to identify prognostic factors in patients with folli-

cular thyroid carcinoma and to determine whether the Hürthle cell type is a significant prognostic factor.

Methods: The subjects were 381 follicular thyroid carcinoma patients who underwent initial surgery between 1989 and 2006 at our institution, and they consisted of 73 patients with HCC and 308 patients with ordinary follicular carcinoma (OFC). There were 279 females and 102 males, and their median age was 52 years (rang: 10 to 84 years old). Cumulative cause-specific survival (CSS) was analyzed, and univariate analyses were conducted in relation to CSS by the Kaplan-Meier method for the following variables: age at surgery (< 45 versus 45 years or older), sex, tumor size (< 4 cm versus 4 cm or larger), invasiveness (minimally invasive versus widely invasive), initial distant metastasis (M0 versus M1) and histological type (Hürthle versus ordinary). Multivariate analysis was performed by using the Cox proportional hazard model.

Results: Four of the HCC patients (5.5%) had distant metastasis as opposed to 30 of the OFC patients (9.7%). Significant factors related to CSS in the univariate analysis were age, tumor size, and invasiveness, but there were no significant difference between the HCC group and the OFC group. When CSS was compared according to patient age and tumor invasiveness, there were no significant differences between the HCC group and the OFC group. Age was the only significant factor in the multivariate analysis.

Conclusion: HCC of the thyroid has almost the same prognosis as OFC of the thyroid.

P40

RADIOIODINE REMNANT ABLATION IN LOW-RISK PAPILLARY THYROID CARCINOMA: COMPARISON OF POST-SURGICAL STIMULATED THYROGLOBULIN PROTOCOL VERSUS CONVENTIONAL CARE ON RADIOIDINE ADMINISTRATION RATES AND RECURRENCE

Etarsky D[1], *Orlov S*[1], *Freeman JL*[2], *Walfish PG*[1,2]
[1]Mount Sinai Hospital/University of Toronto, Department of Medicine, Endocrine Division, Toronto, Canada, [2]Mount Sinai Hospital/University of Toronto, Department of Otolaryngology-Head and Neck Surgery, Toronto, Canada

Objective: We designed a case-control study to examine the rate of radioiodine remnant ablation(RRA) and disease recurrence in low-risk papillary thyroid carcinoma(PTC) patients selected for RRA using post-surgical stimulated thyroglobulin(Stim-Tg Protocol) versus conventional care (Association Guidelines).

Methods: A cohort of PTC patients was prospectively followed using the Stim-Tg Protocol(1) which primarily administers RRA based on a 3-month post-surgical Stim-Tg ≥5µg/L. A second cohort of PTC patients followed with conventional care was retrospectively identified and matched to the first cohort according to age and TNM stage. All patients underwent total thyroidectomy with therapeutic central neck dissection if clinically indicated. Low-risk was defined as no metastatic lymph nodes beyond the central compartment(level VI), no extrathyroidal extension, no distant metastases, and no anti-thyroglobulin antibodies. Mean follow-up was 6.9±3.7 years. PTC requiring further therapy after initial RRA was designated as a recurrence.

Results: Findings are summarized in Table 1. There were no significant differences in baseline characteristics between cohorts. Although the Stim-Tg cohort had a lower rate of RRA administration, no significant differences in recurrence compared to the conventional care cohort were detected. Serial follow-up among patients who did not reveive RRA has revealed no evidence of residual PTC.

Conclusion: Compared to conventional care, low-risk PTC patients treated according to the Stim-Tg Protocol have a lower rate of RRA administration with no significant increase in PTC recurrence.

1. Vaisman et. al., Head Neck, 2010;32:689–698.

P41

COMPARISON OF SURGICAL OUTCOMES BETWEEN HARMONIC ACE® AND LIGASURE PRECISE™ HEMOSTASIS IN OPEN THYROIDECTOMY OF PAPILLARY THYROID CANCINOMA : A PROSPECTIVE RANDOMIZED STUDY (PRELIMINARY REPORT)

Kwak HY[1], *Bae JS*[1], *Chae BJ*[1], *Song BJ*[1], *Jung SS*[1]
[1]Seoul Saint Mary's Hospital, The Catholic University of Korea, Department of Surgery, Seoul, Korea, Republic of

Objectives: Over the last few years, many surgeons have begun to use a ultrasonic coagulation device (Harmonic scalpel) or bipolar energy sealing system (LigaSure) to perform thyroid surgery. Recent studies have reported the benefits of these devices over hand-tying techniques. We conducted a prospective randomized study to determine if there is any differences in operative time, clinical results, and morbidities between the two devices.

Methods: A prospective randomized trial was performed. Total of 146 patients who required a thyroidectomy for papillary thyroid cancer were randomized to either Harmonic ACE®(H) or LigaSure Precise™(L). The parameters of operative time, number of retrived & metastatic lymph node and morbidities such as transient recurrent laryngeal nerve injury, hypoparathyroidism were analysed.

Results: There was no statistical difference in operative time (H vs L; 73.4 vs. 76.5, p=0.318), number of retrived lymph node (9.3 vs. 10.1, p=0.486) and metastatic lymph node (1.64 vs. 1.64, p=0.998). In regard to complications, there was no difference in the percentage of patients developing hypocalcemic symptoms (41.6% vs. 39.1%, p=0.449), transient hypoparathyroidism (20.7% vs. 21.7%, p=0.828), and permanent recurrent laryngeal nerve injuries. Although not statistically different, Ligasure group experienced higher rate of vocal cord palsy on postoperative stroboscopy than Harmonic group (8.7% vs. 2.6%, p=0.105).

Conclusions: In this study, there were no significant differences in the postoperative results and complications between the two devices.

Table 1. Comparison of Cohort Characteristics (for Abstract P40).

Cohort variable	RRA using Stim-Tg protocol (n=112)	Conventional RRA administration (n=112)	P value
Female sex (%)	90 (80%)	87 (78%)	0.62
Age at surgery (yrs)	51.7 ± 14.5	51.6 ± 9.6	0.97
Tumour size (cm)	1.8 ± 1.4	1.8 ± 1.4	0.92
LN metastases (%)	9 (8%)	8 (7%)	0.83
Radioactive remnant ablation rate (%)	17 (15%)	100 (89%)	<0.0001
Recurrences (%)	4 (3.6%)	3 (2.7%)	0.70

P42

PERCUTANEOUS LASER ABLATION OF NECK RECURRENCES OF THYROID CANCER. A FEASIBILITY AND CLINICAL STUDY

Papini E[1], Bizzarri G[2], Misischi I[1], Bianchini A[2], Valle D[2], Guglielmi R[1], Crescenzi A[3], Pedrazzini L[4], Baroli A[4], Salvatori M[5], Solbiati L[6], Pacella CM[2]

[1]Regina Apostolorum Hospital, Department of Endocrinology, Albano Laziale, Rome, Italy, [2]Regina Apostolorum Hospital, Department of Radiology and Diagnostic Imaging, Albano Laziale, Rome, Italy, [3]Regina Apostolorum Hospital, Anatomic Pathology Unit, Albano Laziale, Rome, Italy, [4]Circolo Hospital, Nuclear Medicine Unit,, Busto Arsizio, Varese, Italy, [5]Policlinico Universitario A.Gemelli, Catholic University, Nuclear Medicine Institute, Rome, Italy, [6]Circolo Hospital, Department of Radiology, Busto Arsizio (VA), Italy

Background: Most papillary thyroid cancers (PTC) are successfully cured but the incidence of loco-regional recurrences is not negligible. Repeated surgery for central compartment metastasis is at risk of surgical complications due to the presence of extensive scarring.

Aim of the study: To assess the technical feasibility, clinical effectiveness and safety of percutaneous laser ablation (LA) for nonsurgical treatment of neck recurrences of PTC that are not amenable to radioiodine treatment.

Patients and methods: From January 2009 through July 2011 six patients with metastatic lymphnodes were enrolled in the study. All patients had undergone total thyroidectomy and lymphoadenectomy for PTC and presented a further biopsy-proven cervical metastasis. No cervical uptake had been demonstrated at a 131-I post-dose whole-body scan. After local anesthesia, patients were treated under ultrasound (US) guidance with Nd-YAG laser inserting a 300 µm fiberoptic into the lesion according to our previously reported technique. The mean energy delivery was 978 ± 194 Joules with an output power of 3 watts.

Results: One patient gave her informed consent to be operated upon after LA. Histology revealed a well-circumscribed spherical area of necrosis (6 x 7 mm) with absence of viable tumoral cells and no damage to the surrounding tissue. Three of five remaining cases (60%) demonstrated at six-month US examination a nearly complete effacement of the lesion and undetectable Tg levels both in serum and in FNA-wash-out. As a whole, the mean volume of the lesions decreased from 0,6±0,51 ml before LA to 0,05±0,04 ml at six-month US-control. Mean Tg levels decreased from 31,9±26,3 to7,5±14,1 at six months. No major side-effects were registered.

Conclusion: US-guided LA is technically feasible, safe and effective for the debulking of cervical recurrences of PTC. In patients treated with repeated lymphoadenectomy LA is a promising non surgical tool for local control of recurrent non iodine-avid neck metastases.

P43

PROGNOSTIC FACTORS OF REFRACTORY PULMONARY METASTATIC DIFFERENTIATED THYROID CARCINOMAS (DTC)

Wassermann J[1], Bernier M-O[1], Spano J-P[2], Simon J-M[3], Ménégaux F[4], Lepoutre C[1], Aurengo A[1], Leenhard L[1]

[1]Pitié-Salpêtrière University Hospital, Nuclear Medicine, Paris, France, [2]Pitié-Salpêtrière University Hospital, Medical Oncology, Paris, France, [3]Pitié-Salpêtrière University Hospital, Radiotherapy, Paris, France, [4]Pitié-Salpêtrière University Hospital, Endocrine Surgery, Paris, France

Objectives: To describe features and prognostic factors of pulmonary metastatic DTC according to the I131 refractory character of the disease.

Methods: We reviewed clinical and pathological data of patients with pulmonary metastatic DTC treated in our center from 1990 to 2011. Prognostic features associated with survival were studied in Cox-model-based analyses.

Results: We included 124 patients (60% females, n= 75), the median age was 57 years (range 11–83). The initial treatment was total thyroidectomy in 96% (n=108/113), lymph node dissection in 69%, (n=79/115) and radioiodine therapy in 98% (n=121). Pathological features were papillary histology in 65% (n=78/120), pT stage 1ab, 2, 3, and 4 in 16%, 19%, 57% and 8% respectively, pN stage after lymph node dissection 0, 1a and 1b in 32%, 7% and 61% respectively. Metastasis were present at diagnosis in 46% (n=52/113). Fifty-two percent of patients (n=65) meet a criterion of I131 refractory disease: at least one metastases without I131 uptake: 55% (n=36); progressive disease despite I131: 22% (n=14); absence of complete response despite a cumulated dose >600mCi: 20% (n=13) and not available: 3% (n=2). The refractory feature was established at the time of diagnosis and subsequently in 17% and 83% of cases respectively. Patients with refractory DTC were older, with larger tumor size and received more I131 doses than non-refractory ($p< 0.001$). In univariate analysis, variables associated with increased risk of death were: age > 45 years ($p< 0.01$), non papillary histology ($p< 0.001$), refractory feature ($p=0.05$), progressive disease despite I131 ($p< 0.01$) and refractory feature since the time of diagnosis ($p=0.01$). In multivariate analysis, only progressive lesions and initial refractory disease were associated with an increased risk of death.

Conclusions: Prognosis is poor for patients with radioiodine refractory DTC, especially in patients with progressive lesions and refractory disease at diagnosis.

P44

IS THYROID CANCER RECURRENCE RISK INCREASED AFTER TRANSPLANTATION?

Tisset H[1], Kamar N[2], Faugeron I[3], Pouteil-Noble C[4], Klein M[5], Mourad G[6], Frimat L[7], Drui D[8], Docao C[9], Vantyghem M-C[9], Noel C[10], Leenhardt L[11], Rodien P[12], Bonichon F[13], Morelon E[14], Leboulleux S[15], Bournaud C[1], Kelly A[16], Niccoli P[17], Schlumberger M[15], Borson Chazot F[1]

[1]Groupement Hospitalier Lyon-Est, Federation d'Endocrinologie et CMN, Bron cedex, France, [2]CHU Rangueil, Service de Néphrologie, HTA, Dialyse, et Transplantation d'Organes, Toulouse, France, [3]Hôpital de Saint Louis, Service de Médecine Nucléaire, Paris, France, [4]Hôpital Lyon Sud, Service de Néphrologie, Lyon, France, [5]CHU Nancy, Service d'Endocrinologie, Nancy, France, [6]Hôpital Lapeyronie, Service de Néphrologie, Transplantation, Montpellier, France, [7]CHU - Hôpital de Brabois, Service de Néphrologie, Nancy, France, [8]Hôpital G&R Laënnec Saint Herblain, Endocrinologie, Maladies Métaboliques et Nutrition, Saint-Herblain, France, [9]CHRU Lille, Service Endocrinologie, Lille, France, [10]CHRU Lille, Service Endocrinologie CHRU Lille, Lille, France, [11]Hôpital Pitié-Salpetrière, Service de médecine nucléaire, Paris, France, [12]CHU d'Angers, Service d'Endocrinologie, Angers, France, [13]Institut Bergonié Bordeaux, Service de Médecine Nucléaire, Bordeaux, France, [14]Hôpital Edouard Herriot, Service de Néphrologie, Lyon, France, [15]Institut Gustave Roussy, Service de Médecine Nucléaire et Cancérologie Endocrinienne, Paris, France, [16]Centre Jean Perrin, Service de Médécine Nucléaire, Clermont-Ferrand, France, [17]CHU La Timone, Service d'Oncologie Médicale, Marseille, France

Sixty nine patients (35 M/34 F; median age 41 years) with a history of both thyroid cancer and transplantation were recruited via specialized networks (TUTHYREF and DIVAT). Evolution and outcome were retrospectively analyzed after a median follow-up of 13 years. Ninety one per cent were papillary and 9% of the follicular type.

Thyroid cancer had been diagnosed before transplantation in 33/69 patients from whom 36.4% had a high risk cancer. At the time of the graft, 31 were in remission, 4 of them after a recurrence. Two patients recurred after transplantation and a remission was obtained after a complementary treatment. In a young female patient who presented before transplantation lung metastases, a 2 years complete remission was observed after bilateral lung transplantation for cystic fibrosis.

In 36 patients thyroid cancer was diagnosed after transplantation from whom 47% were at high risk of recurrence. After a median follow-up of 14 years, 31 patients were in remission, 4 had persistent disease, one deceased from progression of thyroid cancer. In 9 cases, a second transplantation was performed 6.5 years after thyroid cancer diagnosis. During follow-up, a remission after 2 local recurrences occurred in one patient, persistent disease remained stable in one and there was no recurrence in the 7 other patients.

As a whole, 90% of patients were in remission at the time of the study. Seven per cent of patients experienced a recurrence and all of them were N1.

P45

OFF-LABEL USE OF SUNITINIB IN PATIENTS WITH ADVANCED, EPITHELIAL THYROID CANCER: A RETROSPECTIVE ANALYSIS

Pasqualetti G[1], Ricci S[2], Boni G[3], Tognini S[1], Polini A[1], Mariani G[3], Ferdeghini M[4], Monzani F[1]
[1]University of Pisa, Geriatrics Unit, Internal Medicine, Pisa, Italy, [2]University Hospital of Pisa, Oncology Unit, Pisa, Italy, [3]University Hospital of Pisa, Nuclear Medicine Unit, Department of Oncology and Transplantation, Pisa, Italy, [4]University of Verona, Department of Morphological-Biomedical Sciences, Verona, Italy

Introduction: Tyrosine kinase receptors play an important role in tumor angiogenesis and, their implication in epithelial thyroid tumor growth has been highlighted. Sunitinib is a novel tyrosine kinase inhibitor, approved in 2006 by Food and Drug Administration for the treatment of advanced renal cell and gastrointestinal stromal tumors. Preliminary promising results have been also obtained in patients with RAI-resistant thyroid cancer.

Objective: Primary aim of this retrospective analysis was to evaluate the clinical response to sunitinib by imaging evaluation, progression free survival (PFS) and overall survival (OS) in nine patients with advanced, RAI-resistant epithelial thyroid cancer. Secondary objectives were to assess the long-term safety profile of the drug as well as serum thyroglobulin (Tg) value variations.

Methods: Patients were included into the analysis if at least basal, 3- and 6-month follow-up imaging studies and serum Tg value time course were available. Disease status was assessed at baseline by positron emission tomography (PET)-CT and computed tomography (CT) scan and/or magnetic resonance imaging of the disease sites. Imaging assessment was repeated after 3 and 6 months of treatment and then every 6 months.

Results: According to RECIST criteria, partial response was obtained in 5/9 (55.5%) patients at 3 months and in 6/9 (66.6%) at 6 months. Median treatment follow-up was 13 months (range 7–35) and median overall survival and progression-free survival were 20 [95% confidence interval (CI) 9.3–30.6] and 21 months (95% CI 6.9–35.1), respectively. One case of severe thoracic hemorrhage was observed, the most common adverse events being represented by fatigue, (44.4%), skin rash (33.3%), headache (33.3%), and one case each of hypertension, macrocytosis and acute pneumonia.

Conclusion: Sunitinib represents a potential useful tool for the treatment of advanced thyroid cancers although large, prospective, controlled trials are needed to confirm its safety and effectiveness.

P46

WHAT THE BEST TIME TO PERFORM POST-THERAPEUTIC ^{131}I WHOLE BODY SCAN? COMPARISON BETWEEN EARLY AND LATE IMAGES

Perotti G[1], Mazza R[2], Ianni F[3], Maussier ML[1], Paragliola RM[3], Ricciato MP[3], Salvatori M[1], Pontecorvi A[3]
[1]Catholic University of Sacred Heart, Institute of Nuclear Medicine, Rome, Italy, [2]Azienda Ospedaliera Universitaria, Nuclear Medicine, Parma, Italy, [3]Catholic University of Sacred Heart, Unit of Endocrinology, Rome, Italy

Objectives: Until now there is still no consensus for the optimal time for performing the post-therapeutic ^{131}I whole body scan (TxWBS). The aim of this study was to compare TxWBS scans performed 3 (3-TxWBS) and 7 (7-TxWBS) days after radiodine therapy (RAIT) in patients with differentiated thyroid cancer (DTC), to establish the best time for TxWBS execution.

Methods: We prospectively studied 107 DTC patients (80 women and 27 men, mean age 49 yrs) submitted to RAIT between September 2009 and January 2011. TxWBS was performed three and seven days after RAIT. Each pair of images was classified by the following score: 1, if 3 and 7-TxWBS provided same data; 2, if 3-TxWBS provided more data than 7-TxWBS; 3, if 7-TxWBS provided more data than 3-TxWBS; The nature of the lesions was confirmed by histopatology (16 cases) and clinical follow-up at 12 months (91 cases).

Results: 3-TxWBS showed 82 thyroid remnants, 29 lymph-nodes metastases, 6 bone metastases, and 17 lung metastases; 7-TxWBS showed 82 thyroid remnants, 25 lymph nodes metastases, 7 bone metastases, and 21 lung metastases. Statistical analysis did not show any significant difference between 3 and 7-TxWBS. Score 1 was assigned to 85/107 (79.5%) pts., score 2 to 7/107 pts. (6.5%); score 3 to 14/107 pts. (13%). Semi-quantitative analysis revealed a mean T1/2 of 1.43 days for thyroid remnant, 1.68 for lymph-node metastases, 1.83 for bone mts. and 1.97 for lung mts, respectively. TNM modification was performed in 10/107 pts. (9.3%) and clinical management was modified in 11/107 pts (10%). On the whole, more lymph nodes metastases were observed at 3-TxWBS, while more distant metastases were recorded at 7-TxWBS.

Conclusion: Our data suggest that in low risk patients only 3-TxWBS could be performed, while in high risk patients both studies could be performed to plan the correct clinical management.

P47

CENTRAL PATHOLOGY CONFIRMATION OF ANAPLASTIC THYROID CANCER (ATC) DEMONSTRATES HIGH RATE OF CONCORDANCE WITH LOCAL PATHOLOGY REVIEW IN A RANDOMIZED TRIAL OF THE VASCULAR DISRUPTING AGENT (VDA) FOSBRETABULIN TROMETHAMINE (CA4P) IN COMBINATION WITH CARBOPLATIN (C) AND PACLITAXEL (P) (FACT STUDY)

Balkissoon J[1], Sosa JA[2], Lu S-P[1], Langecker P[1], Jarzab B[3], Bal CS[4], Koussis H[5], Marur S[6], Gramza A[7], Gitlitz B[8], Haugen B[9], Ondrey F[10], Lu C[11], Karandikar SM[12], Licitra L[13], Elisei R[14]
[1]Oxigene, Oncology, South San Francisco, United States, [2]Yale University, School of Medicine, Surgery, New Haven, United States, [3]MSC Cancer Center, Endocrinology, Gliwice, Poland, [4]AIIMS, Nuclear Medicine, New Delhi, Delhi, India, [5]IOV, Policlinico Universitario, Oncology, Padova, Italy, [6]Johns Hopkins University School of Medicine, Sidney Kimmel Cancer Center, Baltimore, United States, [7]National Cancer Institute, "NIH, Oncology, Bethesda, United States, [8]USC/Norris Cancer Center, Oncology, Los Angeles, United States, [9]University of Colorado Cancer Center, Endocrinology, Aurora, United States, [10]University of Minnesota, Otolaryngology, Head and Neck Surgery, Minneapolis, United States, [11]Universtiy of Texas, M.D. Anderson Cancer Center, Thoracic/Head and Neck Oncology, Houston, United States, [12]Ruby Hall Clinic, Oncology, Pune, India, [13]Instituto Nazionale Per Lo Studio E La Cura Dei Tumori, Oncology, Milano, Italy, [14]University of Pisa, School of Medicine, Endocrinology and Metabolism, Pisa, Italy

Background: ATC is a rare and rapidly progressive malignancy, with a high mortality rate, no effective therapeutic options and a median survival of 3 to 4 months. CA4P selectively disrupts tumor blood vessels by destabilizing endothelial cell microtubules. Preclinical studies have shown that CA4P has activity either as monotherapy or in combination with chemotherapy in ATC cell lines and animal models. Further development of CA4P in ATC required a multicenter, open-label, 2:1 randomized, phase 2/3 trial in patients with histologically confirmed ATC (FACT).

Objective: To compare local pathology diagnosis of ATC on FACT with central review confirmation to determine the rate of concordance.

Methods: Between August 2007 and March 2010, 80 patients were randomized (75 treated) to receive up to 6 cycles of C + P with CA4P (CA4P Arm) or without CA4P (Control Arm). The targeted sample size of 180 patients was not reached due to slow enrollment. After 6 cycles of therapy, patients on the CA4P Arm without progression could continue to receive CA4P until disease progression. The primary objective of this study was overall survival (OS). Secondary objectives included safety, 1-year survival, and progression-free survival. Eligibility for enrollment on FACT was determined by review of histology and/or cytology specimens by a preselected local pathologist with expertise in endocrine cancers. Pathology samples from patients would also be sent to ACM Medical Laboratory, Inc. in Rochester, New York, for central confirmation of ATC which would define an evaluable population of definitive ATC.

Results: Of 80 patients randomized,72 had ATC confirmed centrally (90%). In 4 patients ATC could not be confirmed and 4 patients did not have a central read. Of 75 patients treated, 69 had ATC confirmed centrally (92%).

Conclusions: Central pathology review showed a high rate of concordance with local confirmation of ATC on FACT.

PO5 Clinical Thyroid Autoimmunity 1

P48

SERUM PEPSINOGEN I AND GASTRIN-17 LEVELS ARE PREDICTABLE OF ATROPHIC GASTRITIS IN PATIENTS WITH AUTOIMMUNE THYROIDITIS AND ANTI-GASTRIC PARIETAL CELL AUTOANTIBODIES

Russo S[1], Provenzale MA[2], De Bortoli N[1], Martinucci I[1], Fiore E[2], Marchi S[1], Vitti P[2]
[1]University of Pisa, UO of Gastroenterology -Department of Internal Medicine, Pisa, Italy, [2]University of Pisa, Endocrinology, Pisa, Italy

Objectives: Chronic autoimmune thyroiditis (CAT) is associated with autoimmune atrophic gastritis (AG) and approximately 30% of patients with CAT also have anti-gastric parietal cell antibodies (APCAs). Serum APCAs do not represent a predictive marker of AG. The gold standard for diagnosis of AG is histological examination of multiple biopsy of gastric mucosa. Blood levels of pepsinogen I (sPGI), pepsinogen II (sPGII) and antral gastrin (sG17) have been used to predict *Helicobacter pylori* gastritis. The aim of this work is to evaluate the correlation between serum PGI, PGII, G17 levels and AG in patients with CAT and APCAs.

Methods: 23 consecutive patients with CAT were enrolled. APCAs, sPGI, sPGII, sG17 and *Hp* antibodies were evaluated in all patients. All subjects were submitted to urea breath test and upper endoscopy with biopsy sampling of gastric mucosa.

Results: Four males and 17 females were enrolled (mean age was 48.3±14.9 years). Twenty-one patients were APCAs positive and 2 were APCAs negative. APCAs negative patients had normal gastric mucosa, while APCAs positive patients were divided into two groups according to histology: patients with body/fundic atrophic gastritis (CAG; n = 15), and patients with non-atrophic gastritis (NAG; n = 6). sG17 levels were significantly higher in patients with CAG (median 60.2 pmol/L, interquartile range-IR 55.3–63.8 pmol/L) than in patients with NAG (median 0,9 pmol/L, IR 0.4–3.5 pmol/L, p = 0.006). sPGI levels were significantly lower in patients with CAG (median 7.0 µg/L, IR 2.7–17.6 µg/L) than in patients with NAG (median 81.5 µg/L, IR 62.9–94.5 µg/L, p = 0.002). sPGII levels were not significantly different between the two groups.

Conclusions: in patients with CAT and APCAs, sPGI and sG17could be used to recognize patients more likely affected by AG to be submitted to upper endoscopy and gastric histological examination.

P49

HUMAN RADOIMMUNE ASSAYS FOR DIAGNOSTICS AND PROGNOSIS OF MIXED FORMS OF IMMUNTHYROIDITIS

Soukhov V[1], Zaplatnikov K[2]
[1]Militar Medical Academy St. Petersburg, Nuclermedicine, St. Petersburg, Russian Federation, [2]Clinic for Nuclearmedicine Nuernberg, Nuclearmedicine, Nuernberg, Germany

Aim: Hashimoto Thyroiditis have definite signs such as goiter and increased thyroglobulin antibody (TGAb) and thyroid peroxidase antibody (TPOAb) levels. After introduction of routine assessment with help of second generation of human RIA for TSH-Receptor-Ab (TRAb) (Fa. Brahms) in group of "Hashimoto"pts with goiter (n=114).

Methods: After examination with thyroid function/Ab-control, ultrasound and scan was shown that 10% of them pts have a positive TRAb too (Range1,5-22, 2 UI/l), 8/11 pts. having typical hypothyroidism, 3/11 pts - euthyroidism. All these pts. have goiter from 20–42 ml. with moderatly increase of Tc-uptake in thyroid scan: about 4,0%.

Results: During follow-up (6 to 12 mos) stabilization of function without TRAb increase was noted in 4 pts under LT4-substitute. All patients with this pathology were informed about danger of iodine consumption and smoking. 4 pts under thyroxin therapy that initially had positive TRAb (50%) showed spontaneous shift of function towards Graves´ hyperthyroidism and significant increase of Abs within 14–28 mos later. One patient developed endocrine ophtalmopathy. So, in patients with mixed immune thyroiditis positive TRAb is highly prognostic for possible recovery of the disease. With RIA control of TRAb we have sensitivity of 92% and specificity of 85% comparing to group of pts with similar symptoms that were assessed by immunfluorescent methods before introducing of RIA Analysis.

Conclusions: We recommend perform control of all thyroid Abs in patients with lymphocytic Goiter that have increased volume of the gland and high Tc99m uptake for prognosis of the development of Graves disease by mixed forms of Immunthyroiditis and choose adequate diagnostic algorithm and therapeutic strategy for these patients.

P50

NUTRITIONAL FACTORS MAY BE INVOLVED IN THE DEVELOPMENT OF THYROID AUTOANTIBODIES IN WOMEN

Giannakou M[1], Saltiki K[1], Loukari E[1], Philippou G[1], Terzidis K[1], Spina J[1], Lili K[1], Stavrianos C[1], Mantzou E[1], Alevizaki M[1]
[1]Athens University School of Medicine, Dept of Endocrinology and Metabolism "Evgenidion" Hospital, Athens, Greece

Objectives: Various environmental factors such as iodine and selenium exposure have been associated with autoimmune thyroid disease (AITD). The role of other nutritional factors in thyroid autoimmunity is not well established.

Aim of the study: To evaluate possible associations between nutritional factors and the presence of thyroid autoantibodies (ThAb) in women with Hashimoto's thyroiditis.

Patients and methods: 134 women with ThAb(+) (mean age 46.5±12.3, range 20–65 years, 79 on T4 replacement, 55 euthyroid) were examined. 56 women with ThAb(-) and negative family history for AITD served as controls (mean age 44.2±11.9, range 21–65). Thyroid function tests, antiTPO and antiTG ThAb were measured. A questionnaire concerning the type of food, the frequency and the way of cooking was filled.

Results: All women were euthyroid (fT4 levels in the normal range). Of the women with antiTPO(+) 73.9% belonged to the fried meat consumers (≥3 times per month) compared to only 55.3% of those with antiTPO(-) (p=0.011). Similar results were observed concerning the consumption of overheated baked meat (p=0.003). Women with antiTPO(+) consumed more frequently (≥2 times/week) seafood compared to those without (89.2% vs 72.4% in antiTPO(-), p=0.006). Moreover, women with antiTPO(+) drunk tea more rarely compared to those without (10.8% vs 25% in antiTPO(-), p=0.015). No associations were found with antiTPO levels (low-positive, high). No association between the presence of ThAb and fruit or vegetable consumption was observed. No differences in dietary habits were observed concerning the presence of antiTG.

Conclusions: Nutritional factors may be involved in the development of antiTPO ThAb. AntiTPO(+) women consume more frequently overheated cooked meat which has been associated with increased oxidative load (such as reactive glucotoxins); they consume less frequently tea and, as expected, more frequently iodine rich foods. The presence of antiTG ThAb does not seem to be associated with nutritional factors.

P51

DECREASED SERUM 25-HYDROXY-VITAMIN D3 IS ASSOCIATED WITH THE PRESENCE OF THYROID PEROXIDASE ANTIBODY IN PATIENTS WITH AUTOIMMUNE THYROID DISEASE

Shin DY[1], Lim JS[1], Park KH[1], Lee EJ[1]
[1]Yonsei University College of Medicine, Internal Medicine, Seoul, Korea, Republic of

Objective: The increase in autoimmune thyroid diseases (AITDs) has been reported in the setting of vitamin D deficiency. We have demonstrated the relationship between serum 25-hydroxy-vitamin D3 [25(OH)D3] and anti-thyroid antibody levels.

Design: 25(OH)D3, anti-thyroid antibodies, and thyroid function measured in 304 patients who visited the endocrinology clinic due to suspected thyroid dysfunction were retrospectively analysed.

Methods: The patients were subgrouped into the AITDs or non-AITDs category according to the presence or absence of anti-thyroid antibody, regardless of the thyroid functional status. The relationship between anti-thyroid peroxidase antibody (TPOAb) and 25(OH)D3 was evaluated.

Results: The serum 25(OH)D3 level in the patients with AITDs was lower than in patients with non-AITDs (12.6 ± 5.5 ng/ml vs 14.5 ± 7.3 ng/ml, respectively, $P < 0.001$) Importantly, after adjusting age, sex, and BMI, a negative correlation ($r = -0.252$, $P < 0.001$) was recognized between 25(OH)D3 and TPOAb levels in the AITDs group, while such a correlation did not exist in the non-AITDs group ($r = 0.117$, $P = 0.127$). A multiple logistic regression was performed after adjusting for co-factors to examine the factors that may affect the presence of TPOAb in the AITDs group, and 25(OH)D3 level was confirmed as an independent factor.

Conclusions: 25(OH)D3 level is an independent factor affecting the presence of TPOAb in AITDs patients. This finding implies that a low 25(OH)D3 level is correlated to increased autoimmunity, resulting in the increased severity of thyroiditis. Although the causal effect of 25(OH)D3 deficiency to AITDs is to be further elucidated.

P52

HASHIMOTO'S THYROIDITIS MAY HAVE SIMILAR AND DISSIMILAR CHARACTERISTICS IN NEIGHBORING GEOGRAPHIC AREAS. POSSIBLE IMPLICATIONS FOR THE EPIDEMIOLOGY OF THYROID CANCER

Latina A[1], *Gullo D*[1], *Trimarchi F*[2], *Benvenga S*[2]
[1]Garibaldi-Nesima Hospital, University of Catania Medical School, Endocrinology, Catania, Italy, [2]University Hospital of Messina, Department of Clinical and Experimental Medicine, Section of Endocrinology, Messina, Italy

Context: An increased frequency of Hashimoto's thyroiditis (HT) and thyroid cancer (TC), two environmentally influenced diseases, is reported worldwide. In Sicily, Italy, data on HT are available for the province of Messina (1975–2005); data on TC are available for the whole island (2002–2004), with the volcanic province of Catania having the highest incidence.

Objective. To duplicate in Catania, on comparable years, the HT data of Messina.

Methods: Review of the clinical records of patients in years 1995–2005 to compare presentation and yearly changes of HT at our Endocrine Divisions in Catania and Messina.

Results: Catania is outnumbered by Messina (742 *vs.* 3,409 HT patients). Similar were: the linear increase in the yearly number of HT patients (r= 0.953 *vs.* 0.979), rates of thyroid dysfunctions (e.g., hypothyroidism= 43% *vs.* 46%), but with different proportions of subclinical and overt hypothyroidism (53% *vs.* 83% and 47% *vs.* 17%, P< 0.0001), and rates of positiveness for TgAb (52% *vs.* 55%) or TPOAb (64% *vs.* 67%), with TPOAb sharing the linear yearly decrease (r= - 0.656 *vs.* -0.874). Different were: age (42.3±14.5 *vs.* 41.6±2.4, P=0.01) and its yearly trend; gender distribution (females and males= 92.6 and 7.4% *vs.* 89.5 and 10.5%, P=0.10); rates of the sonography variants, though yearly trends were similar (e.g., nodular variant= 24% *vs.* 56, P< 0.0001; r= 0.16 *vs.* 0.35).

Conclusion: The HT epidemics is smaller in Catania, with changes in presentation overlapping partially those in Messina. Whatever environmental factors might be involved, they (and/or their intensity) were not necessarily the same in these provinces. Intriguingly, the expected number of TC in HT patients with thyroid nodules in Catania is congruent with that of the general population of this province, but it is far less in Messina province. Thus, TC and HT incidences could be influenced by distinct environmental factors.

P53

SERUM INTERLEUKIN-22 (IL-22) IS INCREASED IN HASHIMOTO'S THYROIDITIS (HT) COMPARED WITH NON AUTOIMMUNE THYROID DISEASES AND HEALTHY CONTROLS

Ruggeri RM[1], *Minciullo P*[2], *Saitta A*[2], *Giovinazzo S*[1], *Certo R*[1], *Gangemi S*[2], *Trimarchi F*[1], *Benvenga S*[1,3]
[1]Endocrinology Unit, University of Messina, Clinical-experimental Department of Medicine and Pharmacology, Messina, Italy, [2]Unit of Allergy and Clinical Immunology, University of Messina, Department of Human Pathology, Messina, Italy, [3]Programma Interdipartimentale di Endocrinologia Molecolare Clinica e Salute Endocrina della Donna, AOU Policlinico "G. Martino", Messina, Italy

Objectives: HT is an archetype for organ-specific autoimmune diseases (AID), that is considered to be Th1-related. Recent studies revealed that Th17 lymphocytes (producing mostly IL-17, IL-21 and IL-22) play a major role in numerous AID commonly thought to be Th1 diseases. Few data are available in the literature on the role for Th17 cells in HT.

Methods: Using IL-22 Quantikine ELISA Kit (lower limit of detection 0.7 pg/ml) we assayed serum levels of IL-22 in three groups of persons: HT patients (group A, n=40, 5 males and 35 females, age 42±16 years), non-HT patients with nodular euthyroid goiter (group B, n= 22, 2 males and 20 females, age 47±11 years) and an age- and sex-matched group of disease-free, healthy persons (group C). HT patients were euthyroid when sampled. Data are expressed as mean ± SD (pg/ml). Statistical analysis is by the two-tailed Student's t test.

Results: IL-22 levels were 43±37.4 pg/ml in HT patients, 18.7±17 pg/ml in group B and 20.7±12.7 pg/ml in group C. Because IL-22 levels in groups B and C were similar, they were pooled (19±15 pg/ml). These levels were significantly lower (p< 0.001) than in the HT group. In HT patients no significant correlation was found between serum levels of IL-22 and Tg-Ab and/or TPO-Ab levels. Furthermore, IL-22 values did not differ in HT patients positive for both Tg-Ab and/or TPO-Ab compared with HT patients with positivity for only one of these two autoantibodies.

Conclusions: Serum IL-22 is increased in HT, as compared with AID-free individuals. Our data do not support a strong role of Th17 cells, as assessed by their soluble mediator IL-22, in the pathogenesis of HT.

P54

PREVALENCE OF HASHIMOTO'S THYROIDITIS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

Del Ghianda S[1], *Benelli E*[1], *Rinaldi E*[1], *Burelli A*[1], *Cionini R*[1], *Ricci D*[1], *Vitti P*[1], *Pucci E*[1], *Tonacchera M*[1], *Latrofa F*[1]
[1]Pisa, Endocrinology and Metabolism, Pisa, Italy

Objectives: Both polycystic ovary syndrome (PCOS) and Hashimoto's thyroiditis (HT) are common diseases, affecting about 5–10% of fertile women. A previous publication reported an association between PCOS and HT in a small group of patients. Aim of the present study was to confirm this association in a larger cohort. We compared the prevalence of HT in a large number of PCOS patients and in patients with idiopathic hirsutism (IH) (control group).

Patients and methods: 434 PCOS and 124 age-matched IH women were evaluated. FSH, LH, oestradiol, progesterone, testosterone, androstenedione, 3-alpha-androstenediol, HOMA-index and SHBG were measured in all subjects. In addition, we evaluated TPOAb (cut-off=10 IU/ml) and TSH (normal values=0.4–3.4 μU/ml). All patients underwent pelvic ultrasound and 210 had also a thyroid ultrasound. The diagnosis of PCOS was made according to the Rotterdam Consensus Conference, a combination of any two of three findings: hyperandrogenism, menstrual irregularity and polycystic ovaries on ultrasound. At variance, IH patients showed hirsutism and/or acne in presence of normal androgens levels. The diagnosis of HT was based on positive TPOAb, elevated TSH and an hypoecogenic pattern at thyroid ultrasound.

Results: In comparison to IH, PCOS patients had higher levels of testosterone (0.58±0.19 vs 0.79±0.46 ng/ml), androstedione (2.6±1.1 vs 3.2±1.3 ng/ml), 3-alpha-androstenediol (3.9±2.5 vs 4.6±2.9 ng/ml) and lower levels of progesterone (5.7±8.2 vs 2.0±3.5 ng/ml) (all $p < 0.05$). The percentage of positive TPOAb was comparable in PCOS and in IH patients (9.8 vs 10.4%)

and TSH levels were similar in the two groups (1.6±1.1 in PCOS and 1.4±0.9 μU/ml in IH) (both p >0.05). The percent of patients with an hypoechogenic thyroid pattern was also comparable (15.7% in PCOS and 13.8% in IH).

Conclusion: At variance with a previous report, our findings do not support the association between PCOS and HT.

P55

THE PRESENCE OF CIRCULATING AUTOANTIBODIES AGAINST INSULINE, ISLET CELLS AND GLUTAMIC ACID DECARBOXYLASE IN THYROID CARCINOMA PATIENTS

Mityukova T[1], Leonava T[1], Akulevich N[1], Platonova T[1], Drozd V[2]
[1]Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus, [2]International Fund "Arnika", Minsk, Belarus

Aim of the study: To determine insuline- (IAA), islet cells- (ICA) and Glutamic Acid Decarboxylase-(GAD) antibodies positivity rate among patients with well-differentiated thyroid carcinoma (WDTC) according to gender, body weight and type of treatment.

Methods: The study group consisted of 151 WDTC patients, mean age 26,83±5,27 years old. According to body mass index (BMI), patients were divided in two groups: 76 patients with normal BMI (18–24,5 kg/m^2) and 75 patients with high BMI (25–35 kg/m^2). A group of 165 healthy individuals (mean age 28,31±0,48 years old) served as the control. Thyroid hormones levels as three types of autoantibodies: IAA, ICA and GAD, were measured by ELISA.

Results: In the study group, diagnostic autoantibodies' levels were found: IAA (>10,0 IU/ml) in 3 (2%), ICA (>1,05 IU/ml) in 26 (17,2%) and GAD-Ab (>1,05 IU/ml) in 3 patients (2%), respectively. In the control, only one subject (0,6%) had an increased ICA level. In overweight and obese patients, diagnostic ICA level was registered more often compared to the patients with normal BMI (29,3% *vs*.5,3%, P< 0,001). There were no differences in autoantibodies' level found according to gender and WDTC treatment, i.e. levothyroxine dose and 131-I cumulative activity.

Conclusion: High prevalence of ICA in young overweight and obese thyroid carcinoma patients may indicate a high risk of developing diabetes mellitus in such patients. Therefore, careful metabolic and immune control is required during WDTC survivors' life-long follow-up.

P56

THYROID AUTOIMMUNITY AND SPONDYLOARTHROPATHIES: A PREVALENCE STUDY

Lupoli GA[1], Peluso R[2], Granieri L[1], Panico A[1], Martinelli A[1], Lupoli R[1], Di Minno NM[2], Verde N[1], Papa F[1], Scarpa R[2], Lupoli G[1]
[1]University 'Federico II', Dpt of Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]University Federico II, Rheumatology Research Unit, Dpt of Clinical and Experimental Medicine, Naples, Italy

Objectives: The association of thyroid autoimmunity with rheumatic diseases is described, the most common being that with Rheumatoid Arthritis. However, little is known about the thyroid involvement in Spondyloarthritis (SpA), e.g. psoriatic arthritis and enteropatic spondyloarthritides. The aim of this study was to assess the prevalence of Hashimoto's Thyroiditis (HT) in SpA patients.

Methods: We evaluated TSH, FT3, FT4, anti-thyroglobulin (TgAbs) and anti-thyroid peroxidase (TPOAbs) antibodies, ultrasonographic thyroid pattern and rheumatic activity in 357 SpA patients and in 318 age-matched control subjects. Diagnosis of HT was made in presence of elevated TPOAbs and/or TgAbs and of typical thyroid ultrasound pattern.

Results: HT was more frequent in patients with SpA than in controls (24.09% vs 10.69%, p< 0.05) and, among SpA patients, it was more frequent in women (68.6%) than in men (31.4%) (p< 0.05). HT was, in SpA group, more frequent in patients with peripheral (68.6%) than in those with axial involvement (31.40%) (p< 0.05). Moreover, the prevalence of HT and TPOAbs positivity was higher in patients with a longer disease duration (>2 years) than in those with a shorter one (79.07% vs 20.93%; p< 0.05) and in patients with an active disease than in those with a low-moderate one (76.74% vs 34.88%; p< 0.05). The more frequent TPOAbs positivity in longer and more active disease suggests a relationship between this positivity and the maintenance of the inflammatory process. At ultrasonography a higher frequency of hypoechoic pattern was detected in patients with SpA than in controls (p< 0.0005).

Conclusions: With this study, the first evaluating the prevalence of HT in SpA patients, we suggest that thyroid function tests are an important part of the clinical evaluation of SpA patients; in fact, we evidenced a significantly higher prevalence of thyroid autoimmunity in patients with SpA as compared to healthy controls.

PO6 Thyroid Hormone and the Cardiovascular System Clinical

P57

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 IS ASSOCIATED WITH SUBCLINICAL AND OVERT HYPERTHYROIDISM

Duntas LH[1], Boutsiadis A[1], Mantzou E[1], Pitsouni E[1]
[1]Evgenidion Hospital, University of Athens, Endocrine Unit, Athens, Greece

Background: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a novel inflammatory enzyme, which its determination has been recommended as an additional marker of cardiovascular disease (CVD). In patients with hyperthyroidism (HT) mortality may increase up to 20%., though neither the causes nor the impact of confounders and therapy have as yet adequately addressed. On the other hand HT is associated with inflammation and oxidative stress.

Objective: We investigated the association between Lp-PLA2, and FT4, T3 and TSH in hyperthyroidism.

Methods: Serum Lp-PLA2 levels were determined in patients with mild (n=13) and overt (n=19) endogenous hyperthyroidism (HT) as well as in 31 euthyroid controls (EC). In 7/19 patients Lp-PLA2 was measured by achieving euthyroidism following a three-month therapy. Patients with dyslipidemia, diabetes mellitus, arterial hypertension or coronary artery disease were excluded.

Results: Lp-PLA2 levels were found to be statistically significantly increased in HT 249±23 ng/ml as compared to EC (206±18 ng/ml), while a negative correlation between TSH and the Lp-PLA2 levels, using both parametric (Pearson: -0.264; 0.076) and non-parametric (Spearman: -0.412; 0.004) methods, was observed. The lower the TSH the higher the Lp-PLA2. No associations were found with any other confounder or with FT4, or T3. Lp-PLA2 was reduced by achieving euthyroidism in a small group of patients.

Conclusions: The increased levels of Lp-PLA2 represent an indicator of a higher risk for CVD while reflecting an inflammatory state. Therefore, measurements of Lp-PLA2 levels may be useful in stratifying patients according to CV risk in HT.

P58

RELATIONSHIP OF APOLIPOPROTEIN A-1, APOLIPOPROTEIN B AND LP(A) LEVELS TO THYROID FUNCTION STATUS IN KOREANSV

Kim CS[1], Song YD[2], Park SO[3], Lee EJ[4]
[1]Hallym University Sacred Heart Hospital, Endocrinology, Anyang, Korea, Republic of, [2]NHIC Ilsan Hospital, Endocrinology, Goyang, Korea, Republic of, [3]Gwangmyeong Sung-Ae Hospital, Endocrinology, Kwangmyeong, Korea, Republic of, [4], Severance Hospital, Yonsei University, College of Medicine, Endocrinology, Korea, Republic of

Objective: Dyslipidemia is a well-known manifestation of thyroid dysfunction. Recently, ApoA-1, ApoB, Lp(a), C-reactive protein (CRP) have been linked with development of cardiovascular disease. To better understand the effects of thyroid dysfunction on the development of cardiovascular disease, we examined plasma hsCRP and lipid profiles such as apoA1, apoB, and Lp(a) in subjects with different thyroid function.

Methods: Included were 46 patients with overt hypothyroidism, 57 patients with subclinical hypothyroidism, 46 patients with overt hyperthy-

roidism, 51 patients with subclinical hyperthyroidism, and 110 age- and sex-matched healthy control subjects.

Results: No significant differences were found in serum HDL-C, hsCRP, Lp(a), ApoA1 between the groups with different thyroid function. Serum total cholesterol, LDL-C and levels were significantly higher in the cases of hypothyroidism than in the cases of hyperthyroidism and the healthy control subjects. Serum triglyceride levels were higher in subjects with overt hypothyroidism than in those with overt hyperthyroidism or healthy control subjects. Serum ApoB levels were higher in subjects with overt hypothyroidism than in those with overt hyperthyroidism subjects.

Conclusions: Serum hsCRP, ApoA-1 and Lp(a) levels were not found to be significantly affected by the degree of thyroid dysfunction. Increased risk of atherosclerosis in hypothyroidism appears to be associated with atherogenic cardiovascular risk factors, such as serum LDL-C, apoB levels.

P59

RH-TSH ADMINISTRATION DOES NOT AFFECT PARAMETERS OF VASCULAR FUNCTION IN SUBJECTS UNDERGOING EVALUATION FOR DIFFERENTIATED THYROID CANCER (DTC)

Rentziou G[1], Stamatelopoulos K[1], Saltiki K[1], Kazani M[1], Athanasiadou A[1], Kyratzoglou E[1], Papamichael C[1], Alevizaki M[1]
[1]Athens University School of Medicine, Endocrine Unit and Vascular laboratory, Department of Clinical Therapeutics, Alexandra Hospital, Athens, Greece

Background: TSH receptors have been recognized in extrathyroidal tissues including endothelial cells. We investigated whether elevated TSH levels after acute rhTSH administration may result in alterations in endothelial function and parameters of blood pressure (BP) in DTC patients.

Methods: 22 euthyroid females thyroidectomised for DTC and on T4 suppressive dose were evaluated by the rhTSH (Thyrogen) test to assess cure of disease. Flow-mediated dilatation (FMD), pulse wave velocity (PWV) and SphygmoCor - Pulse Wave Analysis were evaluated on day 3 (D3) after the second intramuscular rhTSH injection (0.9 mg/day on D1&2), when TSH levels are highest. TSH levels were measured on D1, D3 and D5. 17 subjects underwent a control study of endothelial function one-three weeks before Thyrogen test. Patients took stable T4 dose throughout the study and had no classical cardiometabolic risk factors.

Results: All subjects were euthyroid. TSH levels were D1: 0.09±0.15 mU/L, D3: 125.20±38.23 mU/L, D5: 15.09±7.16 mU/L. No significant difference was found in FMD and PWV before and after rh-TSH administration (FMD control=4.82±2.67mm, FMD after rh-TSH=4.99±2.85, PWV control=7.55±1.74 m/sec, PWV after rh-TSH=7.42±1.08, ns). No significant association was found between TSH levels at D1, D3, D5 and FMD or PWV either. There was a significant positive correlation of TSH on D5 with central systolic arterial pressure measured by SphygmoCor (r=0.503, p=0.04).

Discussion: This study has not shown any significant differences in endothelial function after rh-TSH administration. The influence of TSH levels on central systolic pressure points to the same direction with our previous report concerning the possible effect of the acute elevation of TSH on BP. It also agrees with reports in hypothyroid and euthyroid subjects showing positive associations of BP with TSH levels.

P60

TOTAL THYROIDECTOMY IN PATIENTS WITH AMIODARONE-INDUCED THYROTOXICOSIS AND SEVERE LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Tomisti L[1], Materazzi G[2], Marchello A[1], Bartalena L[3], Rossi G[4], Moretti M[2], De Napoli L[2], Mariotti R[5], Miccoli P[2], Martino E[1], Bogazzi F[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy, [2]University of Pisa, Department of Surgery, Pisa, Italy, [3]University of Insubria, Department of Clinical and Experimental Medicine, Pisa, Italy, [4]National Research Council, Unit of Epidemiology and Biostatistics, Institute of Clinical Physiology, Pisa, Italy, [5]University of Pisa, Cardio-Thoracic Department, Pisa, Italy

Objective: Patients with amiodarone-induced thyrotoxicosis (AIT) and left ventricular (LV) systolic dysfunction have high mortality rate. Usually, medical therapy is the first choice for AIT patients, whereas the role of thyroidectomy is unsettled. The aim of this study was to evaluate the effect of total thyroidectomy on LV ejection fraction (EF) and survival of AIT patients with severe LV systolic dysfunction.

Methods: 24 AIT patients (9 patients with type 1 AIT, 15 patients with type 2 AIT) referred at our Department and submitted to total thyroidectomy during the period 1997–2010, were retrospectively examined. A cardiological evaluation (including 2D color Doppler echocardiography) was performed before thyroidectomy and 2 months after surgery. The follow up consisted in the period from the diagnosis of AIT and December 31th 2011 or death (at least 12 months).

Results: All enrolled patients had previously been submitted to medical treatment for AIT, as appropriate, without achieving a control of thyrotoxicosis. Patients with moderate-to-severe LV systolic dysfunction (EF< 40%, Group 1, n=9) or with mild systolic dysfunction (40%≤EF≤50%, Group 2, n=5) were compared with patients with normal systolic function (EF>50%, Group 3, n=10). Two months after thyroidectomy, and while under replacement therapy, LVEF improved in patients with LV systolic dysfunction, particularly in those of Group 1, in whom it increased from 28.2±7.2% to 38.3±6% (p=0.007); on the contrary, it did not significantly changed in Group 3 (from 57.1± 3.0% to 59.8±6.6, p=0.242). Mean follow-up was 67±42 months. No death occurred during and two months after surgery. One death occurred in one patient of Group 1, 30 months after thyroidectomy, due to acute myocardial infarction. No relevant complications due to thyroidectomy occurred in patients of each groups.

Conclusions: Total thyroidectomy, rapidly restoring euthyroidism, may improve cardiac function and reduce the risk of mortality in AIT patients with severe LV dysfunction.

P61

POSTOCCLUSIVE REACTIVE HYPERAEMIA OF SKIN MICROCIRCULATION IS ALTERED IN PATIENTS WITH HYPOTHYROIDISM

Gergar M[1], Mihor A[1], Hojker S[2], Gaberscek S[2], Lenasi H[3]
[1]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, [2]University Medical Centre Ljubljana, Ljubljana, Slovenia, [3]Faculty of Medicine, University of Ljubljana, Institute of Physiology, Ljubljana, Slovenia

Objectives: Hypothyroidism is associated with an increased risk of cardiovascular diseases and endothelial dysfunction. Postocclusive reactive hyperemia (PRH) is a transient increase of blood flow following temporary arterial occlusion and has been used for the evaluation of endothelial function in clinical practice. Skin microcirculation could be used as a model to assess microvascular reactivity. We aimed to determine whether hypothyroidism induces changes in skin microvascular reactivity potentially due to endothelial dysfunction.

Methods: Using laser Doppler flowmetry (LDF), we measured skin blood flow in 13 patients with hypothyroidism (mean serum concentrations, TSH 39.05 ± 15.22 mU/L*, fT3 3.95 ± 0.20 pmol/L*, fT4 9.22 ± 0.71 pmol/L*, *p< 0.001 compared to healthy controls) and in 15 healthy controls (mean serum concentrations, TSH 1.97 ± 0.35 mU/L, fT3 4.82 ± 0.11 pmol/L, fT4 14.21 ± 0.47 pmol/L). LD probes were placed on the volar aspect of the forearm and on the finger pulp. PRH was induced by a 3-min occlusion of the left brachial

artery. Simultaneously, skin temperature at the measuring sites as well as systolic and diastolic blood pressure of ´aa. digitales´ in the fourth finger and a 3-channel ECG were assessed.

Results: The baseline LDF, blood pressure of ´aa. digitales´ and heart rate were comparable between both groups. The duration of PRH at the finger pulp was significantly longer in the group of patients ($p< 0.05$). There was a trend toward an increase in the area under the PRH curve on both measuring sites in patients.

Conclusions: Results may indicate that hypothyroidism induces changes in skin microcirculation. Altered parameters of PRH in patients point to increased vasodilator capacity compared to the healthy controls which is in contrast with our hypothesis of endothelial dysfunction. Yet, our results speak in favour of isolated effects of elevated serum TSH.

P62

GRAVES' DISEASE, AUTOIMMUNE THYROIDITIS, INSULIN RESISTANCE AND CARDIOVASCULAR RISK FACTORS

Neves C[1], Esteves C[1], Sokhatska O[2], Palmares C[2], Pereira M[1], Dias CC[3], Carvalho D[1], Delgado L[2], Medina JL[1]
[1]São João Hospital, Faculty of Medicine, University of Porto, Endocrinology Service, Porto, Portugal, [2]São João Hospital, Faculty of Medicine, University of Porto, Immunology Department, Porto, Portugal, [3]São João Hospital, Faculty of Medicine, University of Porto, Department of Biostatistics and Medical Informatics, Porto, Portugal

Objectives: To examine whether Graves' disease (GD) and autoimmune thyroiditis (AIT) are associated with insulin resistance and other cardiovascular risk factors.

Methods: We recorded thyroid function tests, BMI, insulin resistance markers comprising the HOMA-IR and HOMA-B, QUICKI, HISI, WBISI, IGI (Insulinogenic Index) and the levels of total cholesterol (TC), HDL, LDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB), ApoA1, lipoprotein (a) (Lp[a]), homocysteine, CRP (C-reactive protein), folic acid and vitamin B12 levels, in a total of 326 patients, 91.9% female, with a BMI of 26.4±7.9Kg/m^2 and a mean age of 48.8±15.3years. There were 108 patients with GD and 218 patients with AIT. The patients with GD and with AIT were treated, in order to normalize T3, T4 and TSH levels. A 75-g OGTT was performed in the morning, and blood samples were obtained every 30min for 120min for measurements of plasma glucose, insulin, and C-peptide. Statistical analysis was performed with ANOVA and Pearson's correlations test. Results are expressed as mean±SD. A two-tailed p value< 0.05 was considered significant.

Results: There were no significant differences between PCR, Lp(a), homocysteine and insulin-resistance levels in patients with AIT and GD. We found that patients with AIT had significantly higher levels in LDL (137.1±20.6 vs 109.7±33.4mg/dl, $p=0.42$) and ApoB (98.6±25.2 vs 89.9±27.4ml/dl, $p=0.007$). Within the AIT group we found significant correlations between anti-TPO and TC ($R=0.18$; $p=0.02$), HDL ($R=-0.38$; $p=0.01$), LDL ($R=0.16$; $p=0.02$), and ApoA1 ($R=-0.47$; $p< 0.01$). We also found correlations between HDL and HOMA-B ($R=0.19$; $p< 0.05$) and HOMA-IR ($R=-0.29$; $p< 0.01$), and between Lp(a) and anti-TG ($R=-0.19$; $p=0.03$). In the GD group we found significant correlations between PCR and ApoB ($R=0.39$; $p=0.02$), HOMA-IR ($R=0.41$; $p< 0.001$), and WBISI ($R=-0.39$; $p=0.02$).

Conclusion: In our study, HT patients have a higher cardiovascular risk than GD patients, associated with higher levels of LDL and ApoB.

PO7 Graves' Orbitopathy Clinical 1

P63

THE IMPACT OF DRY EYE SYNDROME IN GRAVES' ORBITOPATHY – A PROSPECTIVE AND CONTROLLED TRIAL

Breitenfeld M[1], Matheis N[1], Grus FH[2], Pitz S[2], Kahaly GJ[1]
[1]Gutenberg University Medical Center, Department of Medicine I, Mainz, Germany, [2]Gutenberg University Medical Center, Department of Ophthalmology, Mainz, Germany

Objectives: In patients with Graves' Orbitopathy (GO), symptoms and signs of the dry eye (DE) syndrome may be prevalent. Therefore in this prospective controlled trial, we investigated the impact of DE in the course of GO.

Methods: A total of 147 subjects were recruited. After a complete ophthalmic and endocrine investigation in a university joint thyroid-eye clinic, a basal Schirmer test, measurement of tear film breakup time (TFBUT), staining of the conjunctiva (Oxford system) and lid parallel conjunctival folds (LIPCOF) were performed. All participants filled out the specific GO quality of life (GO-QoL) and the DE symptom and complaint assessment questionnaires.

Results: Fifty (mean age 49.7 years, 40 female) and 30 (51.9 yrs., 25 fem) patients with GO and GO+DE, respectively, 30 patients (54.7 yrs., 23 fem) with DE and 37 (46.3 yrs., 33 fem) healthy controls (C) were investigated. Compared to C, the LIPCOF ($p< 0.001$) and TFBUT ($p=0.035$) values were markedly impaired in GO. TFBUT was markedly lower ($p< 0.0001$) in GO+DE vs. GO alone. Also, LIPCOF and Oxford values were higher ($p< 0.023$ / $p< 0.001$) in GO+DE vs. GO alone. Patients with active GO showed progressive structural changes of the cornea (LIPCOF $p=0.013$; Oxford $p=0.027$). GO-QoL values were markedly lower ($p< 0.001$) in GO vs. DE patients and the DE questionnaire displayed more complaints ($p< 0.001$) in GO vs. DE. With increasing activity and severity of GO, patients reported more DE symptoms (CAS $p< 0.001$; NOSPECS $p=0.005$) and DE complaints (CAS $p=0.002$; NOSPECS $p< 0.001$). Symptoms and signs of DE were more prevalent in older GO patients ($p< 0.05$).

Conclusions: Patients with GO show marked changes of their ocular surface. Dry eye symptoms and signs are common in active and/or severe GO and closely match with patients' quality of life and the complaint questionnaires.

P64

PREVALENCE AND NATURAL HISTORY OF GRAVES' ORBITOPATHY (GO) IN A LARGE COHORT OF NEWLY DIAGNOSED GRAVES' PATIENTS SEEN AT A SINGLE CENTER

Liparulo L[1], Veronesi G[1], Lai A[1], Lombardi V[1], Dalle Mule I[1], Sassi L[1], Pariani N[1], Ferrario M[1], Azzolini C[2], Piantanida E[1], Tanda ML[1], Bartalena L[1]
[1]University of Insubria, Clinical & Experimental Medicine, Varese, Italy, [2]University of Insubria, Surgical Sciences, Varese, Italy

Prevalence and natural history of GO are poorly understood. We followed prospectively 346 consecutive, newly diagnosed Graves' patients (266 women, 80 men, age 15–84 years) seen at our institution during 8 years. At baseline 255 patients (74%) had no GO, 70 (20%) had mild GO, 21 (6%) had moderate-to-severe and active GO, with no differences in gender distribution among groups. Women with moderate-to-severe GO were significantly older than those with no or mild GO. Prevalence of smokers was higher in patients with GO, irrespective of its severity. TRAb levels were higher in patients with GO (mild or moderate-to-severe). At multivariate analysis moderate-to-severe GO was associated with TRAb levels, smoking habits and age, particularly in women. After initial antithyroid drug (ATD) treatment, 74 patients were submitted shortly after to definitive treatment for reasons independent of changes in GO; 43 patients did not complete ATD course for spontaneous progression to hypothyroidism; 16 patients were lost to follow-up. Among the 213 patients who completed the ATD course, at baseline 156 (73%) had no GO, 43 (20%) had mild GO, 14 (7%) had moderate-to-severe GO. Of the 156 patients with no GO, 12 (8%) developed moderate-to-severe GO during treatment, 12 (8%) developed mild GO, while the remaining 132 (84%) had no GO throughout

treatment. Of the 43 patients with mild GO at baseline, 4 (9%) developed moderate-to-severe GO, 15 (35%) still had mild GO, 24 (56%) had no GO at 18 months. In conclusion: i) Prevalence of GO and, in particular, of moderate-to-severe and active GO in newly diagnosed Graves' patients is lower than previously reported; ii) Progression to moderate-to-severe GO occurs in < 10% of patients irrespective of the presence or absence of mild GO at baseline; iii) A large proportion of patients with initially mild GO remit spontaneously.

P65

THERMAL IMAGING AND CHARACTERISTICS IN GRAVES´ ORBITOPATHY

Perros P[1], *Di Maria C*[2], *Dickinson J*[3], *Allen J*[2]
[1]Joint Thyroid Eye Clinic, Newcastle upon Tyne, United Kingdom, [2]Microvascular Diagnostics, Regional Medical Physics Department, Freeman Hospital, Newcastle upon Tyne, United Kingdom, [3]Joint Thyroid Eye Clinic, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom

Objectives: To develop a thermal imaging protocol of eyes of patients with Graves´ orbitopathy (GO) as an objective means of assessing disease activity.

Methods: Fifteen patients with GO were studied, (13 female), mean (SD) age = 52 (17) years. Patients were clinically assessed for disease activity utilising the Clinical Activity Score (CAS) and underwent thermography within a few days from clinical assessment. Active disease (CAS ≥ 3) was found in 6 patients. The thermal imaging protocol included 20 minute acclimatization in 'cooled' measurement room (18 ºC). The thermal imaging system comprised a FLIR SC300 camera. Regional temperatures, and their differences, were measured using dedicated software (FLIR ThermaCam Researcher, skin emissivity assumed to be 0.98). Six tissue sites of interest were studied: (1) Lateral Conjunctiva (2) Cornea (3) Medial Conjunctiva (4) Caruncle (5) Upper Eyelid (6) Lower Eyelid. A further area next to the lateral canthus was used for a thermal reference.

Results: Binary logistic regression identified "Summed R-L averages" and "Summed R-L differences" among thermography parameters as the most important for the best discrimination between active and inactive disease ($p < 0.05$). Using this model, thermography was associated with a specificity of 100%, and a sensitivity of 83% (cut-off = 0.55) in identifying active disease. The area under the ROC curve was 0.89.

Conclusions: Thermographic measurements can detect areas of inflammation in patients with active GO with good classification accuracy when used in multi-feature discriminant analysis. Further work is required to assess the ability of thermography to predict response to medical therapy in patients with GO, compared to CAS.

P66

MORBIDITY AND MORTALITY OF ACUTE LIVER DAMAGE DURING OR AFTER HIGH DOSE INTRAVENOUS GLUCOCORTICOID PULSE THERAPY FOR GRAVES` OPHTHALMOPATHY

Sisti E[1], *Pinchera A*[1], *Marcocci C*[1], *Rocchi R*[1], *Latrofa F*[1], *Leo M*[1], *Profilo MA*[1], *Altea MA*[1], *Mazzi B*[1], *Albano E*[1], *Marinò M*[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy

Acute liver damage (ALD) is known to be one of the most severe and threatening side effects of high dose intravenous (iv) glucocorticoid (GC) pulse therapy in patients with Graves' Ophthalmopathy (GO). Here we analyzed retrospectively the frequency of ALD in 1014 consecutive patients with GO (264 males, 750 females, age 47.9±12.2 yr.) who underwent ivGC between 1992 and 2008 who had a follow-up period of at least 3 months after completion of ivGC. Serum liver enxymes (alanine aminotransferase and aspartate aminotransferase) were measured every two weeks during and after ivGC up to 3 months after completion of ivGC. ALD was defined as the presence of serum alanine aminotransferase values ≥300 U/l and/or serum aspartate aminotransferase values ≥ 200 U/l and was registered in 18 patients, thereby giving a morbidity of 1.7%. As reported previously (Marinò et al, Thyroid 2004 14: 403–406), 3 cases of ALD were fatal. Thus, the overall mortality was 0.29%. The mortality in patients with ALD was 16.6%. In the remaining 15 cases ALD was transient and it underwent remission with normalization of liver enzymes. Although the frequency of fatal ALD seems to be relatively low, our findings prompt a strict selection and a careful monitoring of patients to be subjected to ivGC. For this purpose we are currently performing further studies aimed at identifying risk factors that may help patient selection.

P67

PATIENTS RESPONDING TO INTRAVENOUS STEROID THERAPY FOR ACTIVE GO SHOW CLINICAL IMPROVEMENT AS EARLY AS 6 WEEKS AFTER TREATMENT

Vannucchi GM[1], *Campi I*[1], *Covelli D*[1], *Currò N*[2], *Cirello V*[1], *Dazzi D*[3], *Beck-Peccoz P*[1], *Salvi M*[1]
[1]Endocrine Unit, Fondazione IRCCS Cà Granda, Milano, Milan, Italy, [2]Ophthalmology, Fondazione IRCCS Cà Granda, Milan, Italy, [3]Internal Medicine, Ospedale di Fidenza, Fidenza, Italy

In order to identify parameters influencing the therapeutic response of steroid therapy in GO we have retrospectively studied 58 patients (14 M, 44 F) with autoimmune thyroid disease and moderate-severe active GO, treated with high dose intravenous methylprednisolone (MP; cumulative dose 7.5 g). Ophthalmological assessment was performed at baseline and at 6, 12 and 24–30 weeks after MP infusion. In 43/58 patients glucocorticoid receptor (GR) gene polymorphisms, which has been associated to different sensitivity to steroids, have been also studied. The outcome has been assessed as: 1) reduction of the clinical activity score (CAS) ≥2 points or 2) of proptosis ≥2 mm or 3) improvement of diplopia according to the Gorman score, in relation to age, gender, duration of thyroid or orbital disease, smoking habits, serum TRAb, TSH, FT3, FT4 concentrations and GR polymorphisms. Overall, 67% of patients responded to treatment. Interestingly, 80% of responders showed a significant reduction of the CAS with GO inactivation as early as six weeks after therapy. At 12 weeks the percentage of patients who further became inactive increased of another 10% to a total of 90%. In addition, we observed a significant reduction of the CAS in non-smoking patients (62.5%) compared to smokers (37.5%; $P < 0.045$) and a significant decrease of proptosis in OD at the end of therapy ($P < 0.03$). No significant changes of eye motility have been observed after treatment and no association was found between the therapeutic response to MP and other clinical, serological and genetic parameters. Our data suggest that in most patients with active GO response to MP is seen already after 6 weeks of therapy in particular in non smokers. Questions arise about the need of continuing therapy for 12 weeks in non responders and the possibility in those patients of using other drugs or therapeutic modalities.

P68

THE EVALUATION OF TREATMENT METHODS OF ENDOCRINE OPHTHALMOPATHY

Papava M[1], *Javashvili L*[2], *Dundua T*[2], *Jojua N*[2]
[1]Research Institute of Clinical Medicine, Tbilisi, Georgia, [2]Clinic Cortex, Tbilisi, Georgia

Thyroid gland diseases are one of the most important and frequent pathologies among the endocrine diseases. Graves' disease is characterized with the specific ocular changes. The cardinal symptoms are: exophthalmos and motility disorders caused by orbital tissue edema and ocular muscle enlargement. This condition is called ''endocrine ophthalmopathy'', because of dishormonal and orbital tissue changes. In recent years this disease becomes more frequent in younger age and it is a reason of the ocular disablement of different degrees and the ophthalmologists and endocrinologists interest concerning this condition is increasing.

Objectives: The aim of this research was to choose the optimal treatment method by foreseen the forms of endocrinal opthalmopathy for prevention of severe complications.

Materials and methods: 94 patients with endocrine ophthalmopathy have been examined and treated during the last five years by the research institute of clinical medicine. The age range was 30 to 60, 76 women and 18 men. Endocrine ophthalmopathy was detected in 37 patients, while the rest of patients adressed us, after the visit to the endocrinologist. 9 patients had unilateral exopthalmos. Visometry, tonometry, opthalmobiomicroscopy, exophtalmometry, opthalmoscope, ultrasound research were performed. 9 patients were scanned with MRI. 24 patients had slightly pronounced, 63 patients had moderately expressed, while 7 patients had sharply expressed exophthalmos.

5 patients had diplopia, 27 patients complain about the eye dryness, 1 patient had corneal erosion.

Results: Complex treatment was the same for all patients: thyroidstatics, iodides, beta-adrenoblockers, and steroids (generally and locally) and the best outcome had the steroid therapy (pulse therapy: sol. methylprednisolone 500–1000mg). All of these patients had the positive dynamics. Exophthalmos was reduced and the functions were improving.

Conclusion: According to our data, we suggest to treat endocrine ophthalmopathy individually, with foreseeing the stage, process's acuity and the condition of thyroid gland.

P69

RESPONSE TO HIGH DOSE GLUCOCORTICOID THERAPY IN PATIENTS WITH DYSTHYROID OPTIC NEUROPATHY (DON)

Covelli D[1], *Vannucchi G*[1], *Currò N*[2], *Campi I*[1], *Guastella C*[3], *Pignataro L*[3], *Beck Peccoz P*[1], *Salvi M*[1]
[1]Endocrine Unit, Fondazione IRCCS Cà Granda Policlinico, Milano, Italy, [2]Ophthalmology, Fondazione IRCCS Cà Granda Policlinico, Milano, Italy, [3]Otolaryngology, Fondazione IRCCS Cà Granda Policlinico, Milano, Italy

Dysthyroid optic neuropathy (DON) is a sight threatening complication occurring in 3–5% patients with Graves' orbitopathy. The medical treatment is based on the infusion of high dose methylprednisolone (MP), surgical orbital decompression is mandatory when patients do not respond to medical treatment. We aimed at studying the response to high dose intravenous steroids in DON and parameters for predicting therapy effectiveness. Twenty-three patients with DON were studied by evaluation of visual acuity, Hardy Rand Ritter (HRR) for colour vision defects, visual field and fundoscopy at baseline and 1, 2 and 4 weeks after therapy. We have considered as non responders patients who underwent orbital decompression within 6 months. Eleven patients were treated with 500 mg while 12 with 1000 mg MP for 3 consecutive days over 2 weeks. A complete DON recovery was observed in 4 of 11 (36%) and 5 of 12 (42%) patients who received 500 mg and 1000 mg MP, respectively. No response to treatment was observed in 14 patients (4 in low dose group and 5 in high dose group). At one month of follow-up, a significant improvement of visual acuity ($p< 0.001$) and of colour perception ($p< 0.001$) was observed only in responders. A significant improvement in the mean defect of visual field was observed in all patients, but a normalization of the visual field only in responders. All 5 patients (21%) who presented with optic disk swelling at baseline did not respond to therapy. Our data show that MP may be effective in restoring visual function in about 40% of patients with DON. The efficacy of treatment was not dependent on MP dose but on the severity of baseline optic nerve function impairment. The presence of optic disk swelling and of severe visual field defects seem to be predictive of medical treatment failure.

P70

ADVERSE EFFECTS AND EFFICACY OF METHYLPREDNISOLONE PULSES IN GRAVES OPHTALMOPATHY: COMPARISON BETWEEN ITERATIVE AND WEEKLY REGIMEN

Rabot A[1,2], *Gilly O*[2], *Lagier J*[1], *Brucker-Davis F*[2], *Hiéronimus S*[2], *Fénichel P*[2], *Sadoul J-L*[2]
[1]CHU de Nice, Ophtalmologie, Nice, France, [2]CHU de Nice, Endocrinologie, Nice, France

Objective: To assess whether treatment of active Graves ophtalmopathy (GO) with methylprednisolone (MP) pulses have the same adverse effects (AE) and efficacy with iterative pulses (tree days consecutively) or weekly pulses (EUGOGO protocol).

Design: Retrospective descriptive study.

Methods: Sixty five patients with active, moderately severe sight threatening GO (EUGOGO criteria) participated in the study. 36 patients, Group 1, received iterative pulse of MP (1 gram, 3 consecutive days renewed 2 or 6 time at 4 weekly intervals) and 29 patients, Group 2, received weekly pulse (6 dose of 0.5 grams/week followed by 6 doses of 0.25 or 0.125 grams/week). Comparisons were made for efficacy data and particularly adverse effects identified by changes of some parameters (weight, blood pressure, blood glucose, hepatic enzymes, blood potassium) or occurrence of allergic, cardiovascular or psychiatric symptoms.

Results: There were significantly more AE in Group 1 (48) than in Group 2 (21), p= 0,0014. Namely we observed allergic reactions (2 *vs* 2), weight gain (18 *vs* 7), new or majored hypertension (1 *vs* 0), new or altered diabetes (2 *vs* 1), hypokalemia (10 *vs* 4), hepatitis (1 *vs* 0) and mild psychiatric symptoms (11 *vs* 5), in Group 1 *vs* 2, respectively. No coronary event, nor venous thromboembolism were observed; and mortality was null. The average dose of MP was 10 grams in Group 1 and 4.5 grams in Group 2. The efficacy was similar in both groups.

Conclusion: This retrospective study showed that, although both regimen had a similar efficacy, the weekly MP pulse regimen was responsible for less AE than the iterative MP pulse protocol.

P71

UNILATERAL GRAVES' ORBITOPATHY AND TOXIC MULTINODULAR GOITER

Kermaj M[1], *Ylli A*[1], *Resuli K*[1]
[1]University of Tirana, Endocrinology, Tirana, Albania

Objective: To present the unusual coexistence of Graves' Orbitopathy with toxic multinodular goiter.

Methods: We describe the clinical, laboratory, and radiologic findings, in two cases with toxic nodular goiter and unilateral Graves'Orbitopathy (one of them resulted with papillary thyroid cancer, follicular variant, lying within a toxic adenoma), and review related reports in the literature.

Results: The two cases were diagnosed with hyperthyroidism and Graves 'orbitopathy on the basis of clinical and laboratory findings, by 99mTc shinti scan confirmed toxic nodular goiter as cause of hyperthyroidism, and by biopsy of thyroid nodule after total thyroidectomy was discovered to have a papillary thyroid cancer, follicular variant, lying within a toxic adenoma and a small area of papillary thyroid cancer near the toxic adenoma. The two cases were treated with antithyroid drugs and sintetic glucocorticoid. Once euthyroid they underwent total thyroidectomy.

Conclusion: Toxic multinodular goiter accompanied by infiltrative ophtalmopathy, represents the emergence of Graves' disease as confirmed by the presence of TSH-RAb (thyroid stimulating hormone receptor antibody) of the stimulating variety. When toxic multinodular goiter and active Graves' orbitopathy coexist, surgical approach and high-dose pulse glucocorticoid and orally titrated glucocorticoid dipending on orbitopathy severity, are the treatment of choise (as radioactive iodine treatment may aggravate preexisting ophthalmopathy) and antithyroid drugs as well as thyroidectomy do not influence the course of the ophthalmopathy.

PO8 Hypothyroidism Clinical 1

P72

PREVALENCE OF SUBCLINICAL AND CLINICAL HYPOTHYROIDISM IN WOMEN ABOVE 50, LIVING IN DISTRICT OF MODERATE IODINE DEFICIENCY, WITH PREVIOUSLY UNEXAMINED THYROID FUNCTION

Glonti S[1,2], *Bolkvadze G*[2], *Rukhadze T*[1]
[1]Republican Clinical Hospital, Batumi, Georgia, [2]Rustaveli State University, Clinical Therapy Department, Batumi, Georgia

Objectives: Hypothyroidism is often under-diagnosed due to the lack of symptoms. Problems connected to disorder of early diagnostic and treatment of women above 50, whose prevalence of thyroid pathology, according to the research data, is high enough. In consideration of high prevalence of thyroid pathology of Adjara (moderate iodine deficiency district of Georgia), we have examined it in random selection of women above 50, with an early unexamined thyroid function.

Materials and methods: We examined 1238 women over 50, (middle age 61±1,2) who had no connection with thyroid gland deseases, who applied for

doctors of different specialties (cardiologist, neurologist, gynecologist, etc..). All women were examined TSH, free T4, Anti - TPO and thyroid ultrasound. Hypothyroid patients were defined by TSH>4,0 mU/ml, including subclinical hypothyroidism results.

Results: Subclinical hypothyroidism was found in 238 from 1238 women (18, 4%) (TSH - 5, 2 ±0,9 mU/ml, free T4 -1,1±0,1 mU/ml). In 78 from 1238 (8%) was found hypothyroidism (TSH - 10,2± 0,8 mU/ml; av. free - T4 - 0,90±0,12 mU/ml). In 131 women - (10,2%) had increased degree of Anti - TPO, within all 78 with hypothyroidism, and 31 with subclinical hypothyroid. 22 women with Anti - TPO had no disorder of thyroid gland function. According to the ultrasound thyroid research data, patients with subclinical hypothyroidism had diffuse or nodular goiter (62,3%). In the group of hypothyroidism - hypoplasia or atrophy of thyroid gland (63,4%).

Conclusion: High prevalence of undiagnosed hypothyroidism of women above 50 in Adjara: Subclinical hypothyroidism diagnosed to 18,4%, clinical - to 6,3%. Results favor of screening of hypothyroid for early detection particularly in the mentioned female population, especially in the iodine deficiency districts.

P73

IN PATIENTS WITH NO INTERFERENCE ON THE INTESTINAL ABSORPTION OF L-T4 CAUSED BY GASTRO-INTESTINAL DISORDERS OR DRUGS, A LIQUID FORMULATION OF L-T4 PERMITS TO REACH TARGET TSH LEVELS THAT WERE MISSED BY THE CONVENTIONAL TABLET FORMULATION

Vita R[1], *Saraceno G*[1], *Trimarchi F*[1], *Benvenga S*[1,2,3]
[1]University of Messina, Section of Endocrinology, Department of Experimental and Clinical Medicine & Paharmacology, Messina, Italy, [2]University of Messina, Master on Childhood, Adolescent and Women's Endocrine Health, Messina, Italy, [3]University Hospital, Interdepartmental Program of Molecular and Clinical Endocrinology & Women's Endocrine Health, Messina, Italy

Objective: To demonstrate that in patients under replacement (REP) or TSH-suppressive (SUP) therapy with tablet L-T4, but with TSH levels not entirely normalized or suppressed in the absence of improper modalities of L-T4 ingestion and gastrointestinal disorders or drugs which impair the L-T4 intestinal absorption, switch to a liquid formulation (L-T4 solubilized in 28.8% ethyl alcohol) would solve the problem. Other authors showed that this formulation has a Tmax around 50 min faster than tablet L-T4 [Walter-Sack I et al *Clin Pharmacokinet, 2004*].

Methods: Upon consent, 14 such patients (13 F, 1 M; 6 under REP and 8 under SUP therapy), were switched to Tirosint ® soluzione orale (IBSA Farmaceutici Italia) while maintaining the daily dose of L-T4. Statistics included Mann-Whitney and Fisher's exact tests.

Results: (mean±SD): In the REP or SUP group, serum TSH averaged 24.77±16.9 or 2.23±1.87 mIU/L before therapy, and 4.86±3.74 or 1.28±0.28 under tablet L-T4. After switch, while under liquid L-T4 for 5 months minimum, serum TSH averaged 2.14±2.73 (P= 0.0061 *vs.* 4.86±3.74) or 0.47 ± 0.44 (P= 0.001 *vs.* 1.28±0.28). In 3/6 REP patients, TSH levels of 0.002 to 0.16 with hyperthyroid symptoms obliged to decrease the L-T4 dose. In the SUP group, the rates of TSH levels ≤0.10 mU/L were 0/29 samples under the tablet *vs.* 4/16 samples (25%) under the liquid formulation (P= 0.012). In 2/8 SUP patients, the daily dose had to be decreased.

Conclusions: Some patients could malabsorb L-T4 contained in tablets because intrinsic characteristics of their gastrointestinal tract may prevent optimal dissolution of the tablet and/or subsequent permeation. This malabsorption is circumvented by liquid L-T4, as shown here, because it is a formulation in which L-T4 (a lipophilic hormone) is solubilized in an organic solvent, thus being ready to reach and interact with the lipid bilayer of the intestinal epithelium.

P74

GENETIC ANTICIPATION AND PTPN-22 GENE POLYMORPHISM

Mikitinskaya A[1], *Rymar O*[1], *Maksimov V*[1], *Mustafina S*[1]
[1]Institute of Internal Medicine SB RAMS, Novosibirsk, Russian Federation

Objectives: The aim of this study was to investigate the link of age at diagnosis hypothyroidism and the frequency of PTPN-22 C1858T polymorphism in families with thyroid dysfunction at least two first-degree relatives.

Methods: We have examined 24 families (48 patients). An average age was 44 ± 2,6 year. The female/ male ratio was 7:1. Family history of hypothyroidism was traced for two generations (parent offspring) in 79,2% (19 families) and 20,8% (5 families) for one generation (siblings). An average age of parents and offspring was 58,6 ±1,9 and 32,8±2 years, respectively. Genotyping of C1858T polymorphism was performed by conventional PCR method.

Results: The proportion of patients with onset of hypothyroidism at age less than 35 years was 54,7%, and more than 35 years was 45,3%, p=0,537. Age of disease`s onset for parents and offspring was 45,6±3,7 and 26,5±1,9 year, respectively, p=0,001. The frequency of genotype CT was 56,3% for group with onset at age less than 35 years versus 43,8% for group with later onset, p=0,617. The frequency of homozygote genotype CC was 52% versus 48%, respectively, p=0,841. Only one patient with onset at age less than 35 years was determined by the genotype TT among all examined persons (4,3%). The T allele was increased in patients with onset of hypothyroidism at age less than 35 years 23,9% versus 18,4%, p=0,002: OR=1,17; 95% CI 1,1–1,3.

Conclusions: Positive family history of thyroid dysfunction was associated with a lower median age at diagnosis for hypothyroidism. It indicates the presence of the genetic anticipation of hypothyroidism. The carrier of allele T is associated with the increased risk for early onset of hypothyroidism for persons with positive family history of thyroid dysfunction.

P75

PULMONARY FUNCTION INVOLVEMENT IN PATIENTS WITH CLINICAL HYPOTHYROIDISM

Marinov BI[1], *Nonchev BI*[2], *Sirakova M*[1], *Kumanova I*[2], *Orbetzova M*[2], *Kostianev S*[1]
[1]Medical University, Patophysiology, Plovdiv, Bulgaria, [2]Medical University, Endocrinology, Plovdiv, Bulgaria

Background: There are many reports focused on organ and system manifestation of altered thyroid function. However, pulmonary changes in patients with thyroid hypofunction are poorly investigated.

Aim: To evaluate the deviation in pulmonary function in patients with clinical forms of thyroid hypofunction.

Patients and methods: Sixteen patients with autoimmune thyroiditis in clinical hypothyroid state were included in the study, (male/female - 4/12; age = 41.0±9.5 (mean±SD), TSH=37.12±11.23 mUI/L, FT4=5.80±8.70 pmol/L). The following thyroid markers were analyzed: TSH, FT3, FT4, TAB, TPO-Ab - (hemiluminescent immune analysis), TRAB (ELISA), ultrasonography. Pulmonary function assessment included slow vital capacity, forced spirometry and diffusion measurements.

Results: Most of the hypothyroid patients (13/16) revealed significantly reduced diffusion capacity for carbon monoxide (DL, CO) that correlated with the levels of TSH and FT4. These changes appeared to be reversible with the restoration of euthyroid state. In addition, half of the patients also had slightly decreased mean expiratory flows (MEF50% and MEF25%).

Conclusions: Our preliminary results showed that hypothyroidism is associated with significant reduction of diffusion parameters and slight peripheral obstruction. Changes in pulmonary function should be taken into consideration in the evaluation of patients with hypothyroidism. The data from the interim analysis reveal the need of further investigation.

P76

THE VALUE OF MEASUREMENT OF TSH CONCENTRATIONS AFTER TRH STIMULATION TEST IN PREDICTING DEVELOPMENT OF CENTRAL HYPOTHYROIDISM.

Lombardi M[1], *Urbani C*[1], *Manetti L*[1], *Sardella C*[1], *Scattina I*[1], *Lupi I*[1], *Raffaelli V*[1], *Marchello A*[1], *Nuzzo A*[1], *Calevro A*[1], *Brogioni S*[1], *Campomori A*[1], *Martino E*[1], *Bogazzi F*[1]
[1]University of Pisa, Endocrinology, Pisa, Italy

Objectives: Diagnosis of central hypothyroidism (CH) is not always straightforward through measurement of serum free T4 (FT4) and unstimulated TSH concentrations; on the other hand, measurement of TSH after TRH stimulation is time-consuming and its role in predicting CH is unsettled. We conducted this study to determine the value of TSH measurement after TRH stimulation test in predicting development of CH.

Methods: We retrospectively evaluated TSH concentrations in 1574 subjects submitted to TRH test because suspected to have a pituitary disorder. CH was defined by serum FT4 concentrations < 7 pg/ml. In patients who had normal thyroid hormone levels, serum FT4 was subsequently measured at yearly intervals. TRH test was performed, in most patients, at first evaluation. Delta TSH (difference between peak at 15–60 min and baseline value) was used to categorize TSH response to TRH.

Results: Overall, 43% patients had abnormal response of TSH to TRH stimulation. Twenty-six percent of patients had absent or blunted TSH response ($\Delta < 4.5$), whereas 17% showed an excessive ($\Delta > 20$) or delayed response (with a peak response after 60 minutes) of TSH to TRH stimulation. Among patients with normal FT4, 20% had an abnormal response of TSH to TRH test. Among them, 40% developed a frank CH (as defined by FT4 < 7 pg/ml) and received LT4 replacement therapy.

Conclusions: Measurement of TSH after TRH stimulation test may help in identifying patients who are prone to develop CH.

P77

SERUM LEPTIN AND ADIPONECTIN CONCENTRATIONS AFTER EXOGENOUS THYROTROPIN ADMINISTRATION

Sieminska L[1], *Jarzab B*[2]
[1]Medical University of Silesia, Department of Pathophysiology and Endocrinology, Zabrze, Poland, [2]Cancer Center and Institute of Oncology, Nuclear Medicine and Endocrine Oncology Department, Gliwice, Poland

Objectives: There are interactions between adipocytokines and hypothalamic-pituitary-thyroid axis. Thyrotropin releasing hormone (TRH) synthesis is regulated by leptin and there are connections between thyroid hormones and adiponectin. However, little is known about the influence of thyroid stimulating hormone (TSH) on adipocyte function. TSH-receptors are expressed on the surfaces of adipocytes. The aim of the study was to assess whether elevated serum TSH levels following recombinant human TSH (rhTSH) affect serum leptin and adiponectin.

Methods: 98 women and 17 men with differentiated thyroid cancer after total thyroidectomy and 131-iodine ablation were included in the study. Patients were receiving suppressive therapy with levothyroxine. The recombinant human thyrotropin (rhTSH) was injected i.m. according to the rhTSH test standard protocol. Blood samples were collected at baseline and 24, 48, 96 hours after the first rhTSH injection. TSH, fT3, fT4, leptin and adiponectin were measured periodically in connection with procedures for diagnostic purposes.

Results: After rhTSH administration, a significant increase in TSH and leptin were observed. In comparison to the baseline the mean rise of leptin was 17% after 24 hours, 38% after 48 hours and 40% after 96 hours. Slight decrease of adiponectin was also observed (7% after 24 hours, 5% after 48 hours and 6% after 96 hours). After rhTSH no change occurred in fT3 and fT4 concentrations. Serum leptin were negatively correlated with adiponectin only at baseline.

Conclusions: Administration of exogenous rhTSH has effect on leptin and adiponectin serum levels.

P78

PRIMARY HYPOTHYROIDISM IN PATIENTS WITH PITUITARY INCIDENTALOMAS- A STUDY IN 158 PATIENTS

Poiana C[1,2], *Carsote M*[1], *Ene C*[2], *Popescu M*[2], *Trifanescu R*[1,2], *Samoila R*[2], *Hortopan D*[2], *Paun D*[1,2]
[1]UMPh Carol Davila, Bucharest, Romania, [2]I. Parhon, Bucharest, Romania

Introduction: The patients with a pituitary microadenoma need to be evaluated for the secretor profile, thus the diagnosis of incidentaloma to be sustained. Sometimes primary hypothyroidism (PH) might be found.

Aim: We evaluated the thyroid profile in patients recent incidentaloma.

Patients and method: 158 patients diagnosed with a pituitary tumor (of maximum 1 cm) based on a computed tomography or a magnetic resonance were admitted for the evaluation of the endocrine profile. They were clinically asymptomatic for a pituitary secretor profile and the imagistic scan was performed for enlargement of the skull X-Ray or persistent headache. We evaluated the pituitary hormones including TSH. The patients known with PH under adequate substitution therapy were also included.

Results: The sex ratio was: 10 males/ 148 females. 3 patients had 2 incidentalomas. One had asymptomatic prolactinoma with normal thyroid function. 7 patients (5%) were primarily found with high TSH (av. 19.848 ± 39.32 µUI/mL). We found no correlations between TSH and the diameters of the tumors. The av. vertical diameter (VD) for the PH free patients was 0.571± 0.2 cm, and the transversal diameter was 0.393 ± 0.155 cm. The av. VD for patients with PH was 0.501±0.173 cm, the TD was 0.362±0.024 cm. There was no statistical significance (SS) difference between VD and TD in patients with or without PH (p=0.4, respective e p=0.65). One third of the patients newly diagnosed with PH had chronic thyroiditis, based on specific antibodies levels. The PH free patients were younger at diagnosis (av. age 40.41± 13.63 yrs) compare with those with PH (av. age 47.83± 13.71 yrs) with no SS difference (p=0.12).

Conclusions: The endocrine investigations in patients with pituitary incidentaloma may help in diagnosis of thyroid dysfunctions. The patients with incidentalomas and newly diagnosed primary hypothyroidism seem older and their tumors have smaller diameters but no SS difference was found.

P79

IDENTIFICATION OF A NOVEL MUTATION IN *PAX8* IN A PATIENT WITH THYROID DYSGENESIS

Nettore IC[1], *Ferrara AM*[1], *Cacace V*[1], *Di Mase R*[2], *Salerno MC*[2], *Fenzi G*[1], *Macchia PE*[1]
[1]University of Naples Federico II, Department of Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]University of Naples 'Federico II', Department of Pediatric, Naples, Italy

Congenital Hypothyroidism with thyroid dysgenesis occurs as a sporadic disease, however, there is much evidence indicating that genetic factors are involved in the pathogenesis of this disorder, as *PAX8*.

It is important for initiation thyrocyte differentiation and maintenance of the follicular cell. Recently we have identified a novel mutation in a patient with CH with sublingual thyroid in exon 9 of *PAX8.* The same heterozygous mutation has been detected also in her mother with no signs of hypothyroidism, indicating incomplete penetrance.

The mutation causes the change in the first base of the triplet coding for the aminoacid at position 337 (p.Ser337Ala). Then, the mutation causes the formation of a new restriction site for the enzyme HhaI, and digestion with the enzyme of family members DNA of patients allowed us to demonstrate that the mutation was inherited from the mother. All previously reported missense mutations are situated in paired domain, confined between α1 and α3 helix. Our mutation is in C-terminal region of PAX8, outside a mutational hotspot. This region is responsible for the interaction with NKX2-1 and WWTR1, a cofactor which potentiates the activity of both transcription factors.

We are currently conducting a functional assay of the mutant protein to determine if the presence of the mutation may lead to changes in the function of PAX8 alone or the combination of factors with which this protein cooperates.

In conclusion we have identified a novel mutation in C-terminal region of PAX8 that could compromise the interaction with NKX2-1or WWTR1. Then we aim to sequence both cofactors known of *PAX8* that other genes that play a role in the morphogenesis of the thyroid, to see if the difference in phenotype between mother and daughter is linked to genetic causes or epigenetic events.

PO9 Subclinical Thyroid Diseases

P80

DYSLIPIDEMIA AND ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH THE MILDEST HYPOTHYROIDISM: RELATIONSHIP TO TSH VALUES AND LEVOTHYROXINE TREATMENT

Strongin LG[1], *Nekrasova TA*[1], *Kazakova LV*[2], *Lukushkina AY*[1], *Ledentsova OV*[3]
[1]Nizhny Novgorod State Medical Academy, Endocrinology, Nizhny Novgorod, Russian Federation, [2]Regional Volga Medical Center of MBA, Internal Medicine, Nizhny Novgorod, Russian Federation, [3]Nizhny Novgorod Regional Clinical Diagnostic Center, Endocrinology, Nizhny Novgorod, Russian Federation

Objectives: Subclinical hypothyroidism (SH) is associated with cardiovascular risk attributed to dyslipidemia, overweight, endothelial dysfunction. Recent evidence points to a trend toward an increase in risk at higher TSH levels. It is recommended to treat SH individuals with TSH ≥10 mIU/L; risks and management protocols by lower TSH are controversial. The aim was to assess cardiovascular risk in SH patients having TSH < 10mIU/L with regard to the degree of TSH elevation (below and above 6 mIU/L).

Methods: We studied total cholesterol (TC), low (LDL-C) and high density lipoproteins, flow-mediated endothelium-dependent arterial dilation (FMD) in 54 women with SH and TSH < 10mIU/L divided into group 1 (n=32; TSH < 6 mIU/L) and 2 (n=22; TSH >6 mIU/L). Both were treated by levothyroxine, followed for a 1 year and reinvestigated.

Results: Women with TSH above 6mIU/L more commonly were obese (9.4% vs 40.9%, p=0.008), had elevated TC (31.2% vs 68.2%, p= 0.012) and impaired endothelial function (FMD< 10.0% in 31.22% vs 63.6%, p=0.027). By follow up, the normalization of lipids was confirmed in groups 1 and 2 in 31.2% and 54.5% of patients (p=0.08); decrease in BMI - in 9.4% and 31.8% (p=0.035); FMD improvement - in 46.9% and 77.3% respectively (p=0.047). Regression analysis confirmed the association between positive response to treatment and starting TC (OR 2.84, p=0.026), LDL-C (OR 2.96, p=0.031), TSH values>6 mIU/L (OR 2.57, p=0.10).

Conclusions: SH patients with TSH above 6mIU/L may develop dyslipidemia, overweight and endothelial dysfunction corrected by levothyroxine treatment. In the patients with lower TSH, there is no evidence of a significant cardiovascular risk and treatment is probably not justified in most cases.

P81

SUBCLINICAL HYPOTHYROIDISM AND TOTAL SERUM CHOLESTEROL LEVEL IN THE ELDERLY

Jukić T[1], *Lukinac L*[1], *Kusić Z*[1]
[1]University of Zagreb, School of Medicine, 'Sisters of Charity' University Hospital Center, University Department of Oncology and Nuclear Medicine, Zagreb, Croatia

Subclinical hypothyroidism (SH) is the most prevalent thyroid dysfunction (TD) in elderly. The aim of the study was to investigate prevalence of TD and positive TPO antibodies (TPOAb+) in elderly and association of SH with elevated total serum cholesterol level (CL).

Patients: 204 subjects (136 females and 68 males) older than 60 (mean 71±9) years, resident of old-age nursing home were included in the survey. Controls were 83 subjects (63 females and 20 males) aged 19 to 55 (mean 45±9) years. Subjects with prior TD were excluded from study.

Methods: Serum TSH, FT3, FT4, TPOAb, CL, height and weight measurement. Body mass index was calculated. Mann-Whitney, chi-square test and Student's T-test were used in statistical analysis.

Results: The prevalence of SH in elderly was 7.4% vs 3.6% in younger controls (p=0.2). The highest prevalence of SH was in elderly women (8.8%) vs 4.8% in younger women (p=0.3) and 4.4% in elderly men. TPOAb+ were in 77% elderly women and 67% younger women in SH. Overall prevalence of TPOAb+ was 19.9% in elderly women and 14.3% in younger women. The prevalence of hypothyroidism was 0.5% and subclinical hyperthyroidism 1.5% in elderly. Mean FT3 in elderly women was significantly lower in comparison with elderly men (4.4±0,9 vs 4.9±0.9 pmol/L, p< 0.01) as well as in comparison with younger women (4.4±0.9 vs 4.7±1.2 pmol/L, p< 0.05). Mean CL in elderly was significantly higher in comparison with younger subjects (6.2±1.1 vs 5.6±1.3 mmol/L, p< 0.01) as well as in elderly women vs elderly men (6.3±1.1 vs 5.2±0.7 mmol/L, p< 0.01). No difference in mean serum CL was observed between SH and euthyroid subjects (6.0 mmol/L).

Conclusions: SH is most prevalent TD in elderly, especially in elderly women with association with TPOAb+. Elevated serum CL was more age and gender related than influenced by SH.

P82

DECREASED LEVEL OF SERUM THYROXINE IN SUBCLINICAL HYPOTHYROIDISM

Feldthusen A-D[1], *Toft Kristensen T*[2], *Larsen J*[3], *Pedersen PL*[4], *Kvetny J*[5]
[1]University of Copenhagen, Dept. of Obstetrics and Gynecology, Næstved Hospital, Region Zealand, Næstved, Denmark, [2]University of Copenhagen, Dept. of Otorhinolaryngology, Slagelse Hospital, Denmark, [3]Dept. of Clinical Pathology, Næstved Hospital, Denmark, [4]Dept. of Clinical Biochemistry, Næstved Hospital, Denmark, [5]University of Copenhagen, Dept. of Internal Medicine, Næstved Hospital, Region Zealand, Denmark

Background: Subclinical hypothyroidism (SubHypo) is characterized by serum levels of free thyroxine (T4, 10–26 pmol/l) and triiodthyronine (T3, 1.2–2.8 nmol/l) within reference range and increased thyroid stimulating hormone levels (TSH>3.40 mU/l). Treatment of this condition is a matter of debate.

Objectives: To examine the level of thyroid hormones in a population with SubHypo.

Table for Abstract P82.

	N	SubHypo	Euthyroid	p-value
All	11528	1047 (9.1%)	10481 (90.9%)	
T3 (nmol/l)		*1.708 (1.690–1.726)*	*1.715 (1.710–1.721)*	ns
T4(pmol/l)		*14.55 (14.44–14.67)*	*15.65 (15.62–15.69)*	<0,0001
Female	5936 (51.48%)	580 (9.8%)	5356 (90.2%)	
T3 (nmol/l)		*1.707 (1.699–1.715)*	*1.705 (1.679–1.731)*	ns
T4 (pmol/l)		*14.33 (14.17–14.50)*	*15.40 (15.35–15.45)*	<0,0001
Male	5592 (48.51%)	467 (8.4%)	5125 (91.6%)	
T3 (nmol/l)		*1.712 (1.687–1.737)*	*1.724 (1.717–1.731)*	ns
T4 (pmol/l)		*14.83 (14.66–15.00)*	*15.92 (15.86–15.98)*	<0,0001

Methods: Data from the General Suburban Population Study of Region Zealand, Denmark (GESUS) were analysed to measure the levels of T4 and T3. GESUS is an ongoing population study. All inhibitants in the city of Naestved, Zealand are invited to participate in this large health study. Data presented were collected from January 2010 till March 2012.

Results: We analysed data of 11,528 participants all having levels of T3 and T4 within the reference range, not having any thyroid disease or using thyroid medication. Mean age was 53.6 years. Table 1 demonstrates the prevalence of SubHypo and the levels of thyroid hormones by mean (95% confidence interval). P-values of Wilcoxon rank sum test.

Conclusion: The level of T4 is significantly lower within the reference range in the group of subclinical hypothyroid than in the group of euthyroid independent of sex, suggesting the presence of slight hypothyroidism.

P83

NOVEL TECHNIQUE FOR THE RESECTION OF LINGUAL THYROID: TRANSORAL ROBOTIC SURGERY

Kim S-H[1], *Park YM*[1]
[1]Yonsei University College of Medicine, Otorhinolaryngology, Seoul, Korea, Republic of

Objectives: Treatment of symptomatic lingual thyroid typically involves surgical excision. Transcervical approach, which was usually used to do lingual thyroidectomy has the risk of treatment-related morbidity and leaves a visible scar on the neck. To avoid a visible scar and reduce this morbidity, transoral robotic surgery (TORS) was performed for the resection of lingual thyroid.

Methods: Between October 2009 and October 2010, 3 patients diagnosed with lingual thyroid were enrolled in this study. Main symptoms included swallowing difficulty in 2 patients and blood tinged sputum in 1 patient. A daVinci robotic system (Intuitive Surgical Inc., Sunnyvale, CA, USA) was used to perform TORS in all patients. A face-up 30-degree endoscope was inserted through the oral cavity and two instruments were located in both sides of the endoscope. We evaluated the robotic set up time, operating time, blood loss, and surgery related complications.

Results: Transoral robotic lingual thyroidectomy was performed successfully in all patients. The mean operating time was 43 minutes (range, 35 to 50), and an average of 11 minutes (range, 10 to 15) was required for setting up the robotic system. All patients satisfied with good cosmetic results and the alleviation of their symptom after operation. There was no perioperative complications and significant bleeding. An average of blood loss during the operation was 25mL.

Conclusions: The application of TORS for lingual thyroidectomy was technically feasible and relatively safe. TORS will be a good treatment option for lingual thyroidectomy in patients with symptomatic lingual thyroid.

P84

THYROID FUNCTION AND ULTRASOUND IN THE OFF-SPRINGS OF THE CHERNOBYL-RELATED THYROID CARCINOMA SURVIVORS

Akulevich N[1,2], *Leonava T*[1], *Drozd V*[3], *Mityukova T*[1], *Platonova T*[1], *Korytko S*[2]
[1]Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus, [2]State Center of Medical Rehabilitation, Minsk, Belarus, [3]International Fund “Arnika”, Minsk, Belarus

Objective: The wast majority of children diagnosed with well differentiated thyroid cancer (WDTC) after the Chernobyl accident have a good prognosis for life and fertility. In our study, thyroid function and ultrasound (US) features in the off-springs of paediatric WDTC survivors have been estimated.

Methods: Totally, 155 children, 86 F, aged 5,3±3,1 y.o. (0,3–14,8) born to 127 parents with thyroid carcinoma are under observation. Parents were young children (2,6±2,5 y.o.) at the time of the Chernobyl accident and cancer diagnosis (13,3±4,2 y.o.) and received complex treatment including thyroidectomy, levothyroxine suppressive therapy and radioactive iodine therapy. Mean time since thyroid cancer diagnosis to the first child birth was 9,7±4,6 years. In a part of the off-springs, thyroid US and function were evaluated.

Results: An abnormal thyroid US pattern was seen in 17/44 (38,6%) of children. Low echogenecity, typical thyroiditis picture and nodular lesions were the most common findings (20,5%, 11,4% and 6,8%, respectively). Thyroid hyperplasia was found in 4,5% of cases. Thyroid function tests were checked in 37/155 children. Mean TSH level was 2,6±1,8 mIU/l; however, subclinical hypothyroidism (TSH higher than 4 mIU/l) was observed in 8/37 (21,6%) children and subclinical hyperthyroidism - in 1 boy (2,7%). Elevated TPO-Ab levels were present in 13,5% of the subjects. It should be mentioned that TSH elevation was mostly isolated or combined with minor thyroid US abnormalities.

Conclusion: Children born to childhood thyroid carcinoma parents are at risk for thyroid disorders. The off-springs of paediatric WDTC survivors should be carefully followed-up since early childhood and cured, if necessary, for thyroid abnormalities and dysfunction.

PO10 Goiter and Nodular Disease Clinical 1

P85

EFFECTS OF 0.1 MG RECOMBINANT TSH RADIOIODINE THERAPY IN THYROIDECTOMIZED PATIENTS WITH RECURRENT MULTINODULAR GOITER

Angelopoulos NG[1], *Iakovou J*[1], *Boniakos A*[1]
[1]Thessaloniki University, Nuclear Medicine, Thessaloniki, Greece

Background: Several treatment options exist after thyroid malignancy has been ruled out in patients with multinodular goiter (MG). Surgery efficiently reduces the goiter size but carries a risk of both surgical and anesthetic complications while in recent years, levothyroxine suppressive therapy has been abounded. I131 therapy is the only nonsurgical alternative; however, the effectiveness diminishes with increasing goiter size and depends on iodine sufficiency in some areas. Recombinant human (rh) TSH approximately doubles the thyroid 131I uptake in patients with nodular goiter. Several studies have proved efficacy of rhTSH stimulated 131I therapy on goiter reduction.

Objective: The objective of the study was to assess the efficacy and safety of 0.1 mg rhTSH as an adjuvant to a fix dose of 131I therapy (11 mci) in patients with recurrence of large multinodular goiter several years after the initial thyrodectomy.

Patients and Intervention: 14 (13 females), age 59.1 (35–78) received 11mciu of I131, 24h after the administration of 0.1 mg rhTSH. Main Outcome Measures: The primary end point was a change in thyroid volume (by ultrasound measurements) as well as in the diameter of the predominant nodule during a follow up period of 8 months. Secondary end points were the alterations in thyroid function and potential adverse effects.

Results: Significant decrease in the volume of thyroid remnant was observed at the end of the follow up period (log10 values), mean (95%CI) 1.17(1.03–1.3) after 8 months, compared to 1.45 (1.32–1.59) before. There was a positive correlation between the increments of TSH increase (TSH 24h after the stimulation -TSH before stimulation) with the percentile of thyroid volume decrease. ($r=0.77$, $p< 0.01$).

Conclusion: Further investigation is needed since this approach could be attractive in terms of minimizing the potential risks of reoperation in these patients.

P86

MINIMALLY INVASIVE OPEN APPROACH IN THE SURGICAL TREATMENT OF THE NODULAR THYROID DISEASE

Nenkov RN[1], Radev RS[1]
[1]Medical University-Varna, Thoracic Surgery, Varna, Bulgaria

The minimally invasive approach spreads wider over the surgical treatment of thyroid diseases in recent years.

Aim: To present our results with the application of minimally invasive open approach in the treatment of nodular thyroid disease with harmonic scalpel.

Materials and methods: For the period from 2008 to 2011 year, 576 patients (527 females and 49 males; age ranging from 6 to 68 years) with nodular thyroid disease have been operated on using minimally invasive open approach in our institution using harmonic scalpel. The underlying thyroid disease in this group was: solitary thyroid nodule in 246 patients, multinodular goiter - 152 patients, nodular toxic goiter - 43 patients, nodular form of Hashimoto thyroiditis - 62 patients, thyroid cancer - 73 patients. The resection has been performed through a central collar incision, 2.5–3.0 cm in length. Harmonic scalpel, version Focus (Ethicon Endo-Surgery) has been used.

Results: In 52 patients near total lobectomy, in 194 patients - lobectomy, in 161 patients - near total thyroidectomy, in 23 patients -lobectomy with near total lobectomy of the opposite lobe and in 146 patients total thyroidectomy have been performed. Haemostatic instruments and vessel ligatures have not been used. In most of the cases, the procedure was finished without draining. The incidence of intra- and postoperative complications do not differ from those in conventional thyroid resections. The operative time varied between 28 and 53 minutes, depending on the extent of resection and the postoperative hospital stay did not exceed 24 hours. The cosmetic results was assessed as excellent from most (97%) of the patients.

Conclusions: The minimally invasive open approach with harmonic scalpel is feasible, effective and safe surgical technique in the treatment of selected patients with nodular thyroid disease.

P87

EFFICACY OF PERCUTANEOUS ETHANOL INJECTION IN BENIGN THYROID NODULES CLASSIFIED AS PURE CYSTS, COMPLEX CYSTS, AND SOLID NODULES

Choi SH[1], Jeong JP[1], Kim GW[1], Park CW[1], Lee JH[1], Jung SW[1], Kim YA[1], Kim SH[1], Lim JK[1], Kim TH[1]
[1]Kwangju Christian Hospital, Internal Medicine, Gwang Ju, Korea, Republic of

Objectives: To determine the efficacy of percutaneous ethanol injection (PEI) in benign thyroid nodules associated with pure cysts, complex cysts, and solid nodules.

Methods: A total of 123 patients who were treated with percutaneous thyroid ethanol injection in the authors' hospital between July 2001 and October 2010 were examined. Songraphically, the nodules were classified as pure cysts, complex cysts, and solid nodules. The cystic fluid was aspirated, and absolute ethanol was injected. The initial and final volumes were measured by length, width, and height. The efficacy of PEI was used to determine the volume reduction rate. The patients were classified as follows: those with complete response (≥90%), partial response (>50% and < 90%), and no response (< 50%), according to the volume reduction rate.

Results: The average pre-treatment volumes of the nodules were all 13.5 mL. The average volume reduction was 8.10 mL, and the average reduction rate was 61.47%. 55 patients had complete responses; 29 partial responses; and 39 no response. The average difference in the responses of the three groups (pure, complex, and solid) was significantly correlated with the volume reduction ($p< 0.005$), and the volume reduction rate of the pure cysts was higher than that of the solid nodules. Nine patients had minor complications such as transient neck pain, hoarseness, and ethanol leakage in the surrounding tissue, but there was no severe complication.

Conclusion: Percutaneous ethanol therapy is a safe and effective form of therapy for patients with benign thyroid nodules, especially cystic nodules.

P88

HIGH PREVALENCE OF GOITER IN GUINEA-BISSAU SCHOOLCHILDREN – A CROSS-SECTIONAL SURVEY

Carvalho AC[1], Machado A[2], Bordalo AA[2]
[1]St. Antonio Hospital - Centro Hospitalar Porto, Endocrinology, Porto, Portugal, [2]Institute of Biomedical Sciences (ICBAS) - University of Porto, Laboratory of Hydrobiology, Porto, Portugal

Introduction: Guinea-Bissau is one of the poorest countries in the world, with a largely young and malnourished population. Endemic goiter is known in many districts of the hinterland since the 1950´s but the current iodine deficiency status is unknown.

Objectives: To assess the prevalence of enlarged thyroid volume (Tvol) in the schoolchildren population of Guinea-Bissau.

Methods: A cross-sectional survey was performed during September 2011 in four different areas in Bolama (island), Bissau (coast), Cambadju and Gabu (both hinterland). Tvol was measured by ultrasound in 299 children aged 6–12 years old. A thyroid enlargement above the 97th percentile of the reference volume, corrected for sex and body-surface-area, was considered as goiter.

Results: Enlarged Tvol was found in 73% of the children (79% of the girls and 68% of the boys). Goiter prevalence rates were higher in Bissau (85%) followed by Bolama (75%), Cambadju (72%), and Gabu (67%).

Conclusions: Guinea-Bissau children suffer from endemic goiter probably due to iodine deficiency. This was the first study in Guinea-Bissau to estimate goiter prevalence in schoolchildren by ultrasound. An urgent comprehensive national iodine deficiency survey with implementation of a sustainable iodine supplementation programme is in dear need.

P89

PERCUTANEUS LASER ABLATION IN BENIGN THYROID NODULES: FIRST BRAZILIAN EXPERIENCE

Andreoni DM[1], Garcia RG[2], Janovsky CC[1], Pitman WJ[2], Hidal JT[1], Francisco Neto MJ[2], Maciel RMB[1]
[1]UNIFESP EPM, Sao Paulo, Brazil, [2]HIAE, Sao Paulo, Brazil

Several trials have demonstrated that laser ablation (LA) is a safe and good treatment for the shrinkage of benign thyroid nodules. In Brazil, this modality of treatment has not yet been implemented.

Objectives: As our center was the pioneer to access this type of technology the aim of this study was to determine the implementation of interstitial laser ablation technique to the treatment of benign thyroid nodules, as an alternative to conventional surgical treatment in Brazil. Assesing its effects on nodule volume, thyroid function and nodule-related symptoms referred by the patient.

Methods: 20 euthyroid patients with a benign solitary nodule were recruited from a thyroid disease clinic. The procedure was performed at the Hospital Israelita Albert Einstein (HIAE). All patients had treatment indication due to compressive symptoms, aesthetic disturbances, large size and/or contraindication of surgery.

The clinical and laboratorial evaluation was performed before the procedure and periodically 1 week, 1, 6 and 12 months after. It consisted on physical examination, thyroid ultrasound, TSH, FT4, thyroglobulin (TG), TG-Ab, TPO-Ab and TRAb dosages. The Ethical Committee of the HIAE approved this protocol.

Results: We have already evaluated 20 patients, with a total of 20 nodules submitted to laser ablation. The volumetric reduction of the nodule was approximately 50% after 3 months of the procedure (from average 12.4mL to 6.1mL). No patient have experienced disturbance on thyroid function and there was no modification on the antibodies levels, which remained negative on all patients. As expected, there was a peak on the level of thyroglobulin after the procedure due to tissue destruction. There were no adverse effects referred by the patients, including pain, swelling or hemorrage.

Conclusions: The first Brazilian experience on percutaneus laser ablation was a great success. Our initial results are in congruence with the literature.

P90

THYROID DISORDERS IN ACROMEGALY: A SINGLE CENTER EXPERIENCE

Urbani C[1], Nuzzo A[1], Sardella C[1], Lombardi M[1], Scattina I[1], Calevro A[1], Marchello A[1], Dell'Unto E[1], Lupi I[1], Manetti L[1], Martino E[1], Bogazzi F[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

Objectives: Thyroid diseases are a frequent finding of acromegaly, although their prevalence is unsettled. The purpose of this study was to evaluate the prevalence of thyroid disorders and the effect of biochemical control of acromegaly on thyroid status.

Methods: Clinical records of 209 consecutive acromegalic subjects were analyzed. Two hundred patients affected by non functioning or PRL-secreting pituitary adenoma served as control.

Results: Five patients presented a co-secreting TSH pituitary adenoma. The great majority of patients (n=181, 86.6%) was affected by a thyroid disorder at diagnosis ($p< 0.0001$ vs. controls): 98 (51.7%) had a non-toxic nodular goiter, 32 (15.3%) a non-toxic diffuse goiter, 9 (4.3%) a toxic nodular goiter and 4 patients had Graves' disease. All subjects with Graves' disease had a moderate-severe orbitopathy requiring combination of glucocorticoids, external radiotherapy or orbital decompression. Thyroid autoimmunity was present in 26.3% of patients and was associated with hypothyroidism in 4.8%. Central hypotiroidism was found in 26 patients at diagnosis (12.4%). Nineteen patients (9.1%) presented a papillary thyroid cancer at diagnosis or during follow-up. Any of these subjects at the end of follow-up period had biochemical or morphological persistence of thyroid cancer. Mean thyroid volume at diagnosis was higher in acromegalic patients than in controls ($p< 0.0001$), being higher in subjects with (26.8±17.7 ml) than in those without thyroid diseases (12.7±3.9 ml) ($p< 0.0001$). Thyroid volume was related to the estimated duration of acromegaly ($r=0.50$, $p=0.0083$), age ($r=0.25$, $=0.0128$) and IGF1-index ($r=2,16$, $P=0.0239$) at diagnosis.

Conclusions: Acromegaly is characterized by an increased prevalence of thyroid disorders, particularly non-toxic nodular goiter. The prevalence of thyroid carcinoma was higher than in the general population. In addition, in our series, acromegalic subjects with concomitant Graves' disease present a moderate-severe orbitopathy. Thyroid volume is related to the estimated duration of acromegaly, age and IGF1-index at diagnosis.

PO11 Imaging in Thyroidology

P91

RISK OF MALIGNANCY IN THYROID INCIDENTALOMAS DETECTED BY 18F-FDG-PET IS RELATED TO FOCAL UPTAKE BUT INDEPENDENT OF CONTINENTAL DIFFERENCES IN ABSOLUTE THYROID CANCER INCIDENCES

Soelberg KK[1], Bonnema SJ[1], Brix TH[1], Hegedüs L[1]
[1]Odense University Hospital, Department of Endocrinology, Odense, Denmark

Background: The expanding use of 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG PET) has led to the identification of increasing numbers of patients with an incidentaloma in the thyroid gland. We aimed to review the proportion of incidental thyroid cancers found by 18F-FDG PET or PET/CT imaging.

Methods: Studies evaluating thyroid carcinomas discovered incidentally in patients or healthy volunteers by 18F-FDG PET were systematically searched in the PubMed database from 2000 up to 2011. The main exclusion criteria were known thyroid disease, lack of assigned diagnoses, investigation of diffuse uptake only, or investigation of patients with head and neck cancer, or cancer in the upper part of the thorax.

Results: Twenty-two studies met our criteria comprising a total of 125754 subjects. 1994 (1.6%) had an unexpected focal hypermetabolic activity, while 999 of 48644 individuals (2.1%) had an unexpected diffuse hypermetabolic activity in the thyroid gland. A diagnosis was assigned in 1051 of the 1994 patients with a focal uptake (34.8%, were malignant), and in 168 of 999 patients with diffuse uptake (4.4%, were malignant). The studies were performed in different parts of the world. The prevalence of focal uptake in Asia (2.2%) was 2–3 times that in the studies from America (1.1%) and Europe (0.7%). Despite this difference the rate of cancer was almost the same.

In the eight studies reporting individual maximum standard uptake values (SUVmax), the mean SUVmax value was 4.8 (SD 3.1) and 6.9 (SD 4.7) in benign and malignant lesions, respectively, ($p< 0.001$).

Conclusions: Incidentally found thyroid nodules, using 18F-FDG PET, are at high risk of harboring malignancy if uptake is focal. The rate of thyroid cancer in patients with a focal uptake is similar in Asia, America, and Europe despite differences in absolute thyroid cancer incidence. SUV-values are significantly higher in malignant than in benign thyroid nodules.

P92

REAL-TIME ELASTOGRAPHY IN ADDITION TO TRADITIONAL ULTRASOUND FINDINGS PROVIDES A BETTER SELECTION OF THYROID NODULES TO BE BIOPSIED. RESULTS OF A PROSPECTIVE MULTICENTER TRIAL

Trimboli P[1], Misischi I[2], Monti S[3], Valabrega S[4], Graziano FM[2], Nasrollah N[1], Amendola S[1], Morgante SN[3], Deiana MG[3], Pascucci C[3], Guglielmi R[2], Toscano V[3], Papini E[2]
[1]Section of Endocrinology and Diabetology, Ospedale Israelitico, Rome, Italy, Rome, Italy, [2]Regina Apostolorum Hospital, Department of Endocrinology, Albano Laziale, Rome, Italy, [3]S. Andrea Hospital, 'Sapienza' University', Department of Endocrinology, Rome, Italy, [4]S. Andrea Hospital, 'Sapienza' University', Department of Surgery, Rome, Italy

Aim: To blindly evaluate on a prospective multicenter series of unselected thyroid nodules the diagnostic accuracy of RTE, to compare it with the predictive value of B-mode features and to assess the improvement of diagnostic accuracy provided by its combination with traditional US findings.

Materials and methods: From June 2010 until December 2011, 498 consecutive solid thyroid nodules were evaluated at three thyroid referral centers in Rome. B-mode US and RTE examinations were performed before fine needle aspiration biopsy (FNA) and images were stored and separately evaluated in a blinded fashion by six experienced endocrinologists. After US-guided FNA, patients with a benign cytologic report underwent a clinical and US control after six months, while patients with indeterminate, suspicious and malignant cytology were operated upon.

Results: One hundred-twenty-six nodules (25%) were malignant and 372 (75%) benign. The sensitivity for malignancy of RTE class III and IV scores as a whole was 81% and the NPV was 91%, with a 67% diagnostic accuracy. Strong hypoechogenicity, microcalcifications, irregular margins, "more tall than wide" aspect and intranodular vascularization showed a 83%, 79%, 70%, 69%, and 78% diagnostic accuracy, respectively. The presence of at least one of the US risk factors had 74% sensitivity, 68% specificity, 44% PPV, 89% NPV and 70% accuracy. When RTE class III and IV scores were combined with conventional US risk features, the presence of at least one of the six parameters had 94% sensitivity and 95% NPV, 45% specificity, 37% PPV and 58% accuracy.

Conclusions: In unselected solid thyroid nodules, in absence of confounding sonographic factors, RTE increased the sensitivity for malignancy of conventional US risk factors. The consequent improvement of the NPV of US examination provided a better definition of the thyroid nodule population to be submitted to FNA biopsy.

P93

ULTRASOUND (US) GUIDED RADIOFREQUENCY THERMOABLATION OF THYROID BENIGN AND MALIGNANT NEOPLASMS: A PRELIMINARY EXPERIENCE

Mazzeo S[1], *Battaglia V*[1], *Cappelli C*[1], *Pontillo Contillo B*[1], *Elisei R*[2], *Vitti P*[2], *Bartolozzi C*[1]
[1]University of Pisa, Department of Oncology, Transplants and New Technologies in Medicine, Pisa, Italy, [2]University of Pisa, Department of Endocrinology and Metabolic Diseases, Pisa, Italy

Purpose: To determine the feasibility and the usefulness of radiofrequency ablation (RFA) in patients with benign thyroid nodules, and in patients with inoperable, loco regional recurrence of thyroid malignant masses.

Materials and methods: Our series comprehends 5 patients with loco regional recurrence of papillary thyroid cancer and 3 patients with monolateral multinodular (1 patient) or single macronodular thyroid goither. Neoplastic patients had been judged ineligible for surgery; 2 patients with goither had refused thyroidectomy, while 1 patient was ineligible for surgery for marked compression and deviation of the tracheal lumen.

All the patients had performed a Computed Tomography (CT) examination within 1 month before ablation; in all cases the volumes of target nodules were calculated and registered.

All RF ablations were performed by using an 18-gauge, internally cooled, single tipped electrode, with ultrasonographic guidance; in all cases a single session of treatment was performed under loco-regional anesthesia and mild sedation.

Response to treatment was early evaluated after the procedure, by performig contrast enhanced ultrasound and by CT examination starting 3 months after ablation; volumes of ablated nodules were calculated and compared to pre treatment values.

Feasibility, complicancies were evaluated periprocedurally.

Results: In all patients the procedure was performed and well tolerated. In benign patients, no complicancies were observed. In 1 neoplastic patient, a dysphonia was clinically appreciable after procedure.

In all treated nodules, the mean volume reduction after ablation was greater than 80%.

Conclusions: RFA is a safe, effective and minimally invasive modality, that can be employed as an alternative to surgery in selected patients.

P94

FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA: DISTINCT BIOLOGIC BEHAVIOR ACCORDING TO US FEATURES

Rhee S[1], *Shin JH*[1], *Han B-K*[1], *Ko EY*[1], *Ko ES*[1], *Hahn SY*[1]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Radiology, Seoul, Korea, Republic of

Purpose: Follicular variants of papillary thyroid carcinoma (FVPTC) have a dichotomous ultrasonographic (US) feature. We investigated whether there is a difference in their biologic behavior according to US features.

Materials and methods: We reviewed US findings, pathologic reports and medical charts of 75 consecutive patients with FVPTC who underwent surgery at our institution from March 2006 to March 2008. FVPTCs were divided into PTC-looking and follicular neoplasm (FN)-looking based on US findings. PTC-looking nodules were defined as having at least one of accepted malignant features, whereas FN-looking nodules had no malignant features. Two groups were compared in terms of age, sex, tumor size, multiplicity, extrathyroidal extension, lymph node metastasis, stage, recurrence, and distant metastasis.

Results: Of the 75 FVPTCs, 42 (56%) were PTC-looking and 33 (44%) were FN-looking. The mean tumor size of PTC-looking FVPTC was 1.3cm, that was significantly smaller than 1.6cm of FN-looking (P=0.0483). PTC-looking FVPTC showed a higher multiplicity of 48% compared to 15% in FN-looking (P=0.0031). Extrathyroidal extension occurred in 55% of PTC-looking FVPTCs than in 12% of FN-looking (P=0.0001). Lymph node metastasis was more frequent in PTC-looking FVPTC (36%) than FN-looking (12%) (P=0.0197). PTC-looking FVPTC had a higher stage than FN-looking (P=0.0001). Recurrence and distant metastasis were identified only in each one of PTC-looking FVPTCs. There were differences in age and sex between the two groups.

Conclusion: FVPTC without malignant features that is a limit to US diagnosis is not rare. However, FVPTC with malignant features seems to behave in a more aggressive fashion than FVPTC without malignant features.

P95

FAILED BRAF^{V600E} MUTATION ANALYSIS WITH FINE NEEDLE ASPIRATES OF THYROID NODULES: INCIDENCE AND PREDICTIVE FACTORS OF INADEQUATE SPECIMENS

Kim HS[1], *Shin JH*[1], *Lee KH*[1], *Ki C-S*[2], *Han B-K*[1], *Ko EY*[1]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Radiology, Seoul, Korea, Republic of, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Laboratory Medicine and Genetics, Seoul, Korea, Republic of

Background: BRAF^{V600E} mutation analysis with aspiration specimens is increasingly used to diagnose papillary thyroid carcinoma. However, it is limited in some conditions. The purpose of this study was to assess the incidence and predictive factors of inadequate specimens for BRAF^{V600E} mutation analysis with aspirates of thyroid nodules.

Materials and methods: We performed a retrospective cohort study of consecutive patients who received US (ultrasound)-guided fine-needle aspiration (FNA) and molecular test from aspiration specimens. Patients showed inadequate specimens in both Allele-specific PCR and direct DNA sequencing method. Univariate and multivariate logistic regression analyses were performed to identify risk factors of inadequate specimens for molecular test.

Results: Inadequate specimens for BRAF^{V600E} mutation analysis were obtained in 168 (2.4%) of 7001 patients. Factors associated with inadequate specimens, including patient age, sex, tumor size, US diagnosis, the presence of calcification, and cystic change of thyroid nodules, were not significant determinants in our analysis. The oval-to-round or irregular shape and final benign results were significant factors in univariate analysis (P=0.0002, P=0.0013, respectively). However, nodules where FNA was performed by operators with experience less than 1 year (OR 3.0, P=0.007) and that had infiltrative margin (OR 6.1, P=0.0142), isoechoic nodule (OR 10.4, P=0.0442), and non-diagnostic (OR 31.2, P=0.0177) or indeterminate cytology (OR 73.6, P=0.0055) persisted significant risk factors after adjustment in our multivariable model.

Conclusion: Successful US-guided FNA precedes a perfect BRAF^{V600E} mutation test. Thyroid nodules with inadequate specimens for BRAF^{V600E} mutation analysis show oval-to round or irregular shaped, infiltrative marginated, isoechoic nodule on US and a higher frequency in benign nodules.

P96

THYROID INCIDENTALOMAS DETECTED ON ^{18}F-FDG PET/CT IN NONTHYROIDAL CANCER PATIENTS: CLINICAL IMPLICATION AND VALUE OF US

Lee KH[1], *Shin JH*[1], *Han B-K*[1], *Hahn SY*[1], *Ko EY*[1], *Choi JY*[2]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Radiology, Seoul, Korea, Republic of, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Nuclear Medicine, Seoul, Korea, Republic of

Objectives: To evaluate the clinical implication and the value of ultrasonography(US) of thyroid incidentalomas detected on ^{18}F-FDG PET/CT (PET/CT) in nonthyroidal cancer patients.

Methods: Between March 2006 and March 2008, 3226 PET/CT examinations in nonthyroidal cancer patients were performed. The patients with incidentalomas were divided into US-performing and US-nonperforming group. Two groups were compared with age, death from disease, and stage of nonthyroidal cancer. In US-performing group, diagnostic accuracies of PET/CT and US according to PET/CT findings were assessed.

Results: The incidence of thyroid incidentalomas on PET/CT in nonthyroidal cancer patients was 7.9% (254/3226). Of a total of 226 patients with these incidentalomas, US-performing patients were 78 (35%) and US-nonperforming patients were 148 (65%). Two groups were not significantly different in death from disease and stage except that US-nonperforming

group was older. Malignant rate of US-performing group that had cytopathology was 39% (22/57). All malignancies were primary thyroid cancers except for one metastasis. Eight benign incidentalomas diagnosed with PET/CT showed complete agreement with US and final results. For the 22 nodules with malignant PET/CT findings, diagnostic accuracies of PET/CT and US were 55% and 82%, respectively (P=0.1489). Undetermined nodules on PET/CT were 27, in which the agreement between US and final results was excellent (Kappa value=0.92).

Conclusion: Most malignancies of thyroid incidentalomas detected on PET/CT in nonthyroidal cancer patients are primary thyroid cancers. They have no impact on patients` mortality whether evaluated with US or not. Additional US evaluation is valueless when PET/CT findings are benign.

P97

USEFULNESS OF SALIVARY SCINTIGRAPHY FOR EVALUATION OF DYSFUNCTION OF SALIVARY GLANDS AFTER RADIOACTIVE IODINE THERAPY

Choi J-S[1], *Lim J-Y*[1], *Kim Y-M*[1]
[1]Department of Otorhinolaryngology, Inha University College of Medicine, Incheon, Korea, Republic of

Objectives: Radioactive iodine (RI) therapy for differentiated thyroid cancer may induce unwanted salivary gland (SG) dysfunction. We evaluated salivary dysfunctions of patients using a visual analog symptom scare, and quantitative analysis of salivary flow rates and SG scintigraphy. The usefulness of SG scintigraphy for evaluation of SG dysfunction after RI therapy was assessed.

Methods: Seventy patients who had (1) SG dysfunction such as SG swelling, pain, dryness of mouth, or swallowing difficulty and (2) past history of total thyroidectomy and RI therapy were enrolled. Salivary dysfunction was graded according to a visual analog symptom scale. Salivary flow rate was measured and quantitative SG scintigraphy was performed for analysis of salivary parenchymal function.

Results: SG scintigraphy revealed significant dysfunction of SGs in most enrolled patients. A considerable association between parameters of SG scintigraphy and subjective symptom scores were identified. Parameters of SG scintigraphy were also found to be significantly related to salivary flow rate.

Conclusions: SG scintigraphy is a simple, non-invasive and useful tool of evaluation of SG function in patients with SG dysfunction after RI therapy.

P98

ULTRASONOGRAPHIC AND CLINICAL FINDINGS IN PATIENTS WITH METASTASES TO THE THYROID

Kim HK[1], *Yoon TM*[2], *Kang H-C*[1]
[1]Chonnam National University Medical School, Internal Medicine, Gwangju, Korea, Republic of, [2]Chonnam National University Medical School, Otolaryngology, Gwangju, Korea, Republic of

Background: Cases of metastases to the thyroid seem to be increasing in recent years, but clinical and ultrasonographic (US) findings have been reported sparsely.

Methods: Thyroid US with US-FNA were performed in patients with non-thyroid malignancies who showed abnormalities in imaging studies (CT, FDG-PET) or had thyroid dysfunction on laboratory evaluation. Fifteen cases of metastases to the thyroid gland (13 men, 2 women) were documented by US-FNA between 2004 and 2012.

Results: The most common primary site was the lung (n=9), followed by unknown origin cancers (n=2), cholangiocarcinoma (n=1), invasive thymoma (n=1), penile cancer (n=1) and ovarian cancer (n=1). Thirteen patients were incidentally found to have thyroid metastases via surveillance or staging FDG-PET (n=12) or neck US (n=1). Two patients were diagnosed during the work-up for the hypothyroidism. On ultrasonographic findings, 11 metastases exhibited diffuse enlargement of the thyroid lobes with internal hypoechoic lines without definitive nodular lesions (4 were right lobe, 1 was left lobe and 6 were both lobes), and remaining 4 metastases displayed relatively well-defined nodules. In 6 patients who showed diffuse thyroid enlargement in both lobes, 2 patients revealed hypothyroidism and 1 patient was initially thyrotoxic with rapid progression to the hypothyroidism.

Conclusions: In patients with metastases to the thyroid, most common US finding is diffusely enlarged heterogeneous thyroid with internal hypoechoic lines rather than nodular lesions. Thyroid function test should be performed in all patients with diffuse thyroid metastases, because half of the patients have functional abnormalities.

P99

ANALYSIS OF ULTRASOUND ELASTOGRAPHY, POWER DOPPLER, AND B-MODE ULTRASOUND FEATURES IN DIFFERENTIAL DIAGNOSIS OF MALIGNANT LYMPH NODES IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

Erdoğan MF[1], *Unluturk U*[1], *Güllü S*[1], *Aydoğan İB*[1], *Uysal AR*[2]
[1]Ankara University School of Medicine, Endocrinology and Metabolism, Ankara, Turkey, [2]Ankara University School of Medicine, Ankara, Turkey

Background: There are yet a few studies to evaluate the power of USE on detecting malignant lymph node (LN) in patients with differentiated thyroid carcinoma (DTC).

Objective: To assess the diagnostic power of USE in detecting malignant LNs and to compare this technique with B-mode (BM) and power Doppler US (PD) features.

Method: 75 cervical LNs having suspicious malignant features (short/long ratio>0,5, hilus loss, prominent hypoechogenicity, cystic component, hyperechoic spotting, irregular margin, peripheral blood flow) from 55 patients with DTC were examined using BM, PD, and USE. USE scores were classified from 1 to 3 according to the presence of elasticity in (1: soft, 2: intermediate, 3: hard). The strain ratios (SR) of all LNs were calculated according to adjacent muscle tissue. Fine needle aspiration cytology (FNAC) and LN thyroglobulin washout (LN-Tg) were performed to all LNs. LNs having benign FNAC and low LN-Tg levels (< 18 ng/ml) were accepted as benign.

Results: The sensitivity and specificity of score 3 USE were 61%, and 75%, respectively. The mean SR levels were not different between malignant LNs benign LNs (3.06 ±4.10 vs. 2.37 ± 2.10). The sensitivity and specificity of central and peripheral blood flow pattern in PD were 56% and 95%, respectively.

Conclusion: USE was found to have an inferior power compared to the most of BM features. Power Doppler was also found to have a superior power compared to USE techniques. Although USE was not an alternative to BM, FNAC, LN-Tg, it was found to be an assistant technique to determine the malignancy in LNs.

P100

THE CORRELATION BETWEEN SONOGRAPHIC AND HISTOPATHOLOGICAL FINDINGS IN THYROID NODULES

Dural AC[1], *Gonenc M*[1], *Buyukasik S*[1], *Bozkurt MA*[1], *Kalayci MU*[1], *Gulseven Ciftci S*[2], *Sever N*[3], *Alis H*[1]
[1]Bakirkoy Doctor Sadi Konuk Education and Research Hospital, General Surgery, Istanbul, Turkey, [2]Bakirkoy Doctor Sadi Konuk Education and Research Hospital, Radiology, Istanbul, Turkey, [3]Bakirkoy Doctor Sadi Konuk Education and Research Hospital, Pathology, Istanbul, Turkey

Objective: To assess the correlation between sonographic and cytological findings in thyroid nodules on an institutional base.

Methods: Medical recordings of the patients who had total thyroidectomy for various indications between January 2009 and January 2012 were reviewed, and those who had suspected thyroid nodule(s) were recruited to the study. Sonographic and histopathological diagnosis of thyroid nodules were compared.

Results: Totally 269 patients were included to the study. The number of thyroid nodules that were sampled via fine needle aspiration biopsy was 282. Sixteen percent of nodules that were diagnosed as benign by sonography was found to be malignant on final histopathological examination, whereas this rate was 22% for those that were diagnosed as suspicious for malignancy on sonographic scan.

Conclusion: Sonography is alone inadequate for evaluating thyroid nodules. Therefore, it should be combined with fine needle aspiration biopsy.

PO12 Case Reports 1

P101

CLINICAL CASE OF CONCURRENT GRAVES DISEASE AND PRIMARY HYPERPARATHYROIDISM

Volkova N[1], *Beltsevich D*[2], *Antonenko M*[1]
[1]Rostov State Medical University, Rostov on Don, Russian Federation, [2]National Research Centre for Endocrinology, Moscow, Russian Federation

Objective: Graves disease and primary hyperparathyroidism rare occur simultaneously. To our knowledge, about 50 such cases have been described in the literature. We report a clinical case when resolved Graves disease unmasked primary hyperparathyroidism.

Materials: Patient male 28 y.o. complained of heat intolerance, weight loss despite increased appetite, palpitations, proximal muscle weakness, high blood pressure, easy fatigability, anxiety and irritability. Since these symptoms were consistent with thyrotoxicosis, appropriate workup was performed. Free T4 and free T3 levels were elevated, and thyrotropin was suppressed. Other laboratory tests were notable for leucocytosis and mild hypercalcemia (1.34 mmol/l [normal range, 1.14 to 1.29]). These findings were accounted as a consequences of hyperthyroidism. Assays for thyrotropin-receptor antibodies were strongly positive. Ultrasound showed an enlarged gland with a low thyroid echogenicity. There was also increased thyroid radioiodine uptake. Thus the diagnosis of Graves disease was made. As a treatment patient chose antithyroid agents and beta-blockers. After 2 months on this therapy, thyrotropin, free T4, free T3 levels were in reference ranges and patient´s symptoms were resolved, except high blood pressure. Repeated blood tests showed persisted hypercalcemia (1.32 mmol/l) and low phosphate levels. The level of parathyroid hormone (PTH) was two times upper limit of normal. The left neck ultrasound demonstrated a well defined nodule that was isoechoic to the adjacent thyroid gland and located medial to the common carotid artery. So the primary hyperparathyroidism was diagnosed. A surgical treatment was performed for both diseases. Postoperatively, ionized calcium, phosphate, PTH and levels of blood pressure returned to normal.

Conclusion: Few patient's symptoms were consistent with hyperparathyroidism but were nonspecific and overlapped with symptoms of thyrotoxicosis. In this case persistent hypertension prompted further diagnostic evaluation. Thus in clinical practice there is always needed not only tight laboratory control but also clinical symptoms control.

P102

UNMARKED CASE OF AMIODARONE-INDUCED THYROTOXICOSIS

Davidenko I[1], *Volkova N*[1], *Rudakova J*[2]
[1]Rostov State Medical University, Rostov on Don, Russian Federation, [2]Municipal Centre of Endocrinology, Rostov on Don, Russian Federation

Objective: Today, thyrotoxicosis syndrome remains relevant problem of endocrinology. Prevalence of this thyroid gland`s pathology is 0,8 morbid even on 1000 population. Thyrotoxicosis syndrome could develop because of various causes, one of them is taking of Amiodarone, which contains a high concentration of iodine. Amiodarone-induced thyrotoxicosis I and II type appears at 2–12% patients. It could be diagnose during 18 months after discontinuing.

Materials: Patient I. marked complaints that were typical for thyrotoxicosis syndrome at September 2009. As a results based on depressed level of TSH and increased value of free T4 and T3 Graves´ disease was diagnosed. Thiamazole was prescribed for a time of waiting radioiodine therapy, but patient wasn´t relieved. At the moment of presentation the diagnosis was call into question, because there was no treatment response. It was found out from life personal history that patient had been taking Cordarone (Amiodarone) during 12 months. And it was discontinued 2 years ago. Over the time of taking Amiodarone thyroid function had not been assessed. This fact was led to further differential diagnostics of thyrotoxicosis syndrome. Antibodies to TSH receptors were negative. Decreased radioiodine uptake was also found on radionuclide scintigraphy. Based on these results, Amiodarone-induced thyrotoxicosis II was diagnosed, and glucocorticoids were prescribed. On this therapy the patient's symptoms were resolved.

Conclusion: This clinical case demonstrates the importance of adherence to diagnostic guidelines of thyrotoxicosis syndrome. Its ignoring could lead to mistaken diagnosis and incorrect treatment. Also it should be noted that thyroid function must be assessed in all patients who are taking Amiodarone.

P103

CLINICAL, BIOCHEMICAL CHARACTERISTICS AND TREATMENTS OF PATIENTS WITH TSH SECRETING PITUITARY ADENOMAS

Song YD[1], *Kim CS*[2], *Park SO*[3], *Shin DY*[4], *Lee EJ*[4]
[1]NHIC Ilsan Hospital, Endocrinology, Goyangsi, Korea, Republic of, [2]Hallym University Sacred Heart Hospital, Endocrinology, Anyangsi, Korea, Republic of, [3]Gwangmyeong Sung-Ae Hospital, Endocrinology, Kwangmyeongsi, Korea, Republic of, [4]Yonsei University College of Medicine, Endocrinology, Seoul, Korea, Republic of

Background: Thyroid stimulating hormone (TSH)-secreting pituitary adenoma (TSHoma) is very rare and represents 1~2% of all pituitary adenomas. TSHoma should be distinguished from the syndrome of resistance to thyroid hormone, and it may also be misdiagnosed as primary hyperthyroidism and often receive inappropriate treatment directed towards the thyroid gland.

Methods: We analyzed clinical characteristics of the patients with TSHoma who were presented to Severance hospital, Yonsei University College of Medicine, Seoul Korea from 2005 to 2009.

Results: Among 484 patients with pituitary tumor who underwent pituitary tumor resection, 8 (1.65%) were revealed to be TSHoma. Five were women and 3 were men. Mean age was 40.6±8.9 years at diagnosis (range 28–55 years). The median duration from the onset of symptoms to diagnosis was 17 months (range 4–60 months). Four patients had overt symptoms of hyperthyroidism and 2 had visual field defect. Six patients had elevated free thyroxine (FT4) levels with elevated, or inappropriately normal TSH levels and 2 patients were associated with Hashimoto's thyroiditis. One had normal FT4 normal TSH and the other had normal FT4 with high TSH. The serum levels of free α-subunit measured in 2 patients were elevated. MRI showed that 6 were macroadenomas (>10mm) and 2 were microadenomas. Complete tumor removal was achieved in all patients. Five patients had preoperative anterior pituitary dysfunction. Anterior pituitary function was recovered in 3 after operation. Three patients were lost to follow-up and 5 patients had no evidence of recurrence or hyperthyroidism for 30.8 months (mean, range 3–57months) of follow-up.

Conclusion: Early diagnosis and complete removal of tumor mass may improve the neurological and endocrine defects.

P104

CALCITONIN-NEGATIVE NEUROENDOCRINE TUMOR OF THE THYROID

Jung ED[1], *Jun EJ*[1], *Shon HS*[1], *Kim MK*[2]
[1]Catholic University of Daegu, Internal Medicine, School of Medicine, Daegu, Korea, Republic of, [2]Keimyung University, Internal Medicine, School of Medicine, Daegu, Korea, Republic of

Medullary thyroid cancer (MTC) is a neuroendocrine tumor (NET) that originates in the parafollicular cells (C-cells) of the thyroid. MTC over-produces calcitonin. Therefore, calcitonin is a serum marker of MTC. It is less known about primary NET of the thyroid besides MTC. Here, we describe a young-mail patient presenting with another form of NET originates from the thyroid. This is a thirty-four-old man who underwent left lobectomy for thyroid nodule. Core biopsy showed follicular cells that had features of an NET with immunohistochemical stain negative for calcitonin. His serum calcitonin were normal. Surgical pathology showed a well-differentiated NET with immunohistochemical stains positive for thyroglobulin, a markers of follicular cells, positive for chromogranin A and synaptophysin, a marker of neuroendocrine tumor, but negative for calcitonin, a definite marker of MTC. We suggest that

calcitonin-negative NET of the thyroid may exist. It needs a further evaluation to differentiate between MTC and calcitonin-negative NET of the thyroid.

P105

MYALGIA: A PRESENTING SYMPTOM OF GRAVES´ DISEASE

Papanikolaou N[1], Perros P[1]
[1]Royal Victoria Infirmary, Endocrinology, Newcastle upon Tyne, United Kingdom

A 50 year old female patient presnted with severe myalgia involving proximal muscles for 3–4 weeks. She also reported mild thyrotoxic symptoms over the same time period. Examination revealed mild thyrotoxicosis, a moderate diffuse goitre and no eye signs. The clinical picture was dominated by muscle pain and tenderness involving mainly her proximal arms and legs, calves and fingers, which required opiate analgesia. Muscle power and tendon reflexes were normal. Laboratory evaluation revealed undetectable serum with raised FT4 (54.1 pmol/l) and FT3 (22.7 pmol/l) and positive TSH receptor antibodies. Carbimazole (20mg) was commenced. Additional laboratory investigations were negative (inflammatory markers, Creatine Kinase, antibodies to ANA, Gastric parietal cell, Smooth muscle, Mitochondrial, DS- DNA, Centromere, ENA RNP Sm, ENA Sm Ab, ENA Ro, ENA Anti- La, ENA Scl 70, ENA Jo 1, Anti CCP, Rheumatoid Factor). Further assessment in teh Rheumatology clinic confirmed no small joint tenderness, or loss of range of movement of her limbs, widespread and profound muscle tenderness of the common extensors of the forearms, biceps, trapezious, calves and thighs. A musculoskeletal ultrasound showed no evidence of hand synovitis or tenosynovitis.

She was treated symptomatically with analgesic medication and continued on carbimazole. A month later she was euthyroid and her myalgia had resolved.

Hyperthyroidims has a profound effect on skeletal muscle and often leads to myopathy. Severe myalgia in association with Graves' disease has not been reported, though it can occur in patients with viral thyroiditis or as a result of anti-thytroid drug treament. The lack of an alternative explanation in our case and the parallel improvement in symptoms with restoration of euthryoidism suggests that this association may not be coincidental.

P106

CASE REPORT: PRIMARY SQUAMOUS CELL CARCINOMA OF THYROID – CLINICAL MANIFESTATION MIMICKED ACUTE THYROIDITIS

Kriksciuniene R[1], Knispelis R[1], Makstiene J[2], Sarauskas V[2]
[1]Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Endocrinology, Kaunas, Lithuania, [2]Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Pathological Anatomy, Kaunas, Lithuania

A 67 year-old woman presented with painful tumor and swelling of the neck tissues. She started feeling pain on the left side of the neck and head after she had got cold, about two weeks before the consultation. The pain was intolerable, VAS - 10 scores. She was standing for painkillers all the time.

Physical examination revealed a firm, rigid, painful mass of about 6x4 cm diameter predominantly on left side of the neck, with redness and induration of the overlying skin and without palpable lymph nodes anywhere.

Ultrasound examination of the thyroid showed a solid hypoechogenic lesion of 6.5x3.8 cm diameter with retrosternal extension and fixity. CT scan of the neck region confirmed presence of thyroid mass of about 7 cm diameter with tracheal and neck vessel compression and lymphadenopathy.

Fine needle aspiration biopsy of this nodule was performed. Cytological examination did not show any specific findings. Ultrasound guided core-needle biopsy was performed, the histological examination showed squamous cell carcinoma (SCC). The metastatic disease from another primary localization was considered. Exhaustive clinical, endoscopic and radiologic examinations did not reveal any different primary site of SCC.

A nonradical thyroidectomy was performed, 32 g thyroid mass, which infiltrated surrounding tissues, was removed. Pathological examination showed SSC G3.

It was concluded that the patient had a primary SCC of thyroid. Postoperative radiotherapy with total dose of 70 Gy was administrated.

Our patient had complains which are common in acute thyroiditis, but the histological examination revealed SCC G3 - a thyroid disorder which comprises 1.0% of all malignant tumors of thyroid and has extremely poor prognosis. Clinical manifestation with pain syndrome is quite rare, only a few cases have been reported yet. An extensive evaluation of any tumor like thyroid lesion is recommended.

P107

WHEN THE THYROID REVEALED LANGERHANS'CELL HISTIOCYTOSIS

Gilly O[1], Hofman V[2], Mahdyoun P[3], Marquette C-H[4], Fénichel P[1], Castillo L[3], Sadoul J-L[1]
[1]CHU de Nice, Endocrinologie, Nice, France, [2]CHU de Nice, Laboratoire de Pathologie Clinique et Expérimentale, Nice, France, [3]CHU de Nice, IUFC, ORL, Nice, France, [4]CHU de Nice, Pneumologie, Nice, France

Langerhans'cell histiocytosis (LCH) is a rare disease encountered by endocrinologists because of hypothalamo-pituitary area involvement. Athough exceptionnaly inaugural, thyroid localization has been described.

Case report: MT, a 22 years old medical student referred himself for a neck mass. Clinical examination showed a right lobe goiter. Thyroid ultrasound disclosed a right avascular and hypoechoic lesion (3,3 cm), and a left hypoechoic nodule (1 cm). Thyroid function was normal (TSH 3,03 mUI/l, fT4 16,2 pmol/l, fT3 5,4 pmol/l), with no inflammatory clues nor TPO- or Thyroglobulin-antibodies. Fine needle aspiration showed rare non suspicious epithelial thyroid cell nests, and large cells with basophil cytoplasm of unknown lineage. An open thyroid biopsy revealed LCH : histiocytic-like cells positive for PS100 and CD1a, with a quite complete disappearance of thyroid vesicles. Search for LCH diffusion was negative except bilateral micronodules and micro-cystic pulmonary lesions on CT-scan. Respiratory function, CO ductance and exercise test, were normal. Smoking cessation was advised and obtained. Three months later, CT-scan features were unnoticeable.

Six months after diagnosis, ultrasound showed involvement of the whole thyroid by this hypoechoic aspect, which graded very hard on elastography (> 200 kPa). TSH had increased to 20,0 mIU/l, leading to levothyroxine treatment. Given the potential risk of carcinoma and of compressive goiter, and the ongoing hypothyroidism, total thyroidectomy was scheduled and confirmed LCH. Nine months later, his clinical state is fair. A complete search for LCH is scheduled in 3 months.

Comments: Thyroid LHC cases (roughly 60 cases) often revealed by nodule or goiter, are sometimes associated with hypothyroidism, and less often with papillary carcinoma, or compressive complications. The rapidly progressive involvement of the thyroid gland, both anatomically and functionnally, despite improvement of pulmonary lesions, does not seem to be the rule and prompted us to report this case.

P108

THE ROLE OF OCTREOTIDE THERAPY IN THE TREATMENT OF HYPERTHYROIDISM ASSOCIATED WITH A THYROTROPIN SECRETING ADENOMA

Esteves C[1,2], Alves M[3], Neves C[1,2], Sande AV[1,2], Pereira J[4], Castro L[5], Carvalho D[1,2]
[1]Centro Hospitalar São João, Department of Endocrinology, Diabetes and Metabolism, Porto, Portugal, [2]Faculty of Medicine of the University of Porto, Porto, Portugal, [3]Hospital de Braga, Braga, Portugal, [4]Centro Hospitalar São João, Department of Neurosurgery, Porto, Portugal, [5]Centro Hospitalar São João, Department of Pathology, Porto, Portugal

Introduction: Thyrotropin (TSH)-secreting adenomas are rare tumours of the pituitary and a rare cause of hyperthyroidism, accounting for less than 1% of the cases of both. Surgery is the first choice treatment, although it is frequently unsuccessful.

Case report: We report a case of a 63 year old woman sent to the Endocrinology consultation for multinodular goiter and elevation of free T4 (FT4 1.74 [0.70–1.48] ng/dL) and free T3 levels (FT3 6.53 [1.71–3.71] pg/mL) with normal TSH (4.09 [0.35–4.94] µUI/mL). She had a 6 month history of general malaise, weight loss and tiredness. She had elevated levels of

ferritin (322.4 [14–233] ng/mL) and steroid hormone binding globulin (>200 [14.1–68.9] nmol/L); the TRH test did not result in a significant elevation of TSH nor of the α-subunit. Octreotide test resulted in a 57% reduction in the levels of TSH. These findings were consistent with a TSH-secreting pituitary adenoma. Magnetic resonance imaging (MRI) confirmed the presence of an 8 mm adenoma of the pituitary. The patient was submitted to transsphenoidal resection of the adenoma, which resulted in normalization of thyroid function (TSH 1.51 μUI/mL; FT4 1.09 ng/dL; FT3 2.83 pg/mL). However, three months after surgery there was a relapse of the hyperthyroidism with elevated levels of FT4 (2.06 ng/dL) and FT3 (6.09 pg/mL) and an unappropriately normal level of TSH (3.32 μUI/mL), without evidence of tumour recurrence on MRI. She is currently under treatment with octreotide LAR 10 mg/month with normalization of thyroid function. We also present a case of a 67 year old man whose thyrotropin secreting adenoma was managed solely with octreotide.

Conclusion: Although surgery is the definite treatment for TSH-secreting adenomas, cure will only occur in one third of these individuals. In the remainder, maintenance of euthyroidism depends on the use of medical therapy, such as somatostatin analogs.

P109

THYROID PLASMACYTOMA – A VERY UNCOMMON DISEASE WITH AN UNUSUAL MANAGEMENT AND OUTCOME

Janovsky CPS[1], *Hidal JT*[1], *Dias da Silva MR*[1], *Chiamolera MI*[1], *Maciel RMDB*[1], *Martins JRM*[1]
[1]Federal University of Sao Paulo, Endocrinology, São Paulo, Brazil

Extramedullary plasmacytomas are uncommon malignant neoplasms and those arising from thyroid gland are extremely rare. Here, we describe a 58 year-old man with a history of rapidly enlargement of the gland over the past 8 months. On physical examination, he presented a 3 times enlarged thyroid gland. Thyroid function tests were all negative but he had high level of thyroid antibodies. Thyroid ultrasound showed multiple nodular formations on the left lobe, the biggest measuring 2.5 x 3.0 x 4.5 cm. The FNA of nodule suggested myeloma (rare macrophages, rare epithelial cells, numerous dysplastic plasmatic cells, some lymphocytes, with positive neoplastic cells). Complete workup for multiple myeloma was carried out, but the exams came all negative except for a serum monoclonal peak of gamma-globulin. The patient was submitted to a total thyroidectomy with resection of 2 lymph nodes. The histologic exam revealed an enlarged gland infiltrated by lymphoid cells with great plasmacytoid differentiation distorting the thyroid architecture. There were also focal areas of fibrosis, dilation vessels and hemorrhage. The two lymph nodes resected showed neoplastic invasion. The whole panel was compatible with a Lymphoplasmacytic Non-Hodgkin Lymphoma or Immunocytoma. Immunohistochemistry revealed positivity for kappa antigen. Immunoexpression for thyroglobulin, calcitonin and TTF1 were all negative. After surgery, the patient was referred to external beam radiation and received a total dose of 4,000 Gy on anterior neck and upper mediastinum. At 24 months of follow up, thyroid antibodies and monoclonal peak of gamma-globulin dropped to negative values. After 17 years of initial diagnosis, he is clinically well, on levothyroxine replacement, with no signs of myeloma recurrence. This is a rare case of solitary plasmacytoma of the thyroid gland that, despite the controversial treatment, was cured with total thyroidectomy and external beam radiation.

P110

AN ACCESSORY THYROID GLAND OF THE LATERAL NECK IN A 34-YEAR-OLD TURKISH WOMAN

Sengul I[1], *Sengul D*[2]
[1]Giresun University Faculty of Medicine, General Surgery, Giresun, Turkey, [2]Giresun University Faculty of Medicine, Pathology, Giresun, Turkey

Objectives: Accessory thyroid gland (ATG) is determined as a permanence of thyroidal parenchyma anywhere from the base of the tongue to the thyroid isthmus, with the majority of the functional thyroid in the normal pre-tracheal area. The incidence of ATG is unknown. Of 58 cadavers just one (1/58) was detected as ATG on the thyroid cartilage by Braun et al. Radkowski et al performed ultrasonography on 230 cases of throglossal duct cyst. They detected 4 cases (4/230) of ATG. ATGs are classified into five groups based on their anatomical location: cranial, caudal, lateral, ventral, and dorsal glands. They usually are founded along the former course of thyroglossal duct and emigrate laterally.

Case report: On the physical examination of the thyroid gland and neck of a 34-year-old Turkish woman any nodule or mass could not been palpated. The ultrasonography showed a left-sided cervical accessory thyroid parenchyma adjacent to the inferolateral border of the left lobe. An ultrasonography-guided fine-needle aspiration biopsy were performed and the histopathological examination with Haematoxylin and Eosin revealed a huge cellular cluster including benign thyrocytes. After a benign cytological evaluation, a clinical follow up was planned and recommended for the patient.

Conclusions: Pyramidal lobes, superior accessory thyroids, retrotracheal, inferior/lateral extensions or extrusions are involved in the reasons of recurrent thyroid diseases as the anomalies of the gland. Richards et al asserted that ATGs are vulnerable to the same potential diseases as a normally-situated thyroid gland. ATG do not lead to clinical complication except in cases of pathological conditions such as goitre, malignancy, and others. So, a clinical follow-up was suggested for the present case, after a benign fine-needle aspiration cytology. Training, understanding, and cognition of thyroid anatomy and its associated variations and anomalies are very much essential and it will increase the level of awareness.

P111

A RARE CASE OF DYSHORMONOGENIC FETAL GOITER: RESPONSE TO INTRAAMNIOTIC THYROXINE INJECTIONS

Khamisi S[1], *Lindgren P*[2], *Karlsson A*[1]
[1]Uppsala University Hospital, Institute of Medical Science, Endocrinology and Diabetes, Uppsala, Sweden, [2]Uppsala University Hospital, Women's and Children's Health, Uppsala, Sweden

Fetal goitre was diagnosed by routine ultrasound during the second trimester of pregnancy in a 38-year old woman. The woman was healthy, had no thyroid history and the pregnancy had progressed as normal. Ultrasound demonstrated a female fetus with an enlarged thyroid gland with homogenous texture and high flow. An umbilical cord blood sample was performed gestational week, and analysis indicated hypothyroidism with TSH >100 mU/L (2–12), fT4 3.8 pmol/L (5.1–27). Treatment of fetal hypothyroidism was initiated, at the same occasion, by injection of 10 ug thyroxine per kg fetal weight into the amniotic fluid. Week 27, cordocentesis was repeated, TSH 237 mU/L, fT4 11.7 pmol/L. Throughout pregnancy, intraamniotic injections were given 6 times with 10 ug thyroxine/kg, and 5 ug thyroxine/kg the last two times (g.w. 31 and 33). TSH in amnion fluid was determined to 13.5 mU/L at start of treatment and fell gradually to 2.5 mU/L at week 33. Free T4 in the amniotic fluid was 4.23 pmol/L prior to thyroxine injections and increased during treatment to mean 16 pmol/L. Fetal heart rate and skeletal maturation were within normal limits throughout. In week 34, chorioamnionitis was suspected and the child was delivered by cesarean section. Cord blood revealed TSH 596 mU/L, fT4 4.4 pmol/L and total T3 1.18 nmol/L. No TSH-receptor and thyroid peroxidase antibodies were detected. The newborn was put on thyroxine substitution. Hyperbilirubinemia was threated with light therapy. The size of the thyroid was normal by ultrasound. At 3 months a slight hypotonia, judged within normal range, was noted, but at 6 months tonus was normal. The psychomotor development of the child has been uneventful.

In this rare case, intraamniotic thyroxine supplementation seemingly prevented a further development of fetal hypothyroidism.

P112

TOTAL THYROIDECTOMY AS AN ALTERNATIVE TREATMENT OF LIFE-THREATENING AMIODARONE INDUCED THYROTOXICOSIS.

Fedorowicz A[1], *Hubalewska-Dydejczyk A*[1], *Matyja A*[2], *Cieniawa T*[2], *Kostecka-Matyja M*[1]
[1]Jagiellonian University Medical College, Department of Endocrinology, Krakow, Poland, [2]Jagiellonian University Medical College, Department of General and Gastrointestinal Surgery, Krakow, Poland

Amiodarone is an iodine-rich antiarrhythmic drug that causes thyroid dysfunction in 15–20% of cases. There are two main forms of AIT: type 1, a form

of iodine-induced hyperthyroidism, and type 2, a drug-induced destructive thyroiditis. Mixed/indefinite forms exist that may be caused by both pathogenic mechanisms. The typical treatment consist of antithyroids in type 1 and steroids in type 2. However, the pharmacological treatment is not always effective but, as persistent hyperthyroidism may be life-threatening, a radical treatment must be performed.

We present two cases of patients in which we decided to perform a thyroidectomy because of inefficacy of treatment and a worsening medical condition, i.e. a beginning heart failure.

Case 1 is a 60 year-old man, with the history of 3 years amiodarone therapy for atrial fibrillation that developed a mixed type of amiodarone-induced thyrotoxicosis. During the treatment with thyrostatics he developed thiamazole- induced agranulocytosis that led to withdrawal of thiamazole. Further medical therapy only with steroids didn't bring expected outcome and the patient started to develop a heart failure.

Case 2 is a 40 year-old man, with the history of 2 years amiodarone therapy for atrial fibrillation, that developed type 2 amiodarone induced thyrotoxicosis. The patient was barely responsive to antithyroid and antiarrhythmic therapy, and developed a heart failure with atrial fibrillation with heart rate 170/min.

The same team of experienced surgeons and anesthesiologists performed a successful thyroidectomy in both cases.

Conclusions: Total thyroidectomy in patients in a life-threating amiodarone induced thyrotoxicosis, unresponsive to pharmacological treatment may be successfully performed by an experienced team of endocrinologists, cardiologists, surgeons and anesthesiologists.

P113

PRIMARY THYROID LYMPHOMAS – A CLINICAL STUDY OF FOUR CASES

Trifanescu RA[1,2], Ghemigian AM[1,2], Neamtu C[2], Popescu I[1], Carsote M[1], Tupea C[2], Ioachim D[2], Ghemigian MV[2], Stanescu B[1,2], Poiana C[1,2]

[1]'Carol Davila' University of Medicine and Pharmacy, Endocrinology, Bucharest, Romania, [2]'C.I. Parhon' National Institute of Endocrinology, Bucharest, Romania

Background: Thyroid lymphomas are relatively uncommon.

Methods: 4 patients (3F/1M) with primary thyroid lymphomas; mean age at diagnosis was 64.8 years (range 58–72). Two patients were resident in iodine sufficient areas and two patients in iodine deficient areas. The diagnosis of thyroid lymphoma was made by fine-needle aspiration, core biopsy, or surgery.

Case reports: A rapid growing thyroid and/or lateral cervical mass was described by all patients; all patients but one showed normal thyroid function at diagnosis; one patient showed overt hypothyroidism (TSH= 87 mIU/L, FT4= 3.7 pmol/L). TPO antibodies were positive in 2 cases, and in three cases cytological exam revealed chronic lymphocytic infiltrate suggestive for chronic autoimmune thyroiditis. Ultrasound revealed diffuse hypoechoic parenchima, hypoechoic thyroid nodules (mean diameter= 7.5 cm, range 2.4–14 cm) and large laterocervical and supraclavicular hypoechoic lymph nodes. Mild anemia and elevated ESR were noticed in two patients. Pathology exam revealed 2 cases of diffuse large B-cell thyroid lymphoma, one case of diffuse small cell thyroid lymphoma and one case of Burkitt lymphoma. Total thyroidectomy was performed in all patients but one. Chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and R-CODOX-M (rituximab, cyclophosphamide, doxorubicin, vincristine, intratechal Methotrexate) were administered. Remission occurred in 2 patients.

Conclusion: palliative surgical debulking and aggressive chemotherapy may improve the prognostic in patients with primary thyroid lymphomas.

PO13 Thyroid Hormone Action 1

P114

DEIODINASES IN HUMAN ADIPOSE TISSUE FROM OBESE PATIENTS

Calvo RM[1], Vesperinas G[2], Obregon M-J[1]

[1]Inst. Investigaciones Biomedicas, Endocrine and nervous system Physiopathology, Madrid, Spain, [2]Hospital La Paz, Dpt. Surgery, Madrid, Spain

About 15–30% of the total body weight (BW) in lean humans corresponds to white adipose tissue (WAT). In morbidly obese patients WAT is ≈45–50% BW. Overall, WAT weight is about 20–30% BW in women and 15–25% BW in men, but visceral fat (OM) is higher in men than in women. While visceral obesity is associated with insulin resistance, subcutaneous fat (SC) is associated with improved insulin-sensitivity. Several deiodinase polymorphisms have been associated with body mass index and insulin-resistance.

Aim: To study thyroid hormones and deiodinases in the WAT of morbid obese patients.

Methods: OM and SC WAT were obtained from obese patients (BMI>40) undergoing bariatric surgery. WAT T4 and T3 concentrations were measured by RIA. DIO1, DIO2 and DIO3 activities were measured in WAT as reported, and their mRNA expression by RT-PCR using Taqman probes.

Results: T4 concentration was decreased in male SC WAT, T3 was decreased in female OM and SC fat vs male OM WAT. D2 activity was decreased only in the female SC WAT, whereas no significant changes were observed in DIO1 and DIO3, though DIO3 tended to increase in both depots in women. Thus, lower T3 concentrations in OM and SC WAT from obese women were associated to lower DIO2 and higher DIO3 activities. *DIO1* and *DIO2* mRNA were higher in SC than in OM WAT from both genders but *DIO3* was higher in male OM WAT. *DIOs* mRNAs showed no correlation with DIOs activities in WAT.

Conclusions: Deiodinases 1, 2 and 3 are present in human WAT, likely being involved in the production of T3, a hormone essential for adipogenesis. There are gender differences associated to OM and SC WAT. No correlation is found between DIOs activities and mRNAs. WAT represents a huge metabolic pool of thyroid metabolism.

P115

TR-β SELECTIVE THYROMIMETICS (KB-141) STIMULATES THE PROLIFERATION OF INSULIN SECRETING β CELLS

Kim T[1], Han N[1], Kim SM[1], Lee EJ[1], Kim TN[1], kwon MJ[1], Lee SH[1], Kim MK[1], Rhee BD[1], Grover GJ[2], Park JH[1]

[1]College of Medicine, Inje University, Department of Internal Medicine, Busan, Korea, Republic of, [2]Eurofins-Drug Safety Laboratories, Department of Pharmacology, Dayton, NJ, United States

Backgrounds: Thyroid hormone (T3) influences a variety of physiological processes, including cell growth, differentiation and metabolisms in mammals. Recent studies have indicated that all these effects are mediated by the growth stimulatory effect of T3 to the thyroid hormone nuclear receptors (TRs). Recent studies have reported that the pancreatic β cells also express TRs. KB-141, the TRβ-selective thyromimetics would show its favorable benefits on β-cells without untoward systemic side effects shown in thyroid hormone. The aim of our study is to clarify the effects of KB-141 on the proliferation of insulin secreting β cells by KB-141 and T3.

Materials and methods: RIN5F and INS-1 cells were used in our experiments. Triiodothyronine (T3) and KB-141 were applied to cultured cell lines in various concentrations and time intervals along with vehicle only control. At 24, 48 and 72 h of continuous exposure, viable cells were harvested and counted. TRβ1 expression, viability, proliferation were analyzed by Western blot, BrDU, FACS, TUNNEL assay and Trypan Blue negative cell number in a Thomas's hematocytometer. Insulin secretory function of exposed β-cells were verified by the amount of insulin mRNA and GSIS.

Results and conclusion: T3 and KB-141 significantly promoted the growth of RIN5F and INS-1 cells, and improved glucose stimulated insulin secretion. Thyromimetics would be used as a fundamental diabetes treatment

to increase functioning β-cell mass without untoward systemic side effects caused by non-specific thyroid hormone receptor stimulation.

P116

DETECTION OF IODOTHYRONINES (T4, T3, RT3 AND 3,5-T2) IN HUMAN BLOOD USING LC-MS/MS

Hoefig CS[1], *Wohlgemuth F*[1], *Rijntjes E*[1], *Daniel H*[2], *Köhrle J*[1]
[1]Charité Universitätsmedizin Berlin, Institut für Experimentelle Endokrinologie, Berlin, Germany, [2]Technische Universiät München, Lehrstuhl für Ernährungsphysiologie, München, Germany

Objectives: During the past decades, a lot of diagnostic procedures were presented for experimental and clinical thyroid hormone (TH) analysis. Nowadays, liquid chromatography tandem mass spectrometry (LC-MS/MS) is used in research laboratories as gold standard method in endocrine chemistry. However, clinical routine TH evaluation is still performed by immunoassays. As the nine possible TH metabolites differ only in the number and/or position of iodine atoms and cover a broad concentration range, their distinction and quantification by immunological methods is cumbersome. Here we present a rapid and sensitive LC-MS/MS method for detection of thyroxine (T4), 3,3`,5-triiodo-L-thyronine (T3), reverse triiodo-L-thyronine (rT3) and 3,5-diiodo-L-thyronine (3,5-T2) in a single human serum sample.

Methods: A novel solid-phase-extraction (SPE) method for preanalytical sample workup followed by LC-MS/MS was established for the simultaneous detection and quantification of TH in 200 µl human serum. Spiking experiments used TH deficient serum to obtain calibration curves. Serum analysis (n=10, healthy controls) was performed with two different triple-quadrupole tandem mass spectrometers (QTRAP® 4000 and 5500 from AB SCIEX) and compared to the classical TH immunoassays (cobas 8000, Roche).

Results: We established a sensitive and robust LC-MS/MS method that allows simultaneous detection of eight of nine possible standard TH in one analytical run. While the QTRAP4000 only detects endogenous T4 and T3, the QTRAP® 5500 additionally identifies rT3 and 3,5-T2 in human serum at concentrations allowing quantification. All calibration curves were characterized by a high correlation coefficient (r^2>0.97). The obtained LC-MS/MS results highly correlate with the immunoassays (T4: r^2=0.98, T3: r^2=0.91).

Conclusion: The comparison of the performances of two LC-MS/MS devices with routine immunoassays revealed QTRAP® 5500 as the more sensitive and reliable device for LC-MS/MS quantification of four TH in a single 200 µl sample of human serum.

Supported by DFG grants KFO218 TP3 and GK1208 TP 3 to J.K.

P117

THE NEED OF PATHWAY TO MODULATE LEPTIN MRNA VIA TRIIODOTIRONINE (T3) IN ADIPOCYTES CELL CULTURE

Oliveira M[1], *de Sibio MT*[2], *Olimpio RMC*[1], *Silva CBR*[3], *Luvizotto RDAM*[1], *Ferreira T*[1], *Moretto FCF*[1], *Nogueira CR*[1]
[1]Universidade Estadual Paulista, Clínica Médica, Botucatu, Brazil, [2]Universidade Estadual Paulista, Departamento de Clínica Médica, Botucatu, Brazil, [3]UNIFESP, Clínica Médica, São Paulo, Brazil

Thyroid hormones (TH) are essential for human survival, and they are involved in the processes of development, growth and metabolism. Different organs display different process actions. Actions may occur either through TRα and TRβ receptors, or through alternative pathways, which may involve integrin αvβ3, mitogen-activated protein kinases (MAPK) or phosphatidyl inositol 3 kinase (PI3K). Adipose tissue (TA) is an important target for TH; it produces various biologically active substances called adipokines (including leptin) that present different physiological functions. Leptin is considered an adipostatic signal to the brain and is involved in the regulation of energy balance, as well as TH. The aim of this study was to examine the effects of TH, triiodothyronine (T3), in the modulation of leptin mRNA expression, as well as the involvement of signaling pathway PI3K in adipocytes cell culture, 3T3-L1. We examined the involvement of these pathway in mediating TH effects by treating, 3T3-L1 with 10^{-8} M T3 in the absence or presence of either the PI3K inhibitor (LY294002). To examine whether leptin is directly induced, we used the translation inhibitor cycloheximide (CHX). For the mRNA expression analyzes was used RT-qPCR. All experiments were performed in biological triplicate. Statistical analysis was performed using ANOVA, followed by Tukey´s test and P < 0.05 was considered significant. T3 increased the leptin mRNA expression in 1 (± 0.18) to 2.26 (± 0.36, P < 0.01). This increase was not seen in LY294002 (1.31, ± 0.05, p < 0.05), but was present in CHX (2.05, ± 0.2, p> 0.05). These results demonstrate that the activation of PI3K cytosolic signaling pathway is necessary to direct T3 action to the leptin gene expression in adipocytes, 3T3-L1.

Keywords: Adipocytes, Leptin, PI3K, Triiodothyronine.

P118

THE IMPERMEANT SULFO-NHS-LC-BIOTIN PROBE BLOCKS TYPE 3, BUT NOT TYPE 1, DEIODINASE ACTIVITY IN INTACT HUMAN CELLS

Wajner SM[1,2], *Larsen PR*[3], *Maia AL*[1,2]
[1]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [2]Hospital de Clínicas de Porto Alegre, Endocrinology, Thyroid Section, Porto Alegre, Brazil, [3]Division of Endocrinology, Diabetes and Hypertension, Brigham and Women´s Hospital and Harvard Medical School, Boston, United States

Type 3 deiodinase (D3) is the main inactivating thyroid hormone enzyme. Previous studies have demonstrated that this enzyme is in the plasma membrane but the location of its catalytic site is still a matter of debate.

Objective: To determine if the D3-catalyzed reaction occurs in the extra- or intracellular space.

Methods: HEK-293 cells transiently expressing hD1 or hD3 were incubated for 6 or 24h in media containing either the impermeant sulfo-NHS-LC-Biotin (1mg/ml) or intracellular biocytin (1mg/ml) probe. D3 and D1 activities were measured in intact cells at physiological free T3 concentrations and endogenous cofactor. Similar experiments were performed using cells expressing endogenous D1 (Hep-G2) or D3 (MCF-7). Deiodinase activities were measured by column and/or descending paper chromatography.

Results: The addition of sulfo-biotin to culture medium blocked D3 activity at 6h (19.1±2.2 vs. 5.8±0.7fmol/mg.prot) whereas D1 activity was unaffected (21.2±1.12 vs. 17.55±1.07pmol/mg.prot). The opposite occurred when the intracellular probe, biocytin, was used (D3, 19.1±2.2 vs. 12.3±0.7fmol/mg.prot and D1, 21.2±1.12 vs. 3.6±0.7pmol/mg.prot). The effect of biotin or biocytin was no longer present after 24h incubation, indicating that the covalent modification by the probe causes a reversible time-dependent enzyme inactivation. Similar results, sulfo-biotin inhibited only D3 while biocytin inhibited only D1, were observed using cell homogenates and the artificial cofactor DTT.

Conclusion: These results indicate that the catalytic portion of D3 is located at the extracellular space. The extracellular location of D3 gives ready access to circulating thyroid hormones in physiological and pathophysiological conditions.

P119

DIFFERENTIAL ACTIONS OF 3-T1AM ON TRACE AMINE-ASSOCIATED RECEPTORS

Pratzka J[1], *Kleinau G*[1], *Krude H*[1], *Grüters-Kieslich A*[1], *Köhrle J*[2], *Biebermann H*[1]
[1]Charité Universitätsmedizin Berlin- Campus Virchow, Institute for Experimental Pediatric Endocrinology, Berlin, Germany, [2]Charité Universitätsmedizin Berlin- Campus Virchow, Institute for Experimental Endocrinology, Berlin, Germany

The thyroid hormone derivative 3-iodothyronamine (3-T1AM) was known as a weak agonist for Trace amine-associated receptor 1 (Taar1) until now. 3-T1AM injection in rodents results in decreased heart rate and lower body temperature, which is counterintuitive considering the traditional model of thyroid hormone action. On the other hand gene disruption of Taar1 in mice produces among others no significant changes in body weight or body temperature, and 3-T1AM injection still leads to above mentioned physiological effects.

We here hypothesized that TAAR5, a homologous member of the rhodopsin-like GPCR TAAR group, should be a potential candidate to mediate

3-T1AM functions. Moreover, TAAR5 is the highest conserved TAAR subtype indicating an important physiological role and might compensate TAAR1 function because of its apparent hypothalamic expression.

Our aim was to reveal new information concerning potential 3-T1AM targets and mechanisms as well as for potential interrelations between the two receptors. Of interest are the significant basal ligand independent activities of TAAR1 and TAAR5 which might play a general basic role in cell homeostasis. Known TAAR1-ligands 3-T1AM, β-phenylethylamine (PEA), tyramine (TYR) and octopamine (OA) activated hTAAR1 in the Gαs/adenylate cyclase pathway. In contrast, TAAR5 indeed responded to the tested TAAR1-ligands, but with inverse agonistic effects by a decreasing basal Gq/11 signaling activity. Furthermore, using co-expression studies our data revealed that hTAAR1 and hTAAR5 form homodimers, respectively, as well as heterodimers together.

In conclusion, we found a new GPCR target for 3-T1AM but with antagonistic effects, which is different to 3-T1AM action on TAAR1. By this it is unlikely that TAAR5 compensates TAAR1 function in Taar1-k.o. mice. Most interestingly, the TAAR1 and TAAR5 dimerization will be of interest in future studies to examine dimer-signaling properties. Overlapping hypothalamic expression patterns of TAAR1 and TAAR5 support a suggested neuromodulatory role of these receptors.

P120

CLINICALLY ASYMPTOMATIC HYPOTHYROIDISM SECONDARY TO HYPERCORTISOLISM

Carvalho RR[1], Fonseca FV[2], Melo RL[2], Mecawi AS[3], Silveira AB[2], Império GE[2], Silva ACM[2], Reis LC[2]
[1]UFRRJ, Veterinary Medicine Post Graduation Program, Institute of Veterinary, Seropédica, Brazil, [2]UFRRJ, Physiological Sciences, Institute of Biology, Seropédica, Brazil, [3]University of São Paulo, Department of Physiology, Faculty of Medicine of Ribeirão Preto, Ribeirão Preto, Brazil

Hypothyroidism is the result of inadequate production of thyroid hormone or inadequate action of thyroid hormone in target tissues. Hypothyroidism can be seen in hyperadrenocorticism (Cushing´s syndrome) with an overlapping clinical signs. Male Wistar rats (~ 280g, n = 7) were submitted to daily administration of 0.2 ml adrenocorticotropic hormone (ACTH 1–24 synthetic 1mg/ml) and the vehicle control group received the same volume. Both groups were treated for 7 days. At the end of the experiment, were obtained the values of serum corticosterone, T3 (triiodothyronine) and T4 (thyroxine). The control group presented similar reference values for all parameters. The ACTH-treated group obtained elevated level of corticosterone and low levels of T3 and T4, ie, compatible with hypothyroidism secondary to hypercortisolism. Statistical analysis was performed by using t test with significance $p < 0.05$. Although it has been demonstrated hormonal difference between the groups, the clinical symptoms of hypothyroidism were not observed. In fact, ACTH treated animals experienced weight loss which must be presented with clinically weight gain. These data suggest that in the initial establishment of hypothyroidism no obvious clinical symptoms for this disease. This study suggests that the absence of symptoms of hypothyroidism and hyperadrenocorticism is due to an initial phase of the syndrome.

P121

IMAGING TH AVAILABILITY AND ACTION IN THE NERVOUS SYSTEM

Morvan-Dubois G[1], Préau L[1], Le Blay K[1], Gothié JD[1], Demeneix B[1]
[1]Evolution des Régulations Endocriniennes, UMR 7221 CNRS MNHN,, Paris Cedex, France

Tri-iodothyronine, bound to TRa1, plays a central role controlling stem cell commitment in several organs, such as intestine and brain. The local control of ligand availability is one of the mechanisms regulating this process. Our working hypothesis is that local hypothyroidism is required for neural stem cell maintain. In peripheral tissues, Thyroid Hormones (TH) availability is highly dependent on transporter expression and local TH metabolism. The deiodinases, D1, D2 and D3, are the major actors in TH metabolism, as D2 and D1 convert the pro-hormone T4 into the more active form T3 whereas D3 inactivates TH. D3 activity can therefore provide a local hypothyroid context in a tissue and stage specific manner. Complex cell-cell interactions occur in tissues, some cells being able to produce T3 whereas others inactivate TH. In order to follow *in vivo* the intricate regulation of ligand availability in different cell types within the nervous system, transgenic tadpoles bearing reporter constructs for D2 (activating deiodinase) and D3 (inactivating deiodinase) expression were generated. The identity of the cells expressing the transgenes is determined by immunohistochemistry and *in situ* hybridization. The characterisation of the cell type expressing deiodinases provides a better understanding of the ligand ability in the different cell types of the nervous system. This also indicates which cells are competent to read TH signalling at different stages of development. A comparative *in silico* approach was used to analyse potential factors controlling deiodinases expression in neurogenic areas of the adult mouse brain (the subventricular zone) and in the *Xenopus laevis* tadpole. This approach is of particular relevance given the conservation of TH action in governing stem cell activity in distinct vertebrate species.

PO14 Medullary Thyroid Cancer Clinical

P122

FINE NEEDLE ASPIRATION AND MEDULLARY THYROID CARCINOMA: THE RISK OF UNDERTREATMENT USING FNA ALONE IN PREOPERATIVE EVALUATION

Walz PC[1], Porter K[2], Schneider D[3], Debora A[4], Lindsey S[5], Busonero G[6], Fineberg D[7], Fruci B[8], Boelaert K[9], Smit JW[10], Meijer JA[11], Duntas L[12], Sharma N[13], Costante G[8], Filletti S[14], Sippel RS[3], Biondi B[4], Topliss D[7], Pacini F[6], Maciel RM[5], Essig, Jr GF[1], Kloos RT[15]
[1]Wexner Medical Center at The Ohio State University, Otolaryngology-Head and Neck Surgery, Columbus, United States, [2]The Ohio State University, Center for Biostatistics, Columbus, United States, [3]University of Wisconsin, Department of Surgery, Madison, United States, [4]University of Naples, Federico II, Department of Clinical and Molecular Endocrinology and Oncology, Naples, Italy, [5]Federal University of Sao Paulo, Department of Medicine, Sao Paolo, Brazil, [6]University of Siena, Section of Endocrinology, Siena, Italy, [7]Alfred Hospital, Department of Endocrinology, Melbourne, Australia, [8]University of Catanzaro Magna Graecia, Dipartimento di Scienze della Salute, Catanzaro, Italy, [9]University of Birmingham, Centre for Endocrinology, Diabetes & Metabolism, Birmingham, United Kingdom, [10]Leiden University Medical Center, Internal Medicine and Endocrinology, Leiden, Netherlands, [11]Albert Schweitzer Hospital, Department of Internal Medicine, Dordrecht, Netherlands, [12]University of Athens, Department of Endocrinology and Internal Medicine, Athens, Greece, [13]University of Birmingham, Otolaryngology-Head and Neck Surgery, Birmingham, United Kingdom, [14]University of Rome Sapienza, Department of Medicine, Rome, Italy, [15]Wexner Medical Center at The Ohio State University, Endocrinology and Nuclear Medicine, Columbus, United States

Objectives: Pre-operative diagnosis of medullary thyroid cancer (MTC) is necessary in order to perform the appropriate initial surgical management and to allow for screening for MEN2 associated conditions. Currently, the minimal optimal initial surgical intervention includes total thyroidectomy with central neck dissection. MEN2 screening may discover concomitant hyperparathyroidism, pheochromocytoma, and alter management of visually normal parathyroid glands that are unintentionally devascularized during surgery. The objective of this investigation is to evaluate the diagnostic accuracy of fine needle aspiration biopsy (FNAB) to preoperatively diagnose MTC.

Methods: Retrospective chart review of sporadic medullary thyroid carcinoma (sMTC) patients from 11 institutions over the last 29 years was undertaken. FNAB data without calcitonin washout was compared to final pathologic diagnoses in each case. Assumed therapeutic interventions for FNAB cytology of MTC or possible MTC, non-MTC malignancy or suspicious for malignancy, indeterminate cytology, and benign cytology was assumed to direct a total thyroidectomy (TT) with central neck dissection (CND), TT without CND, diagnostic hemithyroidectomy, and observation, respectively.

Results: Three hundred thirteen patients from 4 continents and 7 countries were included in the sample, 245 of whom underwent FNAB. FNAB revealed MTC in 43.7% and possible MTC in an additional 2.4% while non-MTC malignancy/suspicious for malignancy, indeterminant cytology, and benign

cytology were identified in 15.1%, 32.2%, and 6.1%, respectively. Other cytologic diagnoses were revealed in 0.4%. One hundred thirteen (46.1%) patients with surgical pathology revealing sMTC had FNAB findings that supported TT with CND while 37 (15.1%) supported TT alone. In the remaining cases, diagnostic hemithyroidectomy and observation were directed in 32.7% and 6.1%, respectively.

Conclusions: FNAB is an important diagnostic tool in the evaluation of thyroid nodules, but its low sensitivity in the evaluation of sMTC limits its ability to command an optimal pre-operative evaluation and initial surgery in over half of patients with sMTC.

P123

SERUM CALCITONIN INCREASE-GUIDED EVALUATION OF MTC IN PATIENTS WITH MULTINODAL GOITER

Wiedemann W[1], *Soukhov V*[2], *Zaplatnikov K*[1]
[1]Clinic for Nuclearmedicine Nuernberg, Nuclearmedicine, Nuernberg, Germany, [2]Militar Medical Academy St. Petersburg, Nuclermedicine, St. Petersburg, Russian Federation

Aim: Medullary thyroid carcinoma (MTC) is associated with a high concentration of serum calcitonin. Routine measurement of serum calcitonin concentration has been advocated for detection of MTC among patients with nodular thyroid diseases. We evaluated the usefulness of routine Calcitonin test in these patients with presence of hypoechogenic nodes.

Methods: Routine radio immunological measurements of serum calcitonin concentrations were performed in 1,548 patients (415male; 1,133 female) with ultrasonography (US) revealed nodular thyroid diseases and Pentagastrin stimulation in some of them. The average age was 44 years (range 8–86 years). Additional examination included thyroid Tc-99m scan, measurements of thyroid hormones, TSH and antithyroid autoantibodies.

Results: We found that 44 (2,8%) of all patients with nodular thyroid diseases by US had serum calcitonin level by RIA above 10 pg/mL. Among them 10 patients (22,7%) presented histologically confirmed MTC. 6 of 10 patients with MTC had basal serum calcitonin level above 100 pg/mL. The remaining 4 patients had moderate elevation of basal serum calcitonin (range, 12–66 pg/mL). Serum calcitonin concentration increased to more than 100 pg/mL after administration of Pentagastrin in all patients with MTC (2.4x to 47.7x increase). 4 of 34 pts with Calcitonin levels from 10–33 pg/ml and negative Pentagastrin stimulation had C-cell hyperplasia; the rest had renal failure or other diseases.

Conclusions: These results suggested that routine RIA measurement of serum Calcitonin is useful for early detection of MTC among patients with nodular thyroid diseases, especially in presence of hypoechogenic nodes. Pentagastrin stimulation test may also be a reliable way for evaluating thyroid nodular patients with mild or moderate elevation of serum Calcitonin concentrations.

P124

SURGICAL OUTCOMES IN MEDULLARY THYROID CARCINOMA: SHORT TERM RESULTS

Chun KW[1], *Jun HH*[1], *Kim B-W*[1], *Lee YS*[1], *Chang H-S*[1], *Park CS*[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Korea, Republic of

Objectives: Although the extent of surgical resection and node dissection in medullary thyroid carcinoma is controversial, achieving the biochemical cure is the mandatory in the treatment of medullary thyroid carcinoma. The aim of this study was to review the clinicopathologic features and treatment outcomes of medullary thyroid carcinoma treated in our institution.

Methods: Between January 2009 and December 2010, 22 cases of medullary thyroid carcinoma were treated; among these, 19 patients underwent initial operation were divided into two groups; patients achieving the biochemical cure (serum calcitonin < 2.0 ng/dL) (Group I, n=14) and patients not achieving the biochemical cure (Group II, n=5). The clinicopathological feaures and treatment outcomes were reviewed retrospectively.

Results: Mean patient age was 49.7 years, and male/female ratio was 6:13. As for the extent of surgery, all of 5 patients underwent total thyroidectomy with bilateral neck dissection in Group II, but surgical extension in Group I was various. Mean tumor sizes were 1.55 cm in Group I and 2.5 cm in Group II. Group II patients had more aggressive node metastasis than Group II patients. Furthermore, one patient had mediastinum node metastasis and two had distant metastasis in liver in Group II.

Conclusions: Most of the patients (73.7%) achieved the biochemical cure, but extension of the surgical resection in medullary thyroid carcinoma is the major concern of the achieving biochemical cure.

P125

PROGNOSTIC FACTORS OF MEDULLARY THYROID CARCINOMA

Bae SY[1], *Jung S*[1], *Cho DH*[2], *Nam SJ*[1], *Kim JS*[1]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of, [2]Seoul Medical Center, Seoul, Korea, Republic of

Background: Medullary thyroid carcinoma (MTC) accounts for 5 to 10% of all thyroid cancers but is responsible for a disproportionate number of deaths. The objective of this study was to evaluate the prognostic factors of MTC and to recommend the extent of surgery (CND, central lymph node dissection/ MRND, modified radical neck dissection)

Methods: We performed a retrospective review to describe clinical outcomes in 73 MTC patients who underwent surgery at Samsung Medical Center from 1994 to 2007. The medial F/U duration was 51.2 months. We analyzed their clinicopthologic factors and serum basal calcitonin levels before and after the surgery. We investigated the overall survival and the prognostic factors.

Results: The 73 patients were classified by postoperative calcitonin level (group1: normal level, group 2: persistent hypercalcitoninemia). Thirteen patients underwent reoperation due to clinical recurrence in 25 patients of group 2. However there was no recurrence in 48 patients group 1. On univariate analysis, risk factors of persistent hypercalcitoninemia were male, multiple lesions, capsular invasion, larger tumor size and higher preoperative calcitonin. On multivariate analysis, the size of tumor and high preoperative calcitonin are associated factors. In our study, lateral neck LN metastases are significantly associated ipsilateral/ contralaeral central lymph nodes (CLN) metastases and preoperative calcitonin level. Cut-off values of preoperative calcitonin level were 213.5pg/ml (AUC=0.716) in ipsilateral CLN, 332.5pg/ml (AUC=0.869) in contralateral CLN and 237.0pg/ml(AUC=0.778) in ipsilateral lateral neck LN.

Conclusion: Our study showed that contraleral CLN metastasis was occurred after ipsilateral lateral neck LN metastasis. Patients with contralateral CLN metastases should be considered ipsilateral MRND. If preoperative calcitonin ≥ 237pg/ml, ipsilateral CND and ipsilateral MRND should be considered. And if preoperative calcitonin ≥ 332.5 pg/ml, bilateral CND and ipsilateral MRND should be considered.

P126

CLINICAL SIDE EFFECTS OF CALCITONIN STIMULATION WITH PENTAGASTRIN VERSUS CALCIUM IN PATIENTS WITH THYROID DISORDERS

Ubl P[1], *Ringhofer L*[1], *Dolliner P*[1], *Niederle B*[2], *Dudczak R*[1], *Li S*[1]
[1]Medical University of Vienna, Department of Nuclear Medicine, Vienna, Austria, [2]Medical University of Vienna, Department of Surgery, Vienna, Austria

Objectives: The objectives of the study was to compare the clinical side effects between pentagastrin- and calcium-stimulated serum calcitonin (CT) tests in patients with thyroid disorders.

Methods: A total of 365 patients completed the short form questionnaire regarding the clinical side effects after pentagastrin test or calcium-stimulated tests. 217 patients had calcium stimulated CT test and another 148 patients pentagastrin test. Serum CT samples were obtained before and 2, 5 min after intravenous stimulation using pentagastrin (0.5 microg/kg body weight) (the pentagastrin group) or calcium gluconate (2.5 mg/kg body weight)(the calcium group).

Results: There were significantly higher incidences of nausea, facial- and extremity paresthesia, abdominal cramping and headache in the pentagastrin group as compared to those in the calcium group. The incidence rates of vomiting, retro/substernal tightness and dizziness were non-significantly higher in the pentagastrin group than in the calcium group. Only prevalences of feeling

of warmth, urge to micturate and altered gustatory sensation were non-significantly higher in the calcium group compared with the pentagastrin group.

Conclusion: The calcium stimulated test was associated with fewer adverse clinical effects than the pentagastrin test. Calcium is therefore a better-tolerated CT stimulator than pentagastrin.

P127

THE ROLE OF ^{68}GA-DOTATATE PET/CT IN PATIENTS WITH MEDULLARY THYROID CARCINOMA WITH PERSISTENT OR RELAPSING DISEASE AFTER SURGERY

Marciello F[1], *Carratù AC*[1], *De Luca C*[1], *Esposito R*[1], *Aloj L*[2], *Colao A*[1], *Lastoria S*[2], *Faggiano A*[1,3]
[1]"Federico II" University of Naples, Department of Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]National Cancer Institute, "Fondazione G. Pascale", Nuclear Medicine, Naples, Italy, [3]National Cancer Institute, "Fondazione G. Pascale", Endocrinology, Naples, Italy

Introduction and Objectives: Different radiotracers (pentavalent DMSA, ^{123}I-MIBG and ^{111}In-octreotide) have been tested in medullary thyroid carcinoma (MTC) to improve the diagnostic performance of US, CT and MRI in patients not cured by surgery. However, these techniques show variable and relatively low sensitivity, due to poor spatial resolution and image noises caused by physiological uptake. Aim of this study was to evaluate the role of ^{68}Ga-DOTATATE PET-CT in MTC patients with persistent/relapsing disease after surgery.

Methods: Twelve subjects undergone surgery for MTC were enrolled. ^{68}Ga-DOTATATE PET-TC was performed in all subjects six-twelve months after surgery. This procedure was performed by acquiring whole body studies 40–60 min after the radioligand i.v. injection (74–111 MBq). Tumour persistence or relapse after surgery was based on assessment of detectable and progressively increasing serum calcitonin levels, associated or not with tumour lesions identified at the radiological work-up (including US, CT, MRI).

Results: After surgery, 9/12 patients had tumour persistence/relapse while 3/12 were considered disease free. The combined use of US, CT and MRI detected tumour lesions in 7 of 9 cases, while ^{68}Ga-DOTATATE in 5 of 9 cases. No lesions were detected by either modality in the remaining 2 patients. ^{68}Ga-DOTATATE PET-CT showed a sensitivity and specificity of 55% and 100%, respectively. No correlation was found between SUVmax and calcitonin levels.

Conclusions: ^{68}Ga-DOTATATE PET-CT is highly specific in detecting tumour relapse or persistence in patients surged for MTC. However, its sensitivity is not superior to conventional imaging techniques in case of occult disease. A possible role for ^{68}Ga-DOTATATE PET-CT may be the identification of somatostatin receptor positive MTC lesions to treat with cold or radiolabelled somatostatin analogues.

P128

OUTCOME OF MICROMEDULLARY THYROID CANCER

Marconcini G[1], *Romei C*[1], *Bottici V*[1], *Valerio L*[1], *Cappagli V*[1], *Luchetti F*[1], *Grasso L*[1], *Pinchera A*[1], *Vitti P*[1], *Elisei R*[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

Background: Since MTC < 1–1.5cm (mMTC) are found in 0.2 to 8% at autopsy, they are considered clinically irrelevant. Aim of this study was to verify the outcome of mMTC and the prognostic factors.

Patients: A total of 84 sporadic mMTC (30 males; 54 females) were studied. The mean age was 51.4 yrs. Thirty-four/84(40.5%) had lymphnode metastases and 3/84(3.5%) had liver metastases. Fifty-eight/84(69%) were diagnosed by routine calcitonin (Ct) measurement; the other 26/84(31%) were incidental findings (n=10) or diagnosed with cytology (n=16). After 7 years follow-up, 48/84(57%) patients were cured while 17/84(20%) were biochemically affected and 19/84(22.6%) showed metastases. No patients died for the disease.

Results: According to the diameter of the mMTC we distinguished 12/84(14.3%) mMTC < 0.5cm [group-A]; 52/84(61.9%) >0.5and< 1cm [group-B] and 20/84(23.8%) >1cm [group-C]. The extension of the disease was significantly correlated with the diameter and none (0/12) of group-A showed metastatic lesions (p=0.0033). Conversely, 20/52(38.5%) of group-B and 12/20(60%) of group-C showed lymphnode and/or distant metastases. The 3 cases with liver metastases belonged to group-C. Nine/12(75%) of group-A were cured while 3 remained biochemically affected; 30/52(57.7%) of group-B were cured while 22 were affected (n=13 biochemically, n=9 metastatic); 9/20(45%) of group-C were cured while 11 were affected (n=1 biochemically, n=10 metastatic). Eleven/12(91.7%) of group-A, 39/52(75%) of group-B, 8/20(40%) of group-C were diagnosed with Ct.

Conclusions: this study showed that the cure was correlated with the diameter: in mMTC < 0.5cm we can expect a definitive cure in 75% of cases and a biochemical persistence in 25% of cases, it decreases to 57.7% and 45% in mMTC >0.5and< 1cm and >1and< 1.5cm, respectively. A higher prevalence of metastatic affected patients are present in these groups. The question of whether the mMTC < 0.5cm could be innocuous tumors never developing into bigger tumors remains to be answered.

P129

CARBOHYDRATE ANTIGEN 19.9 (CA 19.9): A NEW POOR PROGNOSTIC FACTOR FOR THE OUTCOME OF MEDULLARY THYROID CANCER (MTC) PATIENTS?

Lorusso L[1], *Romei C*[1], *Bottici V*[1], *Agate L*[1], *Molinaro E*[1], *Cappagli V*[1], *Viola D*[1], *Luchetti F*[1], *Grasso L*[1], *Pinchera A*[1], *Vitti P*[1], *Elisei R*[1]
[1]University of Pisa, Endocrinology and Metabolism, Pisa, Italy

Background: The MTC disease progression is correlated to the increase of serum levels of both calcitonin (CT) and carcinoembryonic antigen (CEA). In particular their doubling time is strictly correlated with the prognosis. We observed a peculiar case of an aggressive MTC in a young patient, who rapidly died for the disease, who had high levels of serum Ca19.9 without any gastrointestinal malignancy. This case arose the question of whether Ca19.9 can be a poor prognostic marker for MTC.

Objective: To evaluate the serum levels of Ca19.9 in a series of advanced MTC patients and their correlation with CT and CEA levels. To this purpose we measured the Ca19.9, CT and CEA in 38 advanced MTC patients. We also evaluated the mean survival of patients with high levels of Ca19.9 (>37 U/ml) compared to those with normal levels of Ca19.9 (≤37 U/ml).

Results: Nine/38 (23%) MTC patients showed high levels of Ca19.9 (mean: 131 U/ml, range: 43–276 U/ml); the mean serum CT and CEA values were 10426 pg/ml and 2070 U/ml, respectively. Six/9 patients (66.6%) died after a mean follow-up of 10 years (survival range:1–29 years). In the group of 29 patients with normal values of Ca19.9 the mean serum CT and CEA values were 2270 pg/ml (p=0.0002) and 107 U/ml (p=0.0003), respectively. Only 2 patients (6.9%) died after a mean survival of 24 years (p=0.0001).

Conclusions: High levels of serum Ca19.9 were correlated with higher serum levels of both serum CT and CEA. Moreover, a higher probability of death was significantly correlated with high levels of Ca19.9. On the basis of these results, Ca19.9 appears to be a poor prognostic factor in patients with MTC. It is still unclear whether the measurement of this marker is useful in the early stage of MTC or only in advanced cases.

P130

PROGNOSTIC FACTORS FOR RECURRENCE, METASTASIS AND DEATH FROM MEDULLARY THYROID CANCER

Mandanas S[1], *Chrisoulidou A*[1], *Doumala E*[1], *Boudina M*[1], *Mathiopoulou L*[1], *Pazaitou- Panayiotou K*[1]
[1]Theagenio Cancer Hospital, Endocrinology and Endocrine Oncology, Thessaloniki, Greece

Objectives: To determine the prognostic factors for recurrence, metastasis and death in medullary thyroid carcinoma (MTC).

Methods: The medical records of 85 patients with MTC were reviewed. The following characteristics were recorded for each patient: year of diagnosis, age at diagnosis, gender, tumor size, lymph node metastases, thyroid capsule and vascular invasion, thyroid parenchyma infiltration and extrathyroidal extension.

Results: Recurrence occurred in 45 patients (52.9%), more frequently in males (77.8% vs. 45.3%; $p < 0.01$), in patients with larger tumors (28.8±15.4mm vs. 18.2±13.8mm; $p < 0.005$), lymph node metastases (82.9% vs. 22.2%; $p < 0.001$), parenchyma infiltration (67.6% vs. 37.1%; $p < 0.01$), thyroid capsule invasion (79.2% vs. 39.6%; $p < 0.005$), vascular invasion (81.0% vs. 42.3%; $p < 0.005$) and extrathyroidal extension (81.0% vs. 43.4%; $p < 0.005$).

Metastasis occurred in 32 patients (37.6%), more frequently in males (63.0% vs. 28.8%; $p < 0.005$), in patients with larger tumors (31.2±14.9mm vs. 19.1±14.3mm, $p < 0.005$), lymph node metastases (65.9% vs. 11.1%; $p < 0.005$), parenchyma infiltration (51.4% vs. 20.6%; $p < 0.01$), thyroid capsule invasion (70.8% vs. 21.3%; $p < 0.001$), vascular invasion (66.7% vs. 25.5%; $p < 0.001$) and extrathyroidal extension (66.7% vs. 26.9%; $p < 0.005$). In Cox regression analysis, independent predictors of recurrence were male gender (risk ratio 2.16) and tumor size > 10mm (risk ratio 4.89) and of metastasis was thyroid capsule invasion (risk ratio 3.63).

Fifteen patients died (17.6%), succumbed to their disease. Compared with alive, patients who died, were more frequently males (42.9% vs. 5.3%; $p < 0.001$), had thyroid capsule invasion (28.0% vs. 9.6%; $p < 0.05$), vascular invasion (31.8% vs. 8.9%; $p < 0.05$) and extrathyroidal extension (36.4% vs. 8.8%; $p < 0.005$).

Conclusion: Male gender, tumor size and invasive characteristics are negative predictive factors for evolution of MTC.

P131

GLUCAGONLIKE PEPTIDE-1 RECEPTOR IMAGING IN THE DIAGNOSIS OF MEDULLARY THYROID CARCINOMA (MTC) – FIRST EXPERIENCES

Hubalewska-Dydejczyk A[1], Sowa-Staszczak A[1], Pach D[1], Jabrocka-Hybel A[1], Tomaszuk M[1], Przybylik-Mazurek E[1], Mikolajczak R[2], Janota B[2]

[1]Jagiellonian University Medical College, Department of Endocrinology, Krakow, Poland, [2]Institute of Atomic Energy, Radioisotope Center POLATOM, Otwock Swierk, Poland

Introduction and aim: MTC is a challenge for clinicists. There are still difficulties with the localization of MTC recurrences by standard diagnostic modalities in some patients with an elevated level of postoperative calcitonin and a short doubling time of calcitonin. Recently the overexpression of GLP-1 receptors have been reported on parafollicular thyroid C-cells. The objective of the study was to present first experiences with the new radiopharmaceutical [Lys^{40}(Ahx-HYNIC-^{99m}Tc/EDDA)NH2]-exendin-4 injected to patients with MTC.

Material and method: ^{99m}Tc-GLP-1 receptor imaging was performed in 3 patients: man 70y, dissemination of MTC (2008), qualified to PRRT, local recurrence of MTC (2011); man 74y, metastatic lesions of MTC in liver and lymph nodes (2009), qualified to PRRT, since then stabilization of disease; man 22y, with genetically confirmed MEN2a syndrome, suspicion of local recurrence after abnormal pentagastric test (2009), USG revealed hypogenic leasion with following negative biopsy result. WB scans were performed at 6 time points and SPECT/CT at 3 points after the injection of the new compound.

Results: The recurrence of the disease was confirmed in the first patient by ^{99m}Tc-GLP-1 scintigraphy. In the second patient, GLP-1 receptor imaging revealed a pathological tracer accumulation in the liver. GLP-1 scintigraphies results were comparable to SRS scintigraphies outcomes for both patients. In the third patient, the GLP-1 scintigraphy showed the tracer uptake in the same place as ^{99m}Tc and ^{131}I scans. Due to lack of other lesion localizations, the patient was qualified to surgery. There were no side effects after the tracer injection.

Conclusion: GLP-1 receptor imaging with [Lys40(Ahx-HYNIC-99mTc/EDDA)NH2]-exendin-4 should be considered as an alternative choice by clinicists especially in case of MTC patients for whom standard imaging techniques does not give a precise answer.

PO15 Thyroid Cancer Diagnostics Basic/Translational

P132

ROLE OF SERUM T1799A BRAF MUTATION IN PREDICTION OF DISEASE STATUS IN PAPILLARY THYROID CARCINOMAS

Bae MJ[1], Kim BH[1], Lee BJ[2], Lee JC[2], Kim IS[3], Kim S-J[4], Jeon YK[1], Kim SS[1], Kim IJ[1]

[1]Pusan National University Hospital, Internal Medicine, Busan, Korea, Republic of, [2]Pusan National University Hospital, Otolaryngology, Busan, Korea, Republic of, [3]Pusan National University Hospital, Diagnostic Medicine, Busan, Korea, Republic of, [4]Pusan National University Hospital, Nuclear Medicine, Busan, Korea, Republic of

Background: The T1799A BRAF mutation represents a novel indicator of the progression and aggressiveness of papillary thyroid carcinoma. The purpose of this study was to determine the clinical significance of free circulating mutant BRAF in the prediction of advanced disease in papillary thyroid carcinoma.

Methods: In this study, 42 matched tumor and serum samples obtained from patients with both benign and papillary thyroid carcinomas(PTC) were analyzed for BRAF mutation using a peptide nucleic acid (PNA) clamp real-time PCR.

Results: The BRAF mutation was absent in tumor DNA samples obtained from patients with benign follicular adenomas or adenomatous goiter. In contrast, 20 of 38 (52.6%) PTC tumors were positive for the BRAF mutation. However, only 1 of 20(5%) patients with PTC was positive for BRAF mutation in serum and tumor. This patient had undergone total thyroidectomy with lymph node dissection 4 years ago. She have 7.3cm recurrent thyroid mass with soft tissue invasion (T4a) and lateral lymph node and axillary lymph node metastasis(N1b).

Conclusions: T1799A BRAF mutation can be detected in the blood of PTC patients with recurrent disease and may provide prognostic information. However, future studies are warranted to determine its clinical significance.

P133

DIFFERENT EXPRESSION OF MIRNA IN THE SERA OF PATIENTS AFFECTED BY THYROID CANCER OR BENIGN THYROID PATHOLOGIES

Cantara S[1], Capuano S[1], D'Angeli F[1], Busonero G[1], Cardinale S[1], Pilli T[1], Pacini F[1]

[1]University of Siena, Department of Internal Medicine, Endocrinology & Metabolism and Biochemistry, Siena, Italy

Background: MicroRNA (miRNA) are small, non-protein encoding RNAs that post-transcriptionally regulate gene expression via suppression of specific target mRNAs. Their expression levels in plasma and serum have been found to be altered in cancer and other disease states. Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are the most common subtypes of thyroid malignancies and account for approximately 80% and 11% of all thyroid cancers, respectively. Some studies have employed miRNA detection systems on thyroid tissues, to demonstrate unique molecular expression signatures between benign and malignant thyroid lesions. In particular, miRNA-21, miRNA-31, miRNA-146b, miRNA-221 and miRNA-222 have been found to be overxpressed in PTC. The specific set of miRNAs associated with FTC is different and comprises miRNA-197 and miRNA-346. All these studies concluded that miRNAs represent a novel molecular marker for the differential diagnosis between benign and malignant lesions.

Aim: We aim to retrospectively analyze sera of patients already operated for thyroid nodules, to identify a set of miRNAs differentially expressed in thyroid cancer (both papillary (PTC) and follicular (FTC) histotypes), follicular adenomas (FA) and hyperplastic nodules (HN).

Methods: We studied the expression of miRNA-146b, miRNA-146a, miRNA-221, miRNA-222, miRNA-21, miRNA-155, miRNA-181a, miRNA-181c, miRNA-7, miRNA-187, miRNA-126 and miRNA-30d against rRNA18S as control with real time RT-PCR in 30 PTCs, 30 FA and 30 HN.

Results: Preliminary results indicated an up-regulation in sera of PTC patients for miRNA-21 (p=0.001), miRNA-146b (p=0.02), miRNA-181c (p=0.004) and miRNA221 (p=0.02).

Conclusion: Our results indicate that miRNA detection may be a promising marker to distinguish benign and malignant thyroid pathologies in the blood of patients. These data need to be confirmed in extended series.

P134

CAVEOLIN-1 IN DIAGNOSIS AND PROGNOSIS OF PAPILLARY THYROID CANCER: COMPARISON OF TWO COMERCIAL ANTIBODIES

Paskaš S[1], *Janković J*[1], *Marečko I*[1], *Božić V*[2], *Cvejić D*[1], *Savin S*[1]

[1]Institute for Application of Nuclear Energy - INEP, Department for Endocrinology and Immunoradiology, Belgrade, Serbia, [2]Clinical Center of Serbia, Department of Endocrine and Cardiovascular Pathology, Belgrade, Serbia

Recent studies have shown that caveolin-1 expression is altered in neoplastic thyroid tissue, suggesting its potential usefulness in thyroid tumor diagnostics or prognosis. The aim of this study was to evaluate the competence of two caveolin-1 antibodies in differential diagnostics of thyroid tumors.

We investigated caveolin-1 expression in the human thyroid neoplasia spectrum: follicular thyroid adenomas (FTA), follicular thyroid carcinoma (FTC), two variants of papillary thyroid carcinoma - classical and follicular (clPTC and fvPTC), as well as in adjacent peritumoral tissue (PT). In this study, two commercially available caveolin-1 antibodies were used: sc894 (Santa Cruz Biotechnology) and AV09019 (Sigma- Aldrich). Immunohistochemical staining with these antibodies revealed that caveolin-1 is generally overexpressed in PTC group as a whole (classical and follicular variant) compared to normal tissue, while this protein was mainly negative in FTC and FTA. Diagnostic accuracy of AV09019 was better then sc894 for discriminating: (1) FTA from FTC, (2) FTA from fvPTC, (3) FTC from fvPTC, (4) total PTC from nonmalignant tissue, and (5) malignant tumors from nonmalignant tissue. We also analyzed the correlation of caveolin-1 expression with clinicopathological features of PTC. Spearman's analysis revealed a positive correlation of caveolin-1 expression and extrathyroidal invasion ($p< 0.05$) in PTC, for both antibodies. Additionally, AV09019 antibody correlated caveolin-1 upregulation with T status.

Our results indicate that caveolin-1 expression decreases in the following order: clPTC, fvPTC, FTC, PT and FTA. We are the first to present the evidence that in immunohistochemistry, AV09019 antibody is somewhat superior to that of sc894 antibody for evaluating caveolin-1 levels in thyroid tissue, and thereby could be helpful for differential diagnostics of benign and malignant thyroid tumors.

P135

ASSESSMENT OF *SPAG9* TRANSCRIPT IN FINE NEEDLE ASPIRATES OF THYROID NODULES

Volard B[1], *Krieger S*[1], *Planchard G*[1], *Hardouin A*[1], *Vaur D*[1], *Rame J-P*[2], *Bardet S*[3]

[1]Centre Francois Baclesse, Department of Biopathology, Caen, France, [2]Centre Francois Baclesse, Department of Head and Neck Surgery, Caen, France, [3]Centre Francois Baclesse, Nuclear Medicine and Thyroid Unit, Caen, France

Objectives: Sperm-associated Antigen 9 (*SPAG9*) has been suggested as a possible biomarker in several malignancies including thyroid cancer (Garg et al. JCEM 2009;94:4613). We investigated the expression of *SPAG9* mRNA in Fine-Needle Aspiration (FNA) material from papillary thyroid carcinoma (PTC) and benign thyroid nodules.

Methods: *SPAG9* expression was assessed in 36 FNA samples corresponding to 16 PTC (common form, n=9; follicular variant, n=7) and 20 benign nodules (follicular adenoma, n=7; hyperplasic nodule, n=11, Hashimoto's thyroiditis, n= 1; Hürthle cell adenoma, n= 1) using the original method detecting the *SPAG9* transcript containing intron 21 (X91879 - NCBI). The presence of *BRAF* V600E point mutation was also tested by pyrosequencing.

Results: Six of 16 (38%) of the PTC samples were positive for X91879 *SPAG9* transcript compared to 8 of 20 (40%) of the benign samples ($P= 0.88$). Out of 12 *BRAF* positive PTC, 3 (25%) also expressed *SPAG9* transcript compared to three out of four *BRAF* negative PTC (75%) ($P= 0.12$).

Conclusions: The X91879 *SPAG9* transcript originally described does not appear to be overexpressed in FNA material from PTC and to be clinically relevant in the diagnosis of thyroid nodules.

P136

A RAPID AND ACCURATE REAL-TIME PCR ASSAY FOR THE DETECTION OF BRAF V600E MUTATION IN FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUE (FFPET) SPECIMENS OF PAPILLARY THYROID CARCINOMA (PTC)

DeMartin K[1], *Walter S*[1], *Shah S*[1], *Soviero S*[1], *Halait H*[1]

[1]Roche Molecular Systems, Pleasanton, United States

Objective: BRAF mutations are found in 45–70% of cases of PTC, where they are considered a negative prognostic biomarker. BRAF mutation testing may be useful in the diagnosis of thyroid nodules and in selecting patients for treatment with BRAF inhibitors, so there is medical value in a well validated and reproducible assay to detect these mutations.

Methods: The performance of the **cobas**® 4800 BRAF V600 Mutation Test was assessed in PTC specimens. This test is a CE-marked, FDA-approved assay for detecting BRAF mutations in FFPET specimens of melanoma. The assay procedures can be performed in < 8 hours; analysis and result reporting are fully automated.

Results: Analytical sensitivity was assessed using FFPET tumor specimens and DNA blends derived from FFPET specimens. The test demonstrated a > 95% detection rate for 5% mutant alleles, as measured by quantitative massively parallel pyrosequencing (454), with a DNA input of 125 ng/ PCR reaction, an amount typically obtained from one 5 micron section. To assess repeatability, a panel of 5 PTC specimens was repeatedly tested using different operators and reagent lots on multiple days. Accurate test results were observed in 100% of cases. In a study of test failure rate, no invalid results were observed in 100 consecutive replicates. The **cobas** test showed an overall agreement of ≥ 91% with 2x bidirectional Sanger sequencing across 159 PTC specimens. In 12 cases the cobas test identified mutations not detected by Sanger sequencing; in all 12 cases a mutation was confirmed by 454 sequencing. In all mutation-positive cases, sequencing showed that the BRAF mutation was the canonical V600E (1799T>A).

Conclusions: The **cobas** test is an accurate, reproducible and robust assay for the detection of BRAF V600E mutation in FFPET specimens of PTC, and is more sensitive than Sanger sequencing.

P137

POTENTIAL CLINICAL APPLICATION OF ONCOFETAL FIBRONECTIN MRNA MEASUREMENT IN TUMOR TISSUES AND BLOOD OF PATIENTS WITH DIFFERENTIATED THYROID TUMORS

Vivaldi A[1], *Molinaro E*[1], *Agate L*[1], *Ciampi R*[1], *Valerio L*[1], *Viola D*[1], *Pinchera A*[1], *Vitti P*[1], *Elisei R*[1]

[1]University of Pisa, Endocrinology, Pisa, Italy

Papillary thyroid carcinoma (PTC) is known to specifically express oncofetal fibronectin (onfFN) mRNA, so that recently, a putative diagnostic role has been proposed for the onfFN mRNA detected in blood of thyroid cancer patients. With the aim to test the performance of onfFN mRNA measurement for both the diagnosis of primary thyroid malignancies and the persistence of disease in patients with already treated PTC, in this study we analyzed onfFN mRNA expression by real time RT-PCR in a group of 188 benign (BN) and malignant thyroid tissues and in 55 blood cDNA samples of PTC patients and 15 normal controls. We found that onfFN mRNA was significantly over-expressed in PTCs with respect to their normal contralateral tissues, while BN and their normal contralateral tissues roughly expressed it similarly. Differently, blood onfFN mRNA levels were not correlated with the severity of the disease of PTC patients: the mean blood onfFN mRNA of "disease free" patients group was higher than that of "with remnant" patients

group and even higher than the mean blood onfFN mRNA of the metastatic patients.

In conclusion, the measurement of onfFN mRNA in tissues has a good possibility of being used for the pre-surgical diagnosis of PTC if measured in FNABs. At variance, the measurement of onfFN mRNA in blood showed that onfFN can not be used as a reliable marker in monitoring residual PTC disease.

P138

STUDY OF PREVALENCE AND FUNCTIONAL SIGNIFICANCE OF RARE VARIATIONS IN THE BRAF GENE IN PAPILLARY THYROID CARCINOMA

Barollo S[1], *Pezzani R*[1], *Cristiani A*[2], *Pelizzo MR*[1], *Mantero F*[1], *Moro S*[1], *Mian C*[1]

[1]University of Padua, Padua, Italy, [2]Center for Advanced Studies, Research and Development in Sardinia -CRS4, Pula, Italy

Aim: In the last 2 years, at our Unit, 518 FNAB samples carcinomas were subjected to molecular analysis for the detection of mutations in the *BRAF* oncogene. This study was conducted to define the prevalence and functional significance of rare sequence variants in papillary thyroid carcinoma (PTC).

Methods: Mutation analysis was performed by direct sequencing. The functional study was conducted by Western blot, using antibodies directed against Akt, phospho-Akt, MEK1/2, phospho-MEK1/2, ERK1/2, phospho-ERK1/2, p70S6K, phospho-p70S6K, and β-actin. Finally, the changes brought about by mutations in the BRAF protein conformation were assessed by *in silico* analysis.

Results: In patients with BRAF mutations, 97,4% had the classical mutation c.1799 T>A (p.V600E), while the remaining 2,6% had rare mutations. The rare mutations found were as follows: an in-frame insertion c.1795_1797dupACA (p.T599dup); a point mutation c.1801A>G (p.K601E); a deletion c.1799_1801delTGA (p.V600_K601>E); a double mutation, which produces a predictive in frame deletion/insertion c.1799_1814>A (p.V600_S605>D). In Western blot, the reactivity obtained in the samples studied described a complex picture, which varied from mutation to mutation. The *in silico* analysis of the BRAF protein for the different variant analyzed showed a change in the output probability, when compared to the native protein.

Conclusions: The prevalence of rare sequence variants in *BRAF* is equal to about 2,6% in our series. By Western blot analysis, the intracellular signaling pathways (MAPK and PI3k/Akt pathways) were modulated by *BRAF* alterations. By *in silico* analysis, the functional role of the rare variants of *BRAF* in thyroid tumorigenesis was evaluated, emphasizing the utility of bioinformatics tools for predicting the genetic mutations effects.

P139

MIRNA EXPRESSION SIGNATURE AS PRE-OPERATIVE DIAGNOSTIC BIOMARKERS FOR THYROID CANCER

Ducena K[1], *Abols A*[2], *Pirags V*[2], *Line A*[3], *Andrejeva D*[3], *Vilmanis J*[4], *Narbuts Z*[4], *Tars J*[5]

[1]University of Latvia, Endocrinology, Riga, Latvia, [2]University of Latvia, Riga, Latvia, [3]Latvian Biomedical Research and Study Centre, Riga, Latvia, [4]Pauls Stradins Clinical University Hospital, Riga, Latvia, [5]Riga Eastern Clinical University Hospital, Latvian Oncology Center, Riga, Latvia

Objectives: Fine needle aspiration biopsy (FNAB) can be used as pre-operative diagnostic method for thyroid cancer, but in 20% of cases it can't reliably discriminate between malignant and benign tumors. The aim of the current study is to identify miRNAs that could serve as molecular biomarkers of thyroid cancer and could improve the diagnostic performance of FNAB.

Methods: In order to identify candidate miRNAs that are overexpressed in thyroid cancer we determined miRNA expression profiles in the training set of 4 specimens of papillary thyroid carcinomas (PTC), 3 follicular thyroid carcinomas (FTC), 2 medullary carcinomas (MTC) and 2 anaplastic thyroid cancers (ATC), 4 benign adenomas and pooled relatively normal thyroid tissues as a reference using microRNA Array. Identified miRNA that were overexpressed in one or more thyroid cancer subtype comparing with normal thyroid tissues and benign nodules where tested in independent patient cohort (35 carcinoma, 35 adenoma and 3 normal thyroid tissues) by applying qRT-PCR.

Results: This resulted in the identification of 11 overexpressed miRNAs. qRT-PCR showed that 3 of them (miR-146b-5p; miR-181a; miR-155) where statistically significantly overexpressed in thyroid cancers ($p< 0,05$). The AUC of the ROC curve for these miRNA as individual biomarkers ranged from 0,61 to 0,70. To improve single biomarker performance, we developed a biomarker model combining these miRNAs and 6-gene mRNA expression signature that we have identified previously by applying multivariate logistic regression analysis. This resulted in the multiplex model that was based on the expression analysis of LGALS3, TFF3, BIRC5, CDH1, DPP4, miR-146b-5p, miR-155 and miR-153 and had AUC of 0.96; $p< 0.0001$; CI 95%=0.91–0.99.

Conclusions: In this study we developed multiplex biomarker model that outperforms the currently known diagnostics tests but this biomarker model still have to be tested in FNAB specimens and validated in clinical trials.

PO16 Thyroid Cancer Diagnostics Clinical 2

P140

SITES OF METASTASES IN ANAPLASTIC THYROID CARCINOMA – AN AUTOPSY STUDY OF 45 CASES

Pirnat E[1], *Gazic B*[2], *Besic N*[3]

[1]University Medical Centre Ljubljana, Department of Nuclear Medicine, Ljubljana, Slovenia, [2]Institute of Oncology, Department of Pathology, Ljubljana, Slovenia, [3]Institute of Oncology, Department of Surgical Oncology, Ljubljana, Slovenia

Background: Despite treatment with surgery, chemotherapy and/or radiotherapy vast majority of patients have dismal prognosis. Better knowledge about the frequency of metastasing into different sites might help us to perform adequate diagnostic tests before the treatment and during the course of disease. The aim of this study was to find out what was the frequency of metastases in different sites found at autopsy.

Methods: Altogether 205 patients were treated because of ATC at the Institute of Oncology in the years 1972–2008. In 45 cases (30 females, 15 males; median age 66 years) an autopsy was performed. Frequencies of metastases in different sites were analyzed with methods of descriptive statistics.

Results: Altogether 41 (=91%) cases had metastases at autopsy. Common sites of metastases were lungs (78%), intrathoracic (58%) and neck (51%) lymph nodes, pleura (29%), adrenal glands (24%), liver (20%), brain (20%), heart (18%) and retroperitoneal lymph nodes (18%). Less common sites of distant metastases were pericardium (13%), bones (13%), kidney (13%), mesentery or peritoneum (13%), skin (9%), pancreas (4%), stomach (4%), diaphragm (4%), hypophysis (2%), ovary (2%), jejunum (2%), axillary lymph nodes (2%) and gingival mucosa (2%). Distant and regional metastases were present in 23 cases, while only distant metastases were present in 18 cases. An extensive local infiltration of primary tumor was found in 76% of cases. The total number of involved organs and involved lymph node basisns was 123 and 58, respectively. Mean number of metastatic sites was 4.02 (± 2.75). Lung metastases were present in 34 of 38 (=89%) of our cases with distant metastases found at autopsy and were known in 27 patients while they were alive.

Conclusion: Two or more metastatic sites were found at autopsy in 84% of cases. The most common metastatic sites are lungs, followed by intrathoracic and neck lymph nodes.

P141

IMPLICATION OF BRAF V600E GENE MUTATION IN PREOPERATIVE DIAGNOCTIC OF THYROID GLAND CANCER

Boriskova ME[1], *Semyonov DY*[1], *Zaraisky MI*[2], *Pankova PA*[1], *Farafonova UV*[1], *Bikov MA*[1]
[1]Pavlovs State Medical Univarsity, General Surgery, St. Petersburg, Russian Federation, [2]Pavlovs State Medical Univarsity, Laboratory Diagnostic Department with course of Molecular Medicine, St. Petersburg, Russian Federation

Objectives: To assess the utility of BRAFV600E mutation in preoperative diagnostic of thyroid gland cancer.

Methods: The study consisted of 215 patients. In the beginning, formalin-fixed paraffin-embedded (FFPE) sections were evaluated for the *BRAF* V600E mutation. 112 surgical tissue samples of high-differentiated thyroid cancer of several histologically distinct subtypes, including the most widely accepted and commonly seen: conventional PTC (64), follicular-variant PTC (28), and follicular carcinoma (20) were analyzed for the *BRAF* V600E activating point mutation. Second part of our study consists of detection of BRAF gene mutation in FNAB samples, taken from 103 patients with thyroid gland nodules. We use standard dewaxing protocols for FFPE samples. Thyroid tissue aspirates DNA was extracted by sorbent method. BRAF gene mutation was analyzed with primers specific for wild and mutant gen type by PCR.

Results: BRAF mutation was detected in 56% samples of classical subtype of PTC, in 32% of follicular subtype of PTC. In all cases of follicular cancer BRAFV600E mutation were not found. Detection of BRAFV600E mutation in FNAB (tab1)

Conclusions: preoperative detection of BRAF gene mutation allows to make more definite diagnosis and to set up the indication for surgical interference in specific group of patient with thyroid cancer. Also it allows to choose the appropriate volume of surgical intervention and to maintain all oncological principles. The absence of BRAF gene mutation also restricts the surgical interventions with diagnostic aims.

P142

OVERCOMING THE LIMITATION OF FINE NEEDLE ASPIRATION CYTOLOGY

Jun HH[1], *Chun KW*[1], *Kim BW*[1], *Lee YS*[1], *Chang H-S*[1], *Park CS*[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Surgery, Thyroid Cancer Center, Seoul, Korea, Republic of

Objectives: This study was designed to analyze the risk of false negative result of fine needle aspiration cytology (FNAC) for lateral neck node metastasis in papillary thyroid cancer.

Methodology: In this study, 132 patients with suspicious lateral neck node metastasis by imaging studies were enrolled. FNAC and thyroglobulin in fine-needle aspirate washout (FNA-Tg) were measured. All cases with negative results underwent intraoperative frozen section.

Results: Among 132 patients were 75 patients diagnosed as metastasis by permanent pathology. Metastases were diagnosed in 52 cases by FNAC. There was 1 case of false positive and 24 patients had false negative result (32.0%). The sensitivity of FNAC was 68% and the specificity of FNAC 98.2%. In the risk analysis of false negativity, patients younger than 45 years and with tumors more advanced than T2 stage significantly increased the false negative rate of FNAC. When the cut-off value of FNA-Tg was 34.4ng/mL, the sensitivity was 63.6% and the specificity was 96.4%. The sensitivity of CT density was 45.8% and the specificity of CT density 78.9% with the cut-off value of 130 HU. The accuracy of FNAC increased significantly when combined with FNA-Tg (p=0.009).

Conclusion: To improve the accuracy, a combined measurement of FNAC and FNA-Tg is needed and to decrease the false negative rate of FNAC, patient's age and tumor size should be considered in preoperative planning. When lateral node metastases are suspected in imaging studies, intraoperative frozen section should be considered even if the FNAC result is negative.

P143

PREABLATIVE STIMULATED THYROGLOBULIN LEVEL IS STRONGLY CORRELATED WITH PREOPERATIVE THYROGLOBULIN LEVEL

Shin DY[1], *Park KH*[1], *Lim JS*[1], *Lee EJ*[1]
[1]Yonsei University College of Medicine, Internal Medicine, Seoul, Korea, Republic of

Objectives: Previous studies have shown that a low serum stimulated thyroglobulin (Tg) level measured at the time of postoperative radioiodine remnant ablation (ablation-Tg) has an excellent negative predictive value in persistence and recurrence of papillary thyroid carcinoma (PTC). Although the measurement of preoperative serum Tg (preop-Tg) in PTC patients is not recommended, the role of ablation-Tg as an initial prognostic factor is on debate. Here, we have determined that the preop-Tg has a distinctive influence over ablation-Tg regardless of any other clinico-pathological parameter.

Methods: Patients with PTC (n=151) who have undergone total thyroidectomy with prophylactic central neck dissection followed by ^{131}I remnant ablation were studied. Total of 114 patients, excluding those with anti-Tg antibodies were investigated.

Results: A strong positive correlation was observed between ablation-Tg and preop-Tg (correlation coefficient 0.396, $p< 0.001$), and the strong correlation has not changed even under a condition where the body mass index and the operator were controlled (correlation coefficient 0.372 ($p< 0.001$)). No differences were noted in the postoperative duration (median 75 vs. 78 vs. 85 days) among the three groups according to ablation-Tg levels (p=0.802). Multivariate analysis showed that ablation-Tg is influenced by only preop-Tg but not tumor size, extra thyroidal extension and lymph node metastasis.

Conclusions: As preablative stimulated Tg level is influenced by a Preoperative Tg level, the clinical implication of ablation-Tg should be interpreted in relations to the preop-Tg.

Table for Abstract P141.

Cytological conclusion	amount	Routine histological conclusion	amount	Positive BRAF mutation	Negative BRAF mutation
Nodular colloid goiter	12	Nodular colloid goiter	12	0	12
PTC	54	PTC	54	46	8
Follicular neoplasia	37	Follicular adenoma	26	0	26
		Nodular colloid goiter	6	0	6
		PTC	5	5	0
Total	103		103	51	52

P144

IS THERE A DIFFERENCE IN TUMOR SIZE AND NUMBER OF FOCI IN HASHIMOTO'S ASSOCIATED THYROID CANCER?

Hristozov KH[1], Siderova MV[1], Krasnaliev IJ[2], Nenkov R[3], Radev R[3]
[1]University Hospital 'St. Marina', Clinic of Endocrinology, Varna, Bulgaria, [2]University Hospital 'St. Marina', Department of Pathology, Varna, Bulgaria, [3]University Hospital 'St. Marina', Clinic of Thoracic Surgery, Varna, Bulgaria

Introduction: The association between thyroiditis of Hashimoto and differentiated thyroid cancer has been discussed in the literature but the relationship is still controversial. Coexistence of these diseases is reported up to 30% suggesting that autoimmune thyroiditis may be a precancerosis. On the other hand, prospective case-control studies didn´t establish an increased risk of thyroid cancer in patients with Hashimoto's thyroditis.

Aim of the study was to determine the coexistence of these two diseases and to analyze the histological features of Hashimoto's associated thyroid carcinoma.

Materials and methods: We reviewed 83 cases of thyroid cancer patients, operated for a period of three years. They were divided in three groups: group A - differentiated thyroid carcinomas without focal or diffuse lymphocytic infiltrates (35 cases); group B - thyroid carcinomas with Hashimoto's thyroiditis (26 cases); group C - thyroid carcinomas with only local lymphocytic infiltration (22 cases).

Results: On histology we found coexistence of thyroid carcinoma and Hashimoto's thyroiditis in 29,2% of the cases (31,9% in women; 28,6% in men). Papillary carcinoma was the most prevalent morphological type (70%) associated with autoimmune thyroiditis. Microcarcinomas below 1 cm were most commonly detected in group B (69%), compared to group A (57,1%) and group C (59%). Another distinct feature was prevalence of multifocal thyroid carcinoma in group B (61,5%) versus 31% in group A and 4,5% in group C. The differences in lymph node metastasis and vascular invasion were not significant between the three groups.

Conclusions: Local lympocytic infiltrates do not change the usual histological appearance of the thyroid carcinoma. True Hashimoto's thyroiditis, however, frequently hosts microcarcinomas, which US can hardly distinguish on the patchy hypoechogenic background. Although of small size below 1 cm, thyroid malignancies associated with Hashimoto's thyroiditis are frequently multifocal, the latter underlining the importance of total thyroidectomy for these patients.

P145

POORLY DIFFERENTIATED THYROID CARCINOMA: CLINICAL AND THERAPEUTIC OUTCOMES

Hasbellaoui F[1], Meziani N[1], Ziani K[2], Khalifa A[1], Benserai FZ[3], Amokrane L[2], Semrouni M[1]
[1]Medical University of Algiers, Endocrinology, Algiers, Algeria, [2]Medical University of Algiers, Nuclear Medicine, Algiers, Algeria, [3]Medical University of Algiers, Pathology, Algiers, Algeria

Poorly differentiated histological type of thyroid carcinoma is considered as most frequent diagnostic problem in thyroid pathology and most difficult therapeutic in clinical practice.

Our experience of 20 patients with poorly differentiated carcinoma diagnosed from 2008 to 2011.

60% had distant metastasis in initial presentation :lung, bones and cerebral.

all patients had total or subtotal thyroidectomy.

Radiotherapy was performed in those with spinal metastases.

Metastases surgery was performed when possible on spinal or other bones sites.

These patients had all bad prognosis factors (age, histology, uncomplete surgery)

most (>85%) of our patients had radioiodine therapy with high doses.

Poorly differentiated thyroid carcinoma has a bad prognosis, even when early diagnosed.

P146

THYROID CARCINOMA IN YOUNG POPULATION

Meziani N[1], Hasbellaoui F[2], Ziani K[2], Khalifa A[2], Amokrane L[2], Semrouni M[2]
[1]Medical University of Algiers, Endocrinology, Algiers, Algeria, [2]Medical University of Algiers, Algiers, Algeria

Thyroid differentiated carcinoma in young represents 15% of all differentiated thyroid cancers. considered more agressive than in adults in initial diagnostic, but have good prognosis after radioiodine therapy.

Our patients n:46 from 1988- 2009.

Most of them were girls (35F - 11M)

Middle age 16 years (4 to 20)

Initial presentation was cervical tumor in 80% and associated with lymph nodes in 15%.

After thyroid surgery and first radioiodine treatment.

The staging T3 T4 in 22%.

Lymph nodes metastases in 21%.

Distant metastases in 7%.

Total thyroidectomy was performed in 98%, lymph node dissection on only 29%.

Radioiodine treatment done in 89%.

P147

F-18 FDG PET/CT IMAGING IN THE DIAGNOSTIC WORK-UP OF THYROID CANCER PATIENTS WITH HIGH SERUM THYROGLOBULIN, NEGATIVE I-131 WHOLE BODY SCAN AND SUPPRESSED THYROTROPIN : 6-YEAR SINGLE INSTITUTION EXPERIENCE

Elboga U[1], Ozkaya M[2], Celen YZ[1], Araz M[2], Akarsu E[2]
[1]University of Gaziantep, Nuclear Medicine, Gaziantep, Turkey, [2]University of Gaziantep, Endocrinology, Gaziantep, Turkey

Objectives: The aim of this study was to evaluate the clinical efficacy of fluor-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging in the follow-up of patients with differentiated thyroid carcinoma who have high serum thyroglobulin, negative I-131 whole body scan and suppressed TSH.

Method: A total of 60 patients (21 male and 39 female) with differentiated thyroid carcinoma who have high serum thyroglobulin and negative I-131 whole body scan were included in the study between July 2006 and January 2012. All patients had undergone surgery (total thyroidectomy ± lymph node dissection) followed by Iodine-131 ablation. Of the patients, 53 had papillary thyroid carcinoma and 7 follicular thyroid carcinoma. Serum thyrotropin was suppressed (< 2 µIU/ml) during the Fluor-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging procedure.

Results: The overall sensitivity of fluor-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging in the detection of metastasis of differentiated thyroid cancer was 91.1%, the specificity 73.3%, the positive and negative predictive values 91.1% and 73.3%, respectively. The sensitivity and specificity of fluor-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging in classic type of papillary cancer was 87.5% and 33.3%, respectively. The corresponding figures for the tall cell variant was 88.8% and 100%, respectively. The difference between the two histological subtypes was statistically significant ($p < 0.005$).

Conclusion: Our results suggest that positron emission tomography/computed tomography imaging could be a valuable test for the routine follow-up of patients with differentiated thyroid carcinoma.

P148

ASSOCIATION BETWEEN EXPRESSION OF X-LINKED INHIBITOR OF APOPTOSIS PROTEIN AND THE CLINICAL OUTCOME IN BRAFV600E PREVALENT PAPILLARY THYROID CANCER POPULATION

Kim TY[1], Yim JH[1], Kim WB[1], Hong SJ[2], Gong G[3], Shong YK[1]
[1]Asan Medical Center, Ulsan University, College of Medicine, Dept of Internal Medicine, Seoul, Korea, Republic of, [2]Asan Medical Center, Ulsan University, College of Medicine, Dept of Surgery, Seoul, Korea, Republic of, [3]Asan Medical Center, Ulsan University, College of Medicine, Dept of Pathology, Seoul, Korea, Republic of

Background: The X-linked inhibitor of apoptosis protein (XIAP) is associated with tumor genesis, growth, progression and metastasis, and acts by blocking caspase-mediated apoptosis. In the present study, we evaluated the association of XIAP expression and the BRAFV600E mutation which is the most common genetic alteration and established prognostic marker in papillary thyroid cancer (PTC). And we additionally analyzed the association of XIAP expression and tumour recurrence in BRAFV600E prevalent PTC population.

Methods: The study involved 164 conventional PTC patients who underwent total or near-total thyroidectomy followed by immediate I-131 ablation of the remnants. DNA was extracted from paraffin embedded tumour specimens, and the presence of the BRAFV600E mutation was evaluated using PCR amplification and direct sequencing. Expression of XIAP was evaluated with immunohistochemical staining using monoclonal anti-XIAP.

Results: The BRAFV600E mutation was found in 123 of 164 conventional PTCs (75%). XIAP expression was significantly higher in BRAFV600E mutated PTC than that in wild type PTC. (p=0.03). Lateral neck lymph node metastases were more frequent in patients negative for XIAP expression (P=0.01). Negative XIAP expression were significantly associated with tumor recurrence in patients with BRAFV600E mutation (p = 0.03).

Conclusion: We found that negative XIAP expression was associated with lateral neck lymph node metastases and an increased risk of recurrence in BRAF mutated PTC patients. XIAP immunohistochemical staining is useful for predicting patient prognosis in in BRAFV600E prevalent PTC population.

P149

PROGNOSTIC FACTORS FOR PERSISTENT DISEASE IN DIFFERENTIATED THYROID CANCER (DTC)-PATIENTS

Giani C[1], Molinaro E[1], Piaggi P[2], Pieruzzi L[1], Agate L[1], Biagini A[1], Lorusso L[1], Grasso L[1], Bianchi F[1], Brozzi F[1], Taddei D[1], Nencetti C[1], Pinchera A[1], Vitti P[1], Elisei R[1]
[1]Department of Endocrinology, University of Pisa, Pisa, Italy, [2]Department of Energy and Systems Engineering, University of Pisa, Pisa, Italy

Objectives: Although total thyroidectomy (TT) and radioiodine (131-I) therapy can guarantee the cure of the majority of DTC-patients, a small percentage, despite a good quality-of-life, will never reach the clinical remission thus requiring either further therapies or a careful monitoring. The aim of this study was to evaluate the prognostic factors associated with persistent disease in DTC-patients.

Methods: 159 consecutive DTC-patients treated with TT and 131-I remnant ablation were prospectively followed for at least 10 years. The epidemiological, clinical and histopathological features at diagnosis were evaluated. Furthermore, we considered the stimulated thyroglobulin (S-Tg) off L-tyroxine (L-T4) therapy 6–12 months after the initial treatment.

Results: after 10 years of follow-up, 140/159(88%) DTC-patients were considered in clinical remission while 19/159(12%) were still affected. The comparison of the epidemiological, clinical and pathological features in these two groups showed that there was a statistically significant higher prevalence of persistent disease in patients with an intermediate-high ATA-risk class (p=0.006), with a greater De Groot's class (p=0.0017) and with a greater TNM stage (p=0.01). In addition we observed a statistical significant correlation between the outcome of DTC-patients and S-Tg (p< 0.0001). In particular a S-Tg cut-off of 2 ng/ml identified patients in clinical remission with a specificity of 84%, a sensitivity of 79%, a negative predictive value of 97% and a positive predictive value of 40%. Age, sex and histological variants did not show any correlation with the outcome of our patients. The multivariate analysis showed that only S-Tg was an independent predicting factor for the outcome of the disease.

Conclusions: Although DTC patients with an advanced disease at the diagnosis were at higher risk for the persistence of the disease, the S-Tg was the only factor statistically significant at multivariate analysis. The limit of this observation is that S-Tg was measured off L-T4 therapy.

P150

CHALLENGES IN INTERPRETING LABORATORIAL, ULTRASSONOGRAPHIC AND CYTOLOGICAL TESTS IN THE FOLLOW UP OF PATIENTS WITH NECK LYMPH NODES SUSPICIOUS OF PAPILLARY THYROID CARCINOMA METASTASES

Martins-Costa MC[1], Kazamatsu TS[1], Nakabashi CCD[1], Crispim F[1], Ikejiri E[1], Mamone MCOC[1], Andreoni DM[1], Camacho CP[1], Hidal JT[1], Vieira JGH[1], Maciel RMB[1], Biscolla RPM[1]
[1]Federal University of São Paulo, Endocrinology, São Paulo, Brazil

Objectives: To evaluate clinical, laboratorial and radiological findings of 144 patients submitted to fine-needle aspiration biopsy (FNAB) of neck lymph nodes (LN) suspicious of papillary thyroid carcinoma (PTC) metastases; to measure anti-thyroglobulin antibodies in FNAB washout fluid samples (TgAb-FNAB) and analyze if they interfere in the diagnostic value of thyroglobulin (Tg-FNAB).

Methods: We studied a historical cohort of 144 patients submitted to FNAB of LN suspicious of PTC metastases by neck US, after total thyroidectomy. The inclusion period was from November 2003 to December 2008. All patients had a minimum follow-up of 3 years after the last FNAB. Patients were followed at the outpatient clinic of the Federal University of São Paulo. The main data analyzed retrospectively were: Serum Tg and TgAb, Tg-FNAB and cytology of LN aspirates (cyto-FNAB). Metastases were confirmed by histopathology or ^{131}I uptake. Patients were divided in Group 1 (patients with negative serum TgAb) and Group 2 (patients with positive serum TgAb). We performed a second Tg measurement in washout fluids of Group 2, and measured TgAb from all available washout fluid samples.

Results: From 75 FNAB with detectable Tg (≥ 1ng/mL) of Group 1(TgAb-), metastases of PTC were confirmed in 53 LN - 29 of them (55%) had positive PTC metastases cytology and 24 of them (45%) had inadequate/not diagnostic cytology. We had 150 FNAB with undetectable Tg (< 1ng/mL) in Group 1, presenting the following cytology: reactive n= 69 (46%), inadequate/not diagnostic n=80 (53%) and positive PTC metastases n=1 (1%). From the 29 FNAB of Group 2 (TgAb +), metastases of PTC were confirmed in 16 LN - 11 of them (69%) had positive PTC metastases cytology and 5 (31%) had inadequate/not diagnostic cytology. TgAb was negative in all washout fluid samples analyzed.

Conclusion: Serum TgAb did not affect the measurement of Tg-FNAB.

P151

SCREENING DOPPLER US OF THE CAROTID ARTERIES IS NOT MANDATORY BEFORE LATERAL NECK DISSECTION

Lombardi CP[1], Raffaelli M[1], Revelli L[1], De Crea C[1], Kateta Tshibamba P[1], Tondi P[2], Santoliquido A[2], Bellantone R[1]
[1]Catholic University of Sacred Heart, Surgery, Rome, Italy, [2]Catholic University of Sacred Heart, Angiology, Rome, Italy

Objectives: to evaluate prospectively if Lateral Neck Dissection (LND) for thyroid cancer can determine any alterations in Common Carotid Artery (CCA) wall that may involve an increased risk of postoperative cerebrovascular accident (poCVa).

Methods: all the consenting patients scheduled for LND between 1 August 2010 to 30 December 2011 were considered eligible. High Resolution Doppler Ultrasonography (HR-DU) was performed the day before and three days after surgery using the iU22/2D ultrasound system (Philips Electronics, Netherlands). For the purpose of the study HR-DU patterns were graded from I to IV. Pattern I normal wall Intima-Media Thickness (IMT ≤0.9 mm); pat-

tern II IMT >0.9≤1.3, without plaque; pattern III IMT >1.3 and atherosclerotic plaque without stenosis (< 35%); pattern IV IMT >1.3 with stenosing plaque (>35%).

Results: 30 patients were recruited (19 females, 11 males; mean age 42,7±16,4 years; range 17–81). Risk factors for atherosclerosis were found in 20 patients: Smoking Habit (SH) in 10, Hypertension (HT) in 2, Diabetes (D) in 1, SH+HT in 1, SH+D in 1, HT+D in 4, SH+HT+D in 1. All patients underwent LND for metastatic differentiated thyroid cancer (13 in the right neck, 8 in the left and 9 bilateral). Before surgery, the HR-DU pattern were: I in 26 patients, II in 2, III in 2 and IV in 0, bilaterally. Preoperatively, no hemodynamically significant stenoses (>70%) was observed. No modification of the preoperative findings was observed at the postoperative HR-DU evaluation. No poCVa was observed.

Conclusions: In the absence of any significant CCA stenosis, neck surgery does not affect the presence and the extent of arterial wall disease and the consequent risk of CVa. Routine screening HR-DU is not mandatory before LND. Screening HR-DU may be useful in patients with symptoms and/or significant risk factors for CCA stenoses.

PO17 Thyroid Cancer Therapeutics Clinical 2

P152

BURDEN OF THYROID CANCER: THE PATIENT PERSPECTIVE

Perros P[1], *Farnell K*[1], *Bliss R*[1], *Mallick UK*[1]
[1]Freeman Hospital, Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom

Objective: Thyroid cancer is a usually curable disease, though the psychosocial impact may be significant and long-lasting. This survey was conducted aiming to assess the burden experienced by patients following a thyroid cancer diagnosis.

Methods: A patient survey was conducted by the Butterfly Thyroid Cancer Trust (BTCT) between September and December 2011, using a web-based and paper version of a questionnaire available on the BTCT website and at thyroid cancer clinics in Newcastle, Glasgow, Cardiff, Sheffield and the South West. Affiliated patient advocacy groups were asked to inform their members of the questionnaire and direct them to the link on the BTCT website. These included AMEND, British Thyroid Foundation and H.P.T H. All the questionnaires were anonymous and the data was collected centrally in a database for analysis.

Results: 243 thyroid cancer patients completed the survey; 80% of patients were female. The mean age was 46.7 years and mean time since diagnosis 5.43 years. 56% of patients reported being disease free, 20% of patients had disease that had spread. 56% of all patients were experiencing symptoms, the commonest being tiredness (79%), anxiety or depression (53%), weight changes (51%), sleeping problems (47%) and calcium problems (39%).

Conclusions: In this sample of patients with thyroid cancer, more than half experienced significant symptoms. Although the cause of ongoing symptoms is unclear, many could be related to replacement therapy and potentially addressed with relative ease. Further research is necessary to investigate this important question.

P153

HIGH MAD2 EXPRESSION AS A PREDICTOR OF RESPONSIVENESS OF ANAPLASTIC THYROID CANCER TO PACLITAXEL

Suganuma N[1], *Ito K*[1], *Sugino K*[1], *Nagahama M*[1], *Kitagawa W*[1], *Shibuya H*[1], *Okuwa K*[1], *Yano Y*[1], *Uruno T*[1], *Suzuki A*[1], *Magoshi S*[1], *Hames K*[1], *Akaishi J*[1], *Masaki C*[1], *Masuda M*[2], *Yoshida A*[3]
[1]Ito Hopsital, Surgery, Shibuya, Japan, [2]Yokohama City University, Surgery, Yokohama, Japan, [3]Kanagawa Cancer Center, Breast and Endocrine Surgery, Yokohama, Japan

Objectives: Anaplastic thyroid cancer (ATC) is an extremely aggressive disease. Treatment of ATC requires combined modality therapy that includes surgery, radiotherapy, and chemotherapy. Paclitaxel is considered a key drug for the treatment of ATC, and several studies have indicated that mitotic spindle assembly checkpoint (MSAC) proteins are tumor biomarkers that may be predictive of paclitaxel sensitivity in several cancers other than ATC. The aim of this study was to evaluate the expression patterns of these proteins in normal thyroid tissue and ATC, and to evaluate the potential predictive value of these proteins in ATC treated with paclitaxel-containing chemotherapy regimen.

Methods: A series of 53 samples of ATC tissue and normal thyroid tissue was immunohistochemically analyzed for expression of MSAC proteins (Mad1, Mad2, Bub1 and Bub3). Paclitaxel-containing chemotherapy was performed by 12 of 53 patients, and the relationship between expression of the MSAC proteins and the effect of treatment was examined in the group of 12 patients.

Results: No expression of MSAC proteins was found in the normal thyroid tissue samples, but 1.9, 20.8, 22.6 and 13.2% of the 53 ATC tissue samples showed strong expression of Mad1, Mad2, Bub1 and Bub3, respectively. The clinical response rate in the 12 patients who were treated with a chemotherapy regimen that included paclitaxel was 25.0% (complete response 0, partial response 3). The response rate of the group of patients with high Mad2 expression was significantly higher than in the group with low Mad2 expression (75% vs. 0%, P = 0.018, χ^2 test). No significant differences in response rate were found between groups with high and low levels of expression of the other MSAC proteins.

Conclusions: The results of this study suggest that immunohistochemically detected Mad2 expression could be useful as a tumor biomarker for paclitaxel sensitivity in patients with ATC.

P154

SOLITARY LATERAL NECK NODE METASTASIS IN PAPILLARY THYROID CARCINOMA

Lee YS[1], *Kim SM*[1], *Jun HH*[1], *Chun KW*[1], *Chang HJ*[1], *Kim B-W*[1], *Chang H-S*[1], *Park CS*[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Korea, Republic of

Objectives: Although occult lymph node metastasis to the lateral neck compartment is common in papillary thyroid carcinoma (PTC), the patterns of lateral neck node metastasis(LNM) are various. Sometimes solitary LNM can be seen in PTC patients. This study was carried out to determine the clinicopathologic characteristics of PTC with solitary LNM.

Methods: Between January 2010 and December 2011, the medical records of 331 patients who underwent total thyroidectomy with central neck dissection plus ipsilateral modified radical neck dissection (RND) for PTC (subtype: conventional) were reviewed. The patients were analyzed in two groups; group I, patients with solitary LNM (n = 59) and group II, patients with multiple LNM (n = 272). The clinicopathologic characteristics were statistically analyzed.

Results: The study groups were similar in terms of age and gender ratio. The numbers of lateral neck nodes harvested from solitary LNM and multiple LNM group were similar (29.8 ± 8.6, 32.0 ± 10.0, $p = 0.258$). For groups I and II, respectively, the mean primary tumor size was 1.02 cm and 1.37 cm (p = 0.012), the tumor ≤1 cm in diameter was 57.6% and 37.9% (p = 0.005), capsular invasion frequency was 66.1 and 82.4% (p = 0.005). In addition, Skip metastases were more common in patients with solitary LNM than multiple LNM (39% vs. 22.4%, $p = 0.008$).

Conclusion: The selective single level neck dissection may be considered for PTC patients who show the solitary LNM present in imaging studies, the

primary tumor ≤1 cm in diameter, negative of central neck node and no capsular invasion.

P155

FDG-PET TO PREDICT RESPONSE TO SORAFENIB IN PATIENTS WITH IODINE-REFRACTORY DIFFERENTIATED THYROID CANCER

Marotta V[1], *Ramundo V*[1], *Del Prete M*[1], *Marciello F*[1], *Esposito R*[1], *Carratù AC*[1], *De Luca C*[1], *Fonti R*[2], *Camera L*[2], *Salvatore M*[2], *Colao A*[1], *Faggiano A*[1,3]
[1]University Federico II, Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]University Federico II, Biomorphological and Functional Sciences, Naples, Italy, [3]Endocrinology, National Cancer Institute, "Fondazione G. Pascale", Naples, Italy

Objectives: The tyrosine-kinase inhibitor Sorafenib has been demonstrated to be effective in patients with progressive iodine-refractory differentiated thyroid cancer (DTC). Aim of the study was to assess the role of fluorodeoxyglucose (FDG) positron emission tomography (PET) for predicting response to Sorafenib in these patients.

Methods: A retrospective analysis of 8 patients affected with progressive iodine-refractory DTC subjected to off-label treatment with Sorafenib was performed. Computed tomography (CT) scans were performed at baseline and at 12-weeks intervals to assess objective response. FDG-PET scans were performed at baseline and 15 days after starting treatment to assess early metabolic response. Radiological response was computed by means of RECIST criteria version 1.1. Average standard uptake value maximum (SUVmax) of target lesions (TLs) monitored for objective assessment was used to obtain a quantitative measure of FDG uptake. One-way analysis of variance was used to compare baseline FDG uptake and early metabolic response between groups.

Results: Six patients achieved control of disease progression (3 stable disease and 3 partial response) while 2 subjects showed persisting progressive disease (PD) despite treatment with Sorafenib. All TLs recorded at baseline CT scans presented significant metabolic activities with SUVmax greater than 3 in all cases (mean±DS 11.3±8.8). Baseline average SUVmax was significantly higher in patients with PD (means 22.5vs7.6; p=0.02). Early FDG-PET scans showed reduction of average SUVmax in all cases (mean±DS decrease 30.8%±16.2, range 10–50). The decrease of SUVmax was significantly higher in patients who experienced clinical benefit than those who did not respond (means 37.6vs10.5%; p=0.02).

Conclusions: FDG-PET could play a role in decision making and clinical management of patients with aggressive iodine refractory DTC. Baseline FDG-PET could be useful for selection of patients with a likely response to treatment with Sorafenib. Early FDG-PET assessment could be helpful for a timely identification of non responding patients.

P156

EFFICACY OF SUBFASCIAL APPROACH IN THYROIDECTOMY TO QUALITY OF LIFE IN THYROID DISEASE PATIENTS: PROSPECTIVE RANDOMIZED STUDY

Jung S[1], *Lee SK*[1], *Kim S*[1], *Choi M-Y*[1], *Bae SY*[1], *Kim J*[1], *Park YS*[1], *Kil WH*[1], *Kang B*[1], *Choe J-H*[1], *Kim J-H*[1], *Lee JE*[1], *Nam SJ*[1], *Kim JS*[1]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Division of Breast and Endocrine Surgery, Department of Surgery, Seoul, Korea, Republic of

Background: Voice, sensory and swallowing symptoms are frequently reported after thyroidectomy. We evaluated the efficacy of the subfascial approach on the phonation, sensory and swallowing outcomes in patients undergoing thyroid surgery.

Methods: Eighty-eight patients undergoing thyroidectomy were recruited. Eligibility criteria were: thyroid papillary carcinoma with tumor size ≤ 10 mm, age from 18 years to 75 years. Exclusion criteria were: previous neck surgery, metastsized to lateral neck node, extracapsular invasion, vocal fold paralysis, history of voice or laryngeal disease. Patients were randomized for conventional sub-platysmal muscle (subplatysmal) approach group or sub-anterior fascia of strap muscle (subfascial) approach group. Voice handicap index (VHI), acoustic voice analysis (AVA), voice impairment score(VIS), light touch and pain sense test, swallowing impairment score (SIS), swallowing time, hyoid bone movement range were evaluated preoperatively, 2 weeks and 3 months after open thyroidectomy.

Results: Fourty four in the subplatysmal group, and 44 in the subfascial group. Mean VHI, light touch sense and pain sense 2 weeks and 3 months after surgery were significantly reduced in both group. Mean SIS 2 weeks after thyroidectomy was significantly worsened in both group, however, mean SIS was recovered 3 months after subfascial approach but not after subplatysmal approach. Mean swallowing time after 2 weeks was significantly delayed in subplatysmal group.

Conclusions: This prospective randomized study revealed that the subfascial approach could reduce postthyroidectomy swallowing symptoms compared with subplatysmal approach.

P157

MANAGEMENT OF PROGRESSIVE PAPILLARY THYROID CARCINOMA (PTC) WITH UNRESECTABLE LOCAL INVASION OR GROSS LYMPH NODE INVOLVEMENT

Tomemori T[1], *Mitsuhashi T*[1], *Watanabe R*[1], *Hiruma K*[1], *Sakitani E*[1], *Sugisaki H*[1], *Yanagi Y*[1]
[1]Tokyo Metropolitan Cancer and Infectious Diseases Center KOMAGOME Hospital, Otorhinolaryngology, Head and Neck Oncology, Tokyo, Japan

Objectives: Although surgery and radioactive iodine (RAI) therapy are the standard curative therapy for PTC, management of progressive PTC, especially unresectable or postoperative gross local residues, are still discussed. The aim of this study is to assess our treatment regimens and these results for such severe cases.

Table 1. Patient data (for Abstract P157).

Case	Age/sex	TNM	Stage	Treatment	Outcome
1	51F	T4bN1bM0	IVB	Surgery* → Anaplastic transformation	Died in 0.5 years
2	44M	T4aN1aM1	II	Surgery* → RAI → Anaplastic transformation → EBRT → CT	Died in 4.4 years
3	56M	T4aN1bM0	IVA	Surgery → RAI → Recurrence → Surgery* → RAI	Died in 11 years
4	71M	T1N1bM0	IVA	Surgery* → EBRT (→RAI)	Alive (Treatment still go on)
5	69M	T4aN1bM1	IVC	Surgery* (→ EBRT →RAI)	Alive (Treatment still go on)

EBRT: External Beam Radiotherapy, CT: Chemotherapy, Surgery*: unresectable

Methods: Investigation of 350 cases of thyroid tumor resections, which were performed at our faculty in recent 12 years (2000–2011), revealed 5 severe cases. We evaluated these cases retrospectively.

Results: All cases were summarized in Table. Recent cases (4 & 5) are under treatment with combination of EBRT and RAI. Three other cases were all died of anaplastic transformation (AT) and local relapse.

Conclusions: From our study, gross residue of PTC was significant bad prognostic factor as shown in former reports. Furthermore, we experienced two cases of AT evoked from gross postoperative residues. This fact indicates that patients with gross residual PTC are at relatively high risk of AT.

P158

MANAGEMENT OF MEDIASTINAL METASTASIS FROM THYROID CANCERS

Park CS[1], *Lee YS*[1], *Kim B-W*[1], *Chang H-S*[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Korea, Republic of

Objective: The purpose of this study was to update our 11-year experience of 66 cases involving mediastinum.

Methods: From Oct. 2000 through Dec. 2010, in Thyroid Cancer Center of Gangnam Severance Hospital, a total of 66 consecutive patients were enrolled in this study. Mean follow-up period was 35.1 months (12–134 months). Clinicopathologic data were evaluated statistically.

Results: Mediastinal LN metastases were diagnosed at the first presentation with primary thyroid cancers in 25 cases (37.9%), and the others (41 cases, 62.1%) were recurrent cases. The curative resection was done in 56 cases (84.4%), and for the other cases with unresectable distant metastasis the surgery was done as cytoreductive intent. Combined resection was performed for the invasion to organs in neck and mediastinum in 47 cases (71.2%). Complications were developed in 13 cases (19.7%). There were 7 cases (10.6%) of operative mortality. In the patients older than 65 years, the morbidity (p=0.014) and the operative mortality rates (p=0.032) were significantly higher than younger group. In this series, overall and disease free survival rate were 74.2% and 56.1%, respectively. In the patients with papillary thyroid cancer, overall and disease free survival rates were 81.4% and 72.1% respectively. There were 19 cases of loco-regional recurrences. The recurrence rate was lower in the patients without synchronous distant metastasis. (p=0.044)

Conclusion: For patient less than 65 years, with papillary thyroid cancer, and without distant metastasis, the aggressive surgical treatments for mediastinal metastasis should be considered for the local control, and also the improved survival.

P159

IMPACT OF CLINICAL AND PATHOLOGICAL LYMPH NODE METASTASIS ON CLINICAL OUTCOMES IN PAPILLARY THYROID CANCER PATIENTS

Matsuzu K[1,2], *Sugino K*[1], *Ito K*[1], *Masaki C*[1], *Akaishi J*[1], *Suzuki A*[1], *Uruno T*[1], *Yano Y*[1], *Ohkuwa K*[1], *Shibuya H*[1], *Kitagawa W*[1], *Nagahama M*[1], *Masudo K*[3], *Yoshida A*[2], *Masuda M*[3], *Ito K*[1]
[1]Ito Hospital, Tokyo, Japan, [2]Kanagawa Cancer Center, Yokohama, Japan, [3]Yokohama City University, Yokohama, Japan

Objectives: Though prognostic predictors of papillary thyroid cancer patients, such as; TNM, AGES, AMES, MACIS, and EORTIC, have several factors in common, lymph node metastasis is adopted only in TNM staging. The purpose of this study was to investigate the impact of clinical and also pathological lymph node metastasis on clinical outcomes.

Methods: Consecutive 963 papillary thyroid cancer patients treated by hemithyroidectomy with lymph node dissection were adopted as the subject. Median follow-up period was 17.5 years. There were 99 males and 864 females with a median age of 46 years old. Median tumor size was 22 mm. Clinical lymph node metastasis at the time of surgery and pathological lymph node metastasis were recognized in 63 (7.2%) and 775 (80.5%) patients, respectively. Impact of lymph node metastasis on clinical outcome was analyzed with other possible risk factors by univariate and multivariate analyses using the Cox proportional hazard model.

Results: Recurrences in residual thyroid grand, local lymph nodes, and distant organ were developed in 44 (4.6%), 82 (8.5%), and 35 (3.6%) cases, respectively. 20 patients died of this disease, while 50 died of other reasons. Clinical lymph node metastasis was an independent risk factor for recurrence in local lymph nodes (HR: 3.3, p=0.0001), along with extrathyroidal invasion (HR: 3.7, p< 0.0001), but it was not associated with other type of recurrence or disease death. Pathological lymph node metastasis was an independent risk factor for recurrence in local lymph nodes (HR: 4.5, p=0.0013), with extrathyroidal invasion (HR: 3.9, p< 0.0001), but it was not associated with other type of recurrences or disease death.

Conclusion: Patients with clinical and pathological lymph node metastasis need to be followed as potential candidates for recurrence in local lymph nodes, but it is not necessary to be treated as higher risk of distant metastasis or disease death.

P160

COMPARISON OF LOW AND HIGH DOSES OF IODINE-131 FOR THE POSTOPERATIVE ABLATION OF REMNANT THYROID IN LOW-RISK DIFFERENTIATED THYROID CANCER PATIENTS

Kim D-Y[1], *Hong I-K*[1]
[1]Kyung Hee University Hospital, Nuclear Medicine, Seoul, Korea, Republic of

Objective: The aim of the study is to compare the success rate of low (1,110 MBq) and high doses (3,700 MBq) of I-131 for postoperative remnant thyroid ablation.

Methods: A total of 127 low-risk patients (mean age: 49.6, 88.1% female) with papillary and follicular carcinoma who had I-131 ablation for the postoperative remnant ablation were retrospectively studied. Sixty-four patients received a low dose (1,110 MBq) and 63 patients received a high dose (3,700 MBq) of I-131. The success rate of I-131 ablation was assessed based on serum thyroglobulin and I-131 diagnostic whole-body scintigraphy 6–12 months after total thyroidectomy. Ablation was considered to be successful if the patients' serum thyroglobulin was less than 0.2 ng/ml and I-131 diagnostic whole body scan was negative (no tracer uptake or less than twice the background activity in the thyroid bed).

Results: The ablation was successful in 33 out of 64 (51.5%) and 58 out of 63 (92%) patients for low- and high-dose group, respectively. The difference was statistically significant between the two groups (P< 0.0001).

Conclusion: Our results suggest that remnant thyroid tissue in patients with low-risk, well-differentiated thyroid cancer after total thyroidectomy can be ablated more successfully with 3,700 MBq than 1,110 MBq.

P161

TUBERCULOSIS CERVICAL LYMPHADENOPATHY MIMICKING LATERAL NECK NODE METASTASIS FROM PAPILLARY THYROID CARCINOMA

Kim SM[1], *Lee YS*[1], *Chang H-S*[1], *Park CS*[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Korea, Republic of

Objectives: Tuberculosis (TB) lymphadenitis is a common cause of lymphadenopathy in areas where tuberculosis is endemic. Cervical lymphadenopathy of TB can mimic lateral neck node metastasis in PTC. The aim of this study was to find the proper procedure to distinguish TB lymphadenitis from lateral neck metastasis (LNM) for avoiding unnecessary lateral neck dissection (LND).

Methods: In 15,739 thyroid cancer patients who underwent thyroid cancer operation PTC in the Thyroid Cancer Center of Gangnam and Shinchon Severance Hospital between May 2007 and December 2011, thirty seven patients had papillary carcinoma in thyroid and TB lymphadenopathy in cervical node. The results of the preoperative evaluation of cervical lymphadenopathy were compared with the histopathologic results.

Results: All patients were diagnosed with PTC and had cervical lymphadenopathy in preoperative evaluation. Radiologic characteristics of metastatic lymph nodes were found in all patients. Twenty eight patients did not undergo LND due to preoperative measurement of Tg in fine needle aspiration biopsy (FNAB-Tg) or polymerase chain reaction (PCR) for detecting TB or

findings of intraoperative frozen sectioning. Six patients of nine patients who underwent LND had metastasis combined with tuberculous lymphadenopathy, and the remaining 3 patients were negative of LNM.

Conclusions: To avoid unnecessary lateral neck node dissection for tuberculous lymphadenopathy, Preoperative FNAB-Tg, combined FNAB with PCR for detecting TB and intraoperative frozen sectioning lymph nodes suspicious for LNM can be helpful for avoiding unnecessary LND.

P162

TREATMENT OF DISTANT METASTASIS FROM DIFFERENTIATED THYROID CARCINOMA (DTC) IN OUR HOSPITAL

Watanabe R[1], *Mitsuhashi T*[1], *Tomemori T*[1], *Hiruma K*[1], *Sakitani E*[1], *Sugisaki H*[1], *Yanagi Y*[1]
[1]Tokyo Metropolitan Cancer and Infectious Diseases Center KOMAGOME Hospital, Otorhinolaryngology, Head and Neck Oncology, Tokyo, Japan

Objects: In Japan, there are relatively less radioactive iodine (RAI) therapeutic facilities than other countries. Our hospital is one of RAI facility in Tokyo, therefore, some patients are secondary introduced to our hospital for subsequent RAI therapy. Our aim is to analyze clinical results of distant metastasis from DTC.

Methods: Retrospective analysis revealed 36 cases of patients with distant metastasis from DTC in a total of 131 cases between May 2005 and March 2012. Statistical data was as follows: age; 14–86 years (median: 59.9), sex; 10 males and 26 females, pathology; 23 papillary thyroid carcinomas and 13 follicular thyroid carcinomas.

Results: 31 patients were diagnosed as M1 at first examination, and 5 other patients showed distant metastasis under treatment courses. Metastatic organs were as follows: lung/ bone/ brain/ kidney/ mediastinum = 18/ 18/ 3/ 1/ 1. Details of thyroidectomies were as follows: 14 cases were combination of primary hemi-thyroidectomy and second total thyroidectomy, while 22 cases were only total thyroidectomy. Treatment for metastatic lesions were as follows: RAI/ intra-operative radiology (IOR)/ external radiation therapy (ERT)/ surgery of metastatic lesion =31/ 10/ 11/ 7. Cause-specific survival rate in total was 67.9% at 5 years. 31 patients were treated by RAI and its cause-specific survival rate was 71.5% at 5 years. 5 other patients gave up RAI and could NOT showed 5-year survivals. Patients with lung, kidney or mediastinum metastasis were treated by RAI only. On the other hand, patients with bone or brain metastasis were treated by combination of surgery and several radiation methods such as RAI/ ERT/ IOR to minimize severe neuropathy.

Conclusions: Further and long-term studies are necessary for standardizing the treatment of distant metastasis of DTC.

P163

PROGNOSIS OF THE EXTRATHYROIDAL EXTENSION IN PAPILLARY THYROID CARCINOMA

Bae JS[1], *Kwak HY*[1], *Chae BJ*[1], *Song BJ*[1], *Jung SS*[1]
[1]Seoul Saint Mary's Hospital, The Catholic University of Korea, Department of Surgery, Seoul, Korea, Republic of

Objectives: Extrathyroidal invasion is one of the most significant risk factors for patients with papillary thyroid carcinoma (PTC). However, the definition of minimal thyroidal extension is ambiguous. The purpose of this study is to evaluate the prognostic factors according to the extent of extrathyroidal extension (ETE) in PTC.

Methods: The retrospective study was conducted for 1385 patients with primary PTC who received open surgery from September 2008 to February 2012. Patients were put into three groups according to ETE. Patients without ETE were classified as group A, those with ETE limited to perithyroid soft tissue as group B, and those with ETE invaded to sternothyroid muscle were group C. Clinicopathologic characteristics and thyroglobulin (Tg) level were analyzed.

Results: Tumor smaller than 1 cm were more frequent in group A than in group B ($p< 0.0001$). More node metastasis was found in group B than A ($p< 0.0001$), and more in group C than B ($p< 0.0001$). Lateral neck node metastasis was more frequent in group B than A ($p< 0.0001$), and also more frequent in group C than B ($p=0.015$). More metastatic neck nodes were seen in group C than B ($p< 0.0001$), and more in group B than A ($p< 0.0001$). In patients with total thyroidectomy (TT) and without radioactive iodine therapy (RI), mean Tg level 4 months after operation was lower in group A than B ($p=0.039$). In patients with TT and RI, Tg level at pre-131I-whole body scan was higher in group C than B ($p=0.006$).

Conclusions: Patients with ETE limited to the perithyroid soft tissue have poor prognostic factors than those without ETE, and have better prognostic factors than those with ETE invaded to muscle. However, to determine the prognosis according to the extent of ETE, further evaluation about complications and long-term follow-up should be followed.

PO18 Thyroid Autoimmunity and Hypothyroidism Basic

P164

CTLA-4 GENE POLYMORPHISMS AND AUTOIMMUNE THYROID DISEASES IN THAI PATIENTS

Mayurasakorn N[1], *Puttipokin S*[1], *Houngngam N*[1], *Sunthornyothin S*[1], *Chusrichun W*[1], *Snabboon T*[1]
[1]Chulalongkorn, Medicine, Bangkok, Thailand

Background: Cytotoxic T lymphocyte-associated antigen-4 (*CTLA-4*) gene has been proposed as a susceptibility gene of autoimmune thyroid diseases (AITD) and may predict the clinical course of Graves' disease (GD).

Aim: To analyze an association between two *CTLA-4* polymorphisms (SNPs), *A49G* and *CT60*, and AITD in Thai patients and also evaluate their relationships in the relapse of GD after antithyroid withdrawal.

Methods: A case-control study was performed in 113 patients with antithyroid-treated GD, 47 patients with Hashimoto's thyroiditis (HT) and 113 gender-matched control subjects. The *CTLA-4* SNPs,*+49A/G* and *CT60A/G*, were genotyped by using polymerase chain reaction-restriction fragment length polymorphism method. We also studied the relationship between these polymorphisms and clinical course in GD by categorized in relapse (recurrence within 3 years after medication withdrawal) and remission (maintained in euthyroid state for at least 3 years) groups.

Results: A significant increase of the *G* allele at position 49 in exon 1 was seen in GD patients compared with controls (89% vs. 76% respectively, $p=0.008$; odd ratio 2.642); however, this finding was not observed in HT patients. No significant association was found for the *CT60A/G* SNP with AITD. In addition, the frequency of *G* allele of *+49A/G* SNP was not significantly different among the patients in relapse and remission groups of GD (61% vs. 62% respectively, $p=0.867$). However, the patients who carried the genotype *AG* or *GG* have a chance about early relapse compared with those with genotype *AA*, mean time 15.9±6.6 and 22.7±9.2 months; $p=0.026$).

Conclusion: These results suggest that the *CTLA-4* SNP*,+49A/G*, is involved in the susceptibility of GD for Thais. However, the association between this gene and other subtypes of AITD or clinical course of GD were not observed.

P165

SERIAL DILUTION ANALYSIS IMPROVES THE CLINICAL UTILITY OF A CHIMERIC TSH RECEPTOR BIOASSAY FOR THYROID STIMULATING AUTOANTIBODIES

Leschik JC[1], *Diana T*[1], *Olivo PD*[2], *König J*[3], *Krahn U*[3], *Li Y*[2], *Kanitz M*[1], *Kahaly GJ*[1]
[1]Gutenberg University Medical Center, Department of Medicine I, Mainz, Germany, [2]Diagnostic Hybrids, Inc, R & D, Athens, United States, [3]Gutenberg University Medical Center, Institute of Medical Biostatistics, Epidemiology and Informatics, Mainz, Germany

Objectives: The analytical and clinical performance of a FDA-cleared bioassay for measurement of thyroid stimulating immunoglobulins (TSI)

was compared with an automated TSHR binding inhibiting immunoglobulin (TBII) assay.

Methods: Limits of detection (LoD) and quantitation (LoQ), cut-off and EC50 were measured using a thyroid-stimulating monoclonal antibody (M22). The clinical utility of dilution analysis was evaluated in 237 serum samples of 40 hyperthyroid patients with Graves' disease (GD) prior to and during antithyroid drug treatment (ATD). Titer was defined as the first dilution step at which measurement of TSI or TBII was below the assay cut-off.

Results: The LoD, LoQ, cut-off and EC50 of the TSI bioassay were 251-fold (0.02 vs. 5.02 ng/ml); 298-fold (0.02 vs. 5.95 ng/ml), 814-fold (0.017 vs. 13.83 ng/ml) and 827-fold (0.20 vs. 165.3 ng/ml) lower than for the TBII assay. In dilution studies there were 22%, 42%, 23% and 14% more positive samples in the TSI compared to the TBII assay at dilutions 1:3, 1:9, 1:27 and 1:81, respectively which revealed a mean percent difference of 25% ± 6% (SE), $p< 0.0001$. Mean TSI titers at all times during ATD were 1.13 ± 0.07 dilution steps higher than mean TBII titers ($p< 0.0001$). In 19/40 patients with TSI titer ≥ 4, compared with the undiluted SRR% values dilution analysis provided additional substantial quantitative information. ATD responders (euthyroidism after ATD withdrawal) demonstrated marked differences in titers with the bioassay compared with non-responders (persistent hyperthyroidism or relapse). In non-responders versus responders, baseline mean TSI titers were 4.0 ± 0.39 and 2.9 ± 0.25 ($p=0.018$) whereas the mean difference in TSI titer increased to 2.0 ($p< 0.0001$) at completion of ATD treatment.

Conclusions: The TSI bioassay has a higher analytical performance than the binding assay. Serum dilution analysis was clinically useful and prognostically informative in GD patients undergoing ATD.

P166

PTPN-22 GENE POLYMORPHISM AND FAMILIAL AUTOIMMUNE THYROID DISEASE

Rymar O[1], *Mikitinskaya A*[1], *Maksimov V*[1], *Mustafina S*[1]
[1]Institute of Internal Medicine SB RAMS, Novosibirsk, Russian Federation

Objectives: The aim of this study was to determine the frequency of PTPN-22 C1858T polymorphism in families with autoimmune thyroid disease (AITD) at least two first-degree relatives.

Methods: We have performed genotyping of 126 persons with respect to sex parameters: 42 patients with AITD and 84 persons of control healthy group. An average ages was 50,1 ± 11,5 year. The condition for inclusion in the study was the presence of a family member first-degree relatives with Hashimoto`s thyroiditis (HT) or Grave`s disease (GD), so the study included 21 families.

The estimate number of patients with GD and HT was 26,2% (11 persons) and 73,8% (31 persons), respectively. Family history of AITD was traced for two generations (parent offspring) in 80.9% (17families), and 19.1% (4 families) for one generation (siblings). Genotyping of C1858T polymorphism was performed by conventional PCR method.

Results: The frequency of genotype CT and T allele was increased in patients with family cases of AITD 38,1% versus controls 21,4%, p=0,041 и 21% versus 11%, p=0,054, respectively. Only one patient with GD was determined by the genotype TT among all examined persons (2,4%), p=0,043. The genotype CT and T allele were associated with the increased risk for familial AITD: OR=1,7; 95% CI 1,1–2,8 and OR=1,4; 95% CI 1,1–1,8, respectively. But a strong association was observed only in case of TH, and not in GD. The frequency of genotype CT and T allele was 41,9% versus controls 21,4%, p=0,028, и 21% versus 11%, p=0,05, respectively. They were associated with the increased risk for familial TH: OR=1,9; 95% CI 1,1–3,5 and OR=1,4; 95% CI 1,1–1,8, respectively.

Conclusions: The carrier of the genotype CT and allele T of C1858T polymorphism PTPN-22 gene were associated with the occurrence of familial TH.

P167

PHYSIOGICAL IODINE SUPPLEMENTATION DOES NOT INDUCE CLINICALLY RELEVANT CELLULAR IMMUNITY IN A TRANSGENIC AUTOIMMUNE THYROIDITIS MODEL

Thiel A[1], *Ehlers M*[1], *Papewalis C*[2], *Domröse A*[3], *Stenzel W*[1], *Bernecker C*[1], *Schinner S*[1], *Willenberg H*[1], *Schott M*[1]
[1]Heinreich-Heine-University Duesseldorf, Division of Endocrinology, Düsseldorf, Germany, [2]University Hospital Bonn, Department for Pediatrics, Bonn, Germany, [3]Heinreich-Heine-University, Düsseldorf, Germany

Different studies already demonstrated that iodine supplementation may induce autoimmune reactions in mice and humans in terms of humoral immunity. This, however, has mostly been demonstrated for excessive iodine dosages. Moreover, only a limited amount of data is available regarding cellular immunity in this context. The aim of our study was to investigate the impact of physiological and excessive iodine supplementation on the cellular immunity and course of disease in a transgenic mouse model for AIT (TAZ10 mice; kindly provided by S. Quaratino).

Mice were supplemented with 15 ng versus 30 ng iodine per ml drinking water, which equates to a daily supplementation of 200 µg versus 400 µg ID per 70 kg. The autoimmune thyroiditis defining parameters (gain in weight, elevation of serum TSH-levels and cellular infiltration of the thyroid) were analyzed after 10 and >23 weeks and compared to untreated control mice. Furthermore, immunological effects were monitored by FACS.

After 23 weeks of age we observed an increased thyroid infiltration with CD8+ cells by immunofluorescence-staining and FACS-analyses in treated mice. This may be associated with an enhanced production of Interleukin-1 in all treated mice. However, clinically no significant differences were displayed when comparing the gain in weight and serum TSH-levels in the supplemented versus control groups. The marginal clinical impact and the only slight increase of CD8+ T cell infiltrations could amongst others be explained by a significant increase of FOX+/CD25+ regulatory T cells in mice supplemented with physiological iodine.

In summary, our data show that physiological and slightly upper-physiological iodine supplementation does only marginally influence the autoimmune process in a transgenic AIT mouse model. Even though data from a randomized trial in humans and further functional in-vitro studies are still missing, these results may have a direct implication for AIT patients e.g. in iodine insufficient areas.

P168

HUMAN THYROCYTES IN PRIMARY CULTURES SECRETE CXC CHEMOKINES CXCL8 AND CXCL10 BY DISTINCT PRO-INFLAMMATORY PATHWAYS: A FIRST STEP TOWARD A DIFFERENTIATION BETWEEN AUTOIMMUNE AND TUMOR-RELATED INFLAMMATION?

Coperchini F[1], *Rotondi M*[1], *Pignatti P*[1], *Sideri R*[1], *Groppelli G*[1], *Leporati P*[1], *de Martinis L*[1], *La Manna L*[1], *Magri F*[1], *Mariotti S*[2], *Chiovato L*[1]
[1]FSM, Pavia, Pavia, Italy, [2]Università di Cagliari, Cagliari, Italy

Chemokines are chemotactic cytokines responsible for the attraction and recruitmentof different cell types during leukocytes infiltration, the histopathological hallmark ofautoimmunity. Previous data demonstrate that thyrocytes may secrete CXCchemokines, particularly CXCL8 and CXCL10. However, the physiopathologicsignificance of such release and the secretion pathways of CXCL8 and CXCL10remains only partially understood. Aim of this study was to investigate the proinflammatorystimuli leading to the secretion of specific chemokines by humanthyrocytes. CXCL8 and CXCL10 were measured in supernatants of human thyrocytesin primary cultures basally and after 24-hours stimulation with IFNγ (1000U/ml) andTNFα (10ng/ml), alone or in combination. CXCL8 but not CXCL10 was detected inbasal conditions. The two chemokines showed striking differences in their response toproinflammatory cytokines. Indeed, significant secretion of CXCL10 was induced byIFNγ ($p< 0.01$) and not TNFα, while CXCL8 was secreted in response to TNFα ($p< 0.01$) with an inhibitory effect of IFNγ ($p< 0.01$). The combination

of TNFα+IFNγ synergistically increased the IFNγ-induced CXCL10 secretion ($p< 0.01$) and reversed the TNFα-induced CXCL8 secretion ($p< 0.01$). These results demonstrate that a preferential secretion of CXCL8 and CXCL10 chemokines by human thyrocytes depends upon stimulation by specific pro-inflammatory cytokines or their combination.

The resulting chemokine profile might play an important role in determining the nature of the infiltrating lymphocytes in human thyroid diseases. These results indirectly support a major role for CXCL10 in thyroid autoimmunity while CXCL8 might be involved in tumor related inflammation.

P169

CYTOPHILIC ANTIBODIES AND MONOCYTE-MEDIATED CYTOTOXICITY IN HASHIMOTO'S THYROIDITIS

Milicevic Z[1]

[1]Laboratory for Molecular Biology and Endocrinology, Vinca Institute of Nuclear Science, University of Belgrade, Belgrade, Serbia

In order to delineate monocyte-mediated cytotoxicity in Hashimoto's thyroiditis and its relationship to monocyte cytophilic anti-thyroglobulin antibodies present in Hashimoto sera, we studied antibody-dependant monocyte-mediated cytotoxicity and tried to clarify the pathogenic significance of cytophilic antibodies. Effector cells were normal human peripheral monocytes adhered to cover slip in Leighton tubes or bottom of test tubes. Target cells were human-thyroglobulin-coated erythrocytes (E-Tg). Arming of monocytes with cytophilic anti-thyroglobulin antibodies were confirmed by observing rosette formation of E-Tg with monocytes pretreated with Hashimoto sera. These cytophylic antibodies were found in 23 sera out of 29 anti-thyroglobulin antibody positive Hashimoto sera. Activities of cytophilic antibodies were evaluated by counting rosette forming cells with more than 2 E-Tg among 500 monocytes and these activities were correlated with serum hemagglutination titers for anti-thyroglobulin antibodies. More than 90% of cytophilic antibody activity was recovered in the purified IgG fraction of Hashimoto sera by Sephadex-G 200 column chromatography. Cytotoxicity assay using ^{51}Cr labelled E-Tg rivealed that normal human monocytes armed with cytophylic anti-thyroglobulin antibodies in vitro were cytotoxic against E-Tg and significant ^{51}Cr release was observed at effector: target cell ratio of 5:1. But the cytotoxic reaction was mild and slow as compared to that of normal monocytes against E-Tg sensitized with anti-thyroglobulin antibodies. Light and scanning electron microscopic observations also revealed that armed monocytes did not phagocytize target cells but destroyed them by extracellular mechanisms. Although the cytotoxicity of normal monocytes against antibody-sensitized E-Tg was suppressed significantly by the addition of normal human serum or Cohn's faction II into the incubation mixture, the reaction of armed monocytes with E-Tg or antibody-sensitized E-Tg was not significantly suppressed in the same conditions.

Conclusions: some anti-thyroid autoantibodies in Hashimoto sera were cytophilic for monocytes and conter them the specific cytotoxic activity against antigen bearing target cells in vivo.

P170

DETERMINATION OF BIOLOGICAL ACTIVITIES OF TSH RECEPTOR (TSHR) AUTOANTIBODIES (TRABS) IN SERUM SAMPLES CONTAINING A MIXTURE OF STIMULATING AND BLOCKING ANTIBODIES

Young S[1], *Betterle C*[2], *Zanchetta R*[2], *Sanders J*[1], *Kabelis K*[1], *Sanders P*[1], *Evans M*[1], *Furmaniak J*[1], *Rees Smith B*[1]

[1]FIRS Laboratories, RSR Ltd, Cardiff, United Kingdom, [2]University of Padua School of Medicine, Department of Medicine, Padua, Italy

Stimulating and blocking type TRAbs can be present in a patient at the same time and determination of the biological activities of TRAbs in samples containing a mixture of stimulating and blocking antibodies can be difficult due to interference of the antibodies on each other in the respective bioassays.

In this study, serum samples were obtained at presentation (sample A) from a male patient with hypothyroidism who after one year on thyroxine became spontaneously euthyroid (sample B) and no longer required thyroxine supplementation. He remained euthyroid without any medication for 5 years and then became clinically and biochemically thyrotoxic (sample C) and was treated with carbimazole.

Samples A, B and C were TRAb positive by TSH binding inhibition assay at 1385U/L, 615 U/L and 205U/L, respectively. Samples A, B and C stimulated cyclic AMP production in CHO cells expressing the wild-type TSHR with increasing potency over time (226%, 639% and 1269% stimulation, respectively). Samples A and B, but not C, inhibited TSH induced cyclic AMP stimulation in CHO-TSHR cells (88% and 55% inhibition, respectively).

Samples A, B and C were also assessed using CHO cells expressing TSHR containing the R255D mutation that is known to affect the stimulating activity of TSHR antibodies but not TSH. Samples A, B and C were inactive in this assay. In contrast inhibition of TSH induced cyclic AMP stimulation increased to 95%, 89% and 72% for samples A, B and C respectively.

These experiments indicate that when a serum sample contains a mixture of stimulating and blocking TRAbs a bioassay using TSHR R255D allows determination of TSH antagonist activity without the interference of stimulating TRAbs. This could have applications in monitoring of Graves´ patients with fluctuating thyroid status.

P171

PREVALENCE OF *DIO2*^{T92A} POLYMORPHISM AND ITS ASSOCIATION WITH THYROID AUTOIMMUNITY

Guerra A[1], *Sapio MR*[1], *Di Stasi V*[1], *Volpe A*[1], *Murino A*[1], *Izzo G*[1], *Vitale M*[1]

[1]University of Salerno, Department of Medicine and Surgery, Baronissi, Italy

The 3,5,3′-L-triiodothyronine (T3) is partly produced and released into the serum by the thyroid and partly derives by the deiodination of the prohormone 3,5,3′,5'-L-tetraiodothyronine (T4) by the type 2 iodothyronine deiodinase (D2).

The single-nucleotide polymorphism in the D2 gene at position 92 ($Dio2^{T92A}$), generates an enzyme with a reduced T4 to T3 conversion velocity. Recent studies have shown that $Dio2^{T92A}$ is associated with some diseases and metabolic traits and may have relevant pathophysiological effects. The objective of this study was to investigate the $Dio2^{T92A}$ polymorphism in relation to thyroid autoimmunity. We compared the prevalence of $Dio2^{T92A}$ polymorphism and serum thyroid hormone levels in healthy subjects and subjects with thyroid autoimmunity (TA), seeking a possible correlation between this polymorphism and HT.

Patients and methods: A total of 201 consecutive subjects, 101 with TA documented by the presence of serum autoantibodies and 100 controls were genotypized for $Dio2^{T92A}$ polymorphism by pyrosequencing. Free T3 (FT3), free T4 (FT4) and thyrotropin (TSH) were measured and compared with the $Dio2^{T92A}$ polymorphism.

Results: $Dio2^{92T/A}$, $Dio2^{92A/A}$ and $Dio2^{92T/T}$ subjects were 42.4%, 44.9%, and 12.7% respectively. These prevalences were similar to those of some European countries whilst significantly different from that of Brazil. In the two groups of healthy subjects and TA subjects, $Dio2^{T92A}$ polymorphism had a similar distribution and non significant differences were observed. Similarly, no significant differences were observed in the serum concentration of FT3, FT4 and TSH between subjects with different $Dio2^{T92A}$ polymorphism. The FT4/FT3 and TSH/FT3 ratios were higher in $Dio2^{92T/T}$ subjects than in $Dio2^{92T/A}$ and $Dio2^{92A/A}$ subjects in both groups, but these differences were not significant.

Conclusions: The distribution of $Dio2^{T92A}$ polymorphism may reflect geographical and ethnic differences, and it is not associated with thyroid autoimmunity.

P172

ENHANCED EXPRESSION OF THE B CELL ACTIVATION FACTOR (BAFF) AND BAFF-RECEPTOR (BAFF-R) IN THYROID AND ORBITAL ADIPOSE TISSUE (OAT) FROM PATIENTS WITH AUTOIMMUNE THYROID DISEASES (AITD) AND ASSOCIATED ORBITOPATHY (GO)

Campi I[1], *Vannucchi G*[1], *Covelli D*[1], *Rossi S*[2], *Doi P*[2], *Vicentini L*[3], *Currò N*[4], *Pignataro L*[5], *Guastella C*[5], *Beck-Peccoz P*[1], *Salvi M*[1]
[1]University of Milan- Fondazione IRCCS Cà Granda, Department of Medical Science, Endocrine Unit, Milan, Italy, [2]S. Paolo Hospital, Milan, Department of Pathology, Milan, Italy, [3]Fondazione IRCCS Cà Granda, Department of Endocrine Surgery, Milan, Italy, [4]Fondazione IRCCS Cà Granda, Department of Ophthalmology, Milan, Italy, [5]Fondazione IRCCS Cà Granda, Department of Otolaryngology, Milan, Italy

Objectives: To investigate the expression of BAFF, a member of the TNF family involved in B-cells survival and proliferation, and BAFF-R in GO and in autoimmune or non-autoimmune thyroid diseases (NAITD).

Methods: immunohistochemistry, using a panel of antibodies against BAFF, BAFF-R, CD3, CD4, CD8, CD20, CD34, CD79, CD1a, CD68, CD163, on paraffin embedded sections of: 1) 22 OAT and 10 extra-ocular-muscles (EOM) biopsies from patients with GO and AITD; 2) Thyroid tissue from 28 patients with GD, 5 with Hashimoto's thyroiditis (HT), 14 with non-toxic-nodular goiter (NTG) without (n=9) or with increased serum Tg-Ab or TPO-Ab levels (NTG-Ab) (n=5), and 6 with toxic-nodular goiter (TG).

Results: Overall BAFF expression on thyrocytes was not different in AITD and NAITD. On GD thyroid sections BAFF staining was higher on thyrocytes in diffuse hyperplastic (DH) compared with nodular hyperplastic (NH) tissue. In addition, the strongest BAFF-R staining was observed with GD. BAFF and BAFF-R expression on tissue infiltrating lymphocytes was higher in AITD compared with NAITD; interestingly, in the follicular-like-structures found in HT and NTG-Ab, BAFF and BAFF-R were localized in the germinative center or in the mantle, respectively. In lymphocytes infiltrating GD tissue BAFF-R staining was stronger in NH than DH. In OAT, BAFF and BAFF-R expression was found in 15 and 5 of 22 samples, respectively. Interestingly, their expression was stronger on B lymphocytes than T lymphocytes. Orbital fibrocytes were only rarely found to express BAFF and BAFF-R (3 of 22 samples). Tests on EOM were negative.

Conclusions: In this study we report an increased expression of BAFF and BAFF-R in GO and AITD, compared with non-autoimmune controls. This finding, together with a recent observation of increased serum BAFF levels in GD and HT, suggests an involvement of BAFF and its receptors in the pathophysiology of AITD and GO.

P173

EXPRESSION OF DIFFERENT THYROPEROXIDASE (TPO) ISOFORMS IN THYROID (THY), BREAST CANCER (BC) AND OTHER TISSUES

Muller I[1,2], *Giani C*[1], *Fiore E*[1], *Belardi V*[1], *Rosellini V*[1], *Funel N*[3], *Campani D*[3], *Grennan-Jones F*[2], *Zhang L*[2], *Lewis M*[2], *Bakhsh A*[2], *Roncella M*[4], *Ghilli M*[4], *Pinchera A*[1], *Vitti P*[1], *Dayan C*[2], *Ludgate M*[2]
[1]University of Pisa, School of Medicine, Endocrinology, Pisa, Italy, [2]Cardiff University, School of Medicine, Institute of Molecular & Experimental Medicine, Cardiff, United Kingdom, [3]University of Pisa, School of Medicine, Patology, Pisa, Italy, [4]University of Pisa, School of Medicine, Senology, Pisa, Italy

Objectives: Serum anti-TPO-autoantibodies (TPOAb) are common and protective in BC patients. We hypothesized T-lymphocyte immunoreactivity against a shared antigen expressed in Thy and BC: TPO is a logical candidate and we analyzed its expression in tissues/cells samples.

Methods: TPO mRNA expression was evaluated by Reverse-Transcriptase-PCR and measured by Quantitative-PCR. TPO protein expression was studied by Western-Blot (WB) using mouse monoclonal TPO antibody ab76935. Ex vivo tissues included 8 BC, 8 peri-tumoral breast tissues (PT), 3 pancreatic adenocarcinoma (P), 2 kidney cancers (K), 17 adipose tissues (AD) and Thy as positive control. In vitro study included 3 BC cell-lines (C): MCF-7, T47-D and MDAMB-231.

Results: Known TPO mRNA variants were expressed highly in Thy, 103 times less in AD, 104 times less in BC/PT and at the limit of detection in P, K and C. Furthermore we found many new TPO variant mRNAs in Thy and/or other tissues; in particular one TPO isoform was expressed strongly in BC, PT, AD, C, weakly in Thy and absent in P and K. In WB, TPO protein was found at the expected level (105–110 kDa) in Thy, C and many BC, PT, AD, P, K; the signal was reduced after ab76935 pre-absorption with recombinant TPO (but not lactoperoxidase) fragments, indicating specific binding. Moreover lower molecular weight bands were present in Thy and other tissues: they could represent corresponding proteins of smaller TPO isoforms.

Conclusions: TPO no longer seems to be Thy-specific: mRNAs and proteins for known TPO isoforms are weakly but clearly expressed in BC and other tissues. This could explain at least in part the high frequency and protective role of TPOAb in BC patients, hypothesizing an enhancement of specific T-lymphocyte immunoreactivity. Further studies are needed to investigate tissue specificity, function and immunogenicity of several novel TPO variant mRNAs identified in this study.

P174

THYROID HORMONES ARE REQUIRED FOR NORMAL RESPIRATORY FUNCTION IN WISTAR RATS

Pereira VS[1], *Cagido VR*[1], *Machado MN*[1], *Taveira da Silva R*[1], *Einicker-Lamas M*[1], *Zin WA*[1], *Corrêa da Costa VM*[1]
[1]Universidade Federal do Rio de Janeiro, IBCCF - Instituto de Biofísica Carlos Chagas Filho, Rio de Janeiro, Brazil

Objectives: Hypothyroidism has been associated with respiratory symptoms. We evaluate the impact of pharmacological hypothyroidism on respiratory mechanics.

Methods: Rats were divided in: Control (C, n=7), Hypothyroidism (H, n=11), and Hypothyroidism + T4 Replacement (HR, n=7). H and HR received 0.03% methimazole in drinking water for 21 days, followed by saline or T4 (1µg/100g BW) injections daily during the last 10 days, respectively. Rats were anaesthetised, tracheotomised and mechanical ventilation was started. Static elastance (Est), viscoelastic component of elastance (ΔE), resistive (ΔP1), viscoelastic (ΔP2), and total (ΔPtot) pressures were determined for respiratory system (RS), lung (L), and chest wall (W) compartments. Respiratory mechanics was determined during spontaneous breathing and under mechanical ventilation (RS, lung and chest wall). Total lipid content in broncoalveolar lavage fluid (BALF), residual functional capacity (RFC), gas exchange and lung histology were assessed. Type I lung deiodinase activity (D1) as well as serum T3 and T4 were also measured.

Results: H group showed smaller L, Est (p=0,047), RS and L, ΔE (p=0,021 and p= 0,014), RS and L, ΔP1 (p=0.022 and p= 0,011), L, ΔP2 (p=0.013) and L, ΔPtot (p=0,008) than C or HR rats. Gas exchange and chest wall parameters did not differ among groups. During spontaneous breathing, RS elastic recoil and inspiratory muscle pressure (Pmus,i) were lower in H group than in C (p=0.016 and p= 0.011, respectively). The mean time required for Pmus,i to decay to zero was higher in H group compared to C or HR groups (p< 0.001). H D1 lung activity as well as serum T3 and T4 were lower than in C and normal levels were recovered in HR animals. H rats also showed higher RFC (p=0,0128) and lipid content in BALF (p< 0,0001) and smaller alveolar collapse (p=0.026).

Conclusions: Pharmacological hypothyroidism impairs lung mechanics and hormonal reposition was able to revert it.

PO19 Thyroid Hormone Transport

P175

STRUCTURE-FUNCTION RELATIONS IN MCT8

Braun D[1], Köhrle J[1], Schweizer U[1]
[1]Charité Universitätsmedizin Berlin, Institut für Experimentelle Endokrinologie, Berlin, Germany

Introduction: The 3-dimensional structure of the human monocarboxylate transporter 8 (MCT8), a specific thyroid hormone transporter, is unknown thus far and the mechanisms by which MCT8 interacts and transports T3 into target cells remain unclear. In 2010, a homology model of MCT8 was presented, based on the 3D structure of the bacterial glycerol-3-phosphate transporter. The model exhibits pathogenic missense mutations located in the potential transport channel. Mutations of MCT8 lead to the Allan-Herndon-Dudley syndrome, a severe mental retardation disease.

Aim: Analysis of the T3 receptor identified an Arg-His clamp in a distance of 15Å involved in T3 binding, a motif also found twice in the MCT8 homology model. Mutations of the conserved His and Arg residues in human MCT8 were biochemically investigated concerning surface localization and T3 transport activity.

Methods: His192 and His415 were mutated to Gln, Phe or Ala for determining the importance of hydrogen bonds and hydrophobic interactions for T3 binding. For investigating the role of Arg301, the residue was mutated to Lys and Ala.

Madin-Darby-canine kidney (MDCK1) cells do not exhibit endogenous MCT8 expression and show little background thyroid hormone uptake. Thus, MDCK1 cells were chosen for stable transfection of wild type and mutated MCT8. The stably expressing cells were exposed to ^{125}I-T3 and MCT8-mediated uptake was measured.

Results: Mutations of His192, His415 and Arg301 did not impair protein expression or plasma membrane translocation except Arg301 to Ala mutation which failed to be stably expressed in MDCK1 cells. We found pivotal differences in T3 transport for His415 and Arg301 mutants while mutations of His192 do not play a critical role.

Conclusion: Mutations of the conserved His and Arg residues helped to confirm the MCT8 homology model and identified amino acid residues involved in T3 transport.

P176

THYROID HORMONE TRANSPORTER FAMILIES: DIFFERENCES IN SEQUENCES AND TRAFFICKING SUGGEST DIFFERENT MOLECULAR RECOGNITION MECHANISMS FOR TRANSPORT

Kinne A[1], Schuelein R[1], Krause G[1]
[1]Leibniz-Institut für Molekulare Pharmakologie, Berlin, Germany

Research on Thyroid hormone (TH) transporters is at a crossroads, requiring a transition from protein discovery to identification of details in molecular transport mechanisms.

Along the specific TH transporter MCT8 other transporters also accept TH as secondary substrate e.g. members of the L-type amino acid transporter (LAT) and organic anion transporting polypeptide (OATP) families. They are obviously involved in regulation of distinct level of T2, T3, and T4 in different tissues but molecular details are unclear. Gaining insight into structure function relations of TH transporters will help to understand transport mechanisms for TH in and out of cells.

For the TH specific transporter MCT8 the substrate characterization and first structural insight have been shown by us. Until now it has been assumed that TH transporter proteins are functioning by the same mechanisms since all of them consist of 12 transmembrane segments. However, a sequence alignment of TH transporters expressed at the blood brain barrier revealed that known transport sensitive residues occur as conserved amino acids only within each TH transporter family but not over all considered TH transporters. On the other hand, the coincidence of identified sensitive positions for substrate transport (e.g. at TMH8 in MCT8 and OATP1C1) could at least be a hint for shared molecular transport events. Moreover, variations in TH specificities between considered TH transporters could be explained by differences in molecular recognition mechanisms at the transporters. Furthermore, the trafficking mechanism to the cell surface differs e.g. between MCT8 and LAT transporters. Whereas MCT8 need no escort protein for efficiently cell membrane expression LAT2 forms a heterodimer with CD98 to reach the cell surface. By using Flag tagged Lat2 and His tagged CD98 we could detect both chains in different cell types at the cell membrane which indicates the formation of the heterodimer.

P177

UPTAKE OF IODOTHYRONINES AND 3-IODOTHYRONAMINE BY LIVER CELLS

Ghelardoni S[1], Chiellini G[1], Frascarelli S[1], Marchini M[1], Saba A[1], Zucchi R[1]
[1]Università di Pisa, Pisa, Italy

Objectives: 3,5-diiodothyronine (T2) and 3-iodothyronamine (T1AM) are thyroid hormone derivatives which have been shown to produce significant biological effects. Some of these effects appear to involve the interaction with specific intracellular targets. In the present work we investigated whether T2 and T1AM are taken up by hepatocytes. A comparison with the cellular uptake of thyroxine (T4), 3,5,3'-triiodothyronine (T3) and 3-monoiodothyronine (T1) was also performed.

Methods: Human hepatocellular carcinoma cells (HepG2) were exposed to exogenous T4, T3, T2, T1, or T1AM (1μM each) for 120 min, then the above mentioned substances were assayed in the incubation medium and in cell lysate by HPLC coupled to tandem mass spectrometry. In other experiments, isolated rat liver was perfused with 50 nM T4, T3, T2 or T1AM, and tissue concentration was determined after 60 min.

Results: Table 1 reports overall recovery, medium concentration, and lysate concentration in HepG2 cells (mean±SEM of 3 experiments, except for T1 which was used in a single experiment).

Table 1.

	T4	T3	T2	T1	T1AM
Recovery (%)	79±7	79±13	98±8	98	58±14
Medium (nM)	413±91	651±73	977±80	933	489±121
Lysate (nM)	6860±2744	2700±1189	510±74	1333	1740±577

In the case of T1AM, the experiments were repeated in the presence of the amine oxidase inhibitor iproniazide, and under these conditions recovery averaged 99%, while medium concentration and lysate concentration averaged 681 nM and 7240 nM, respectively.

Perfused liver experiments confirmed tissue uptake of T4, T3, T2 and T1AM, whose concentrations averaged 1513, 853, 419, and 113 pmol/g, respectively.

Conclusions: Both T1AM and T2 enter hepatocytes and are accumulated in intact liver. T1AM catabolism is quicker than iodothyronine catabolism, and is largely due to oxidative deamination.

P178

THYROXINE-BINDING GLOBULIN (TTR), TRANSTHYRETIN (TTR), ALBUMIN (HSA), APOLIPOPROTEINS (APOS) AND OTHER PLASMA CARRIERS OF THYROID HORMONES (TH) SHARE LOCAL AMINO ACID SEQUENCE HOMOLOGY (AASH) THROUGHOUT THE PHYLUM

Benvenga S[1], Guarneri F[2]
[1]Università degli Studi di Messina, Dip. Clinico Sperimentale di Medicina e Farmacologia (sez. di Endocrinologia), Messina, Italy,
[2]Università degli Studi di Messina, Dip. di Medicina Sociale del Territorio, Messina, Italy

Objectives: TH stand out as hormones that are transported in plasma by several proteins with a Ka varying from 10^{-10} to 10^{-5} M^{-1} for T4. Some TH

plasma carriers are expressed in relevant tissues, such as brain, placenta, the yolk sac. Local AASH between TBG, TTR, HSA, apoA-I, A-II, A-IV, B-100, C-I, C-II, C-III, E was reported. This AASH agrees with the position of the corresponding TH binding site, when known, and features the very well conserved 5-residue hydrophobic motif "Y, L/I/M, X, X, V/L/I". Subsequently, AASH was shown for a total of 46 apo sequences (A-I, A-II, A-IV, C-I, C-II, C-III, E) from 15 animal species, and TH binding (Ka for T4 of 10^{-6} M^{-1}) was shown for α1-antitrypsin (α1-AT), α1-chymotrypsin (α1-ACT), anti-thrombin III (AT-III), corticosteroid-binding globulin (CBG), α1-acid glycoprotein (α1-AGP) and sex-hormone binding globulin (SHBG). TBG, α1-AT, α1-ACT, AT-III and CBG are SERPINs.

Methods: Because AASH for these last 6 proteins was untested and because we now know the amino acid sequence of all the above 16 proteins in several species, we tested for AASH a total of 264 protein sequences from terrestrial, aquatic and aerial animals. Particularly, sequences (and animal species) of TBG, TTR and HSA were 7, 33 and 22.

Results: While confirming conservation of the said motif intra-protein and inter-proteins, we found that it is located in the middle of a much larger consensus motif that starts with "E/Q/N/D" and ends with "S/T, X, L/V/I/M". Nonconserved residues may explain different Ka values and inhibition patterns by drugs or other compounds.

Conclusions: Keeping into account that: (i) TH have a multitude of target tissues; (ii) deficiency or mutations in any of these proteins do not have clinical consequences, we conclude that evolution may have dictated the multiplicity of TH plasma carriers with conservation of a core TH binding site for serving crucial functions that can be vicariated if one or more carriers are defective/anomalous.

P179

THE ROLE OF MCT10 IN T3 UPTAKE IN LIVER CELLS

Noort S[1], *van Heerebeek REA*[1], *Kersseboom S*[1], *Mol-van Mullem AAA*[1], *Peeters RP*[1], *Visser TJ*[1]
[1]Erasmus MC, Rotterdam, Netherlands

Transporters are very important for cellular uptake and efflux of thyroid hormone (TH). Several transporters are known to transport TH, including MCT8, MCT10, LAT1, LAT2 and various OATPs. However, it is unknown which are the major TH transporters in specific tissues such as the liver. Previous studies have demonstrated that T4 and T3 are taken up by the liver via different transporters. Although MCT8 is abundantly expressed in liver, hepatic TH uptake is not affected in MCT8 knockout mice. Since the liver is a major tissue for TH metabolism and action we aimed to identify the major hepatic T3 transporter in human liver using HepG2 cells as a model.

We tested HepG2 cells for T3 uptake under a variety of conditions. We also transfected COS1 and JEG3 cells with MCT8 or MCT10 to test the effect of these conditions on T3 uptake by these transporters.

We found that T3 uptake in HepG2 cells was sodium independent and largely saturated at 10 μM T3, characteristics in common with both MCT8 and MCT10. T3 uptake in HepG2 cells was not inhibited by Leu or the L-type ligand BCH, excluding the involvement of LAT1 or LAT2. However, T3 uptake was inhibited by Trp, which also inhibits T3 transport by MCT10 but not by MCT8. T3 uptake in HepG2 cells was inhibited by verapamil, which was also found to inhibit T3 transport by MCT8 and MCT10. Neither T3 uptake in HepG2 cells nor T3 transport by MCT8 and MCT10 were inhibited by typical OATP ligands such as BSP, estrone sulfate and rifampicin.

From these data we conclude that MCT10 is an important transporter for T3 in HepG2 cells and probably also in human liver cells. T4 uptake by HepG2 cells was differentially affected under various conditions, indicating the involvement of other transporter(s).

P180

THYROID HORMONE TRANSPORTERS (MCT8 AND MCT10) ARE REGULATED BY THYROID HORMONES IN LIVER AND PITUITARY IN A RAPID AND TISSUE SPECIFIC MANNER

Pereira GF[1], *Ramos RG*[1], *Império GE*[1], *Faustino LC*[1], *Santiago LA*[1], *Ortiga TM*[1]
[1]Universidade Federal do Rio de Janeiro, Instituto de Biofísica Carlos Chagas Filho, Rio de Janeiro, Brazil

Mct8 and Mct10 are important for TH transportation through plasma membrane. Previous results showed that hypo (PTU) and hyperthyroidism (T3) decreased expression of these transporters. Also we observed, 60 minutes after single T3 injection, an increase of these transporters in the liver.

Objective: Evaluate Mct8 and Mct10 expression in TH responsive tissues, as liver, ventricle and pituitary.

Methods: Adult male mice were used. Hypothyroidism (hypo) was induced by feeding mice a PTU diet for 3 weeks. T3 or T4 (50μg/100gBW) was given for 2 weeks to induce hyperthyroidism (hyperT3 and hyperT4). Also, hypothyroidism was induced (PTU) and a single injection of T3 (HYPOT3), T4 (HYPOT4) or saline was given. Mice were sacrificed after 30, 60, and 360 minutes. Levels of mRNA were analyzed by RT-PCR.

Results: LIVER - Hypo and hyperT3 presented decreased mRMA of Mct8 ($P< 0.05$) and Mct10 ($P< 0.05$), while HyperT4 didn´t affect Mct8 and Mct10 expression. In acute experiments, HypoT4 presented important increases of Mct8m RNA after 30 min (227%, $P< 0.05$) and 60 min (169% $p< 0.05$) compared to control. Surprisingly, HypoT3 did not present any difference of Mct8 expression. However, Mct10 expression was increased in hypoT3 after 60 min (294% vs. saline and 379% vs. Hypo T4, $p< 0,001$). VENTRICULE. No significant differences were seen. PITUITARY MCT10 was not detected in the pituitary. Mct8 expression responded to chronic treatment differently from liver: chronically, T3 decreased Mct8 expression (88% less, $P< 0.05$) while hypothyroidism caused no effect. **Conclusion:** Mct8 and Mct10 were regulated by TH acutely and chronically and this regulation was tissue specific. Our preliminary ventricle result suggests that the expression of Mct8 and Mct10 is protected from TH fluctuations. Pituitary and liver presented an important yet different regulation, probably due to the differences of their contributions to serum levels of TH.

PO20 Goiter and Nodular Disease Clinical 2

P181

IMPAIRED THYROID FUNCTION AND WEIGHT GAIN TWO YEARS AFTER HEMITHYROIDECTOMY FOR BENIGN EUTHYROID GOITER

Toft Kristensen T[1], *Feldthusen A-D*[2], *Jacob L*[3], *Pedersen PL*[4], *Jelstrup S*[5], *Kvetny J*[6]
[1]University of Copenhagen, Department of Otorhinolaryngology, Region Zealand, Slagelse, Denmark, [2]University of Copenhagen, Department of Obstetrics and Gynaecology, Region Zealand, Næstved, Denmark, [3]Department of Clinical Pathology, Region Zealand, Næstved, Denmark, [4]Department of Clinical Biochemistry, Region Zealand, Næstved, Denmark, [5]Department of Otorhinolaryngology, Region Zealand, Slagelse, Denmark, [6]University of Copenhagen, Department of Internal Medicine, Region Zealand, Næstved, Denmark

Background: Weight gain is a well known manifestation of hypothyroidism. After total or subtotal thyroidectomy weight gain has been reported even after normalization of TSH. TSH increases after hemithyroidectomy. It is unknown whether increased TSH within the reference range affects the body weight of hemithyroidectomized patients.

Table for Abstract P181.

	Hemithyroidectomy group (n=28)				Control group (n=47)			
	Median	Lower quartile	Upper quartile	p-value (Wilcoxon signed-rank test)	Median	Lower quartile	Upper quartile	p-value (Wilcoxon signed-rank test)
TSH at baseline (mUI/L)	1.23	0.91	1.59		1.70	1.10	2.20	
TSH after two years (mIU/L)	2.08	1.48	2.89	<0.01	1.60	1.10	1.90	0.12
Weight at baseline (kg)	75.0	63.50	85.0		69.30	62.15	81.35	
Weight after two years (kg)	77.30	64.10	89.0	<0.01	69.30	61.60	83.30	0.69

Objective: To examine if TSH is increased and if patients have gained weight two years after hemithyroidectomy for benign euthyroid goiter.

Method: We retrospectively examined TSH and body weight of 28 patients (6 men, 22 women, median age 52 years, median body mass index 26.05) two years after hemithyroidectomy for benign euthyroid goiter. Baseline values of TSH, height and body weight (self-reported) were found in patients' charts. Two years postoperatively (median 25.2 months), patients were re-examined in the outpatient clinic. The patients reported current medication and body weight, and a venous blood sample was drawn and analyzed for TSH (mlU/L). Results were compared to the thyroid function and body weight of 47 matched (sex, age, body mass index, smoking status and anti-TPO positivity) healthy controls (9 men, 38 women), measured at baseline and after almost two years (median 20.3 months).

Results: Table 1 demonstrates a statistically significant increase in TSH within the reference range ($p< 0.01$) two years after hemithyroidectomy. Hemithyroidectomized patients have gained weight significantly ($p< 0.01$), compared to matched healthy controls.

Conclusion: Two years after hemithyroidectomy for benign euthyroid goiter, weight gain seems to be a consequence of a permanently impaired thyroid function.

P182

CHANGES IN THYROID VOLUME AND STRUCTURE AFTER THE DANISH IODINE FORTIFICATION PROGRAM ARE DEPENDENT ON AGE AND REGION

Krejbjerg A[1], *Bjergved L*[2,3], *Jørgensen T*[2], *Perrild H*[3], *Pedersen I*[1], *Rasmussen L*[4], *Knudsen N*[3], *Laurberg P*[1]

[1]Aalborg Hospital, Endocrinology, Aalborg, Denmark, [2]Research Centre for Prevention and Health, The Capital Region of Denmark, Glostrup, Denmark, [3]Department of Endocrinology and Gastroenterology, Bispebjerg University Hospital, Copenhagen, Denmark, [4]Department of Nutrition, National Food Institute, Technical University of Denmark, Søborg, Denmark

Objectives: To evaluate individual changes in thyroid volume and structure after iodine fortification in two regions with respectively mild (Copenhagen) and moderate (Aalborg) iodine deficiency at baseline.

Methods: In a longitudinal population-based study (DANTHYR) we examined 2,465 adults before (1997) and after (2008) the Danish iodine fortification of salt (2000). Ultrasonography was performed by the same sonographers using the same equipment, after controlling performances. Participants treated for thyroid disease were excluded from analyses.

Results: Median thyroid volume in participants < 30 years of age increased in both areas (Copenhagen: 9.9–11.7mL, $p< 0.001$, Aalborg: 11.2–12.0mL, $p< 0.001$), but was unaltered in > 40 years in Copenhagen (12.7–12.8mL, $p=0.28$) and decreased in Aalborg (14.3–12.8mL, $p< 0.001$). Prevalences of having a solitary thyroid nodule were not different before/after (Copenhagen 5.6/4.4%, Aalborg 6.6/6.3%). Multinodularity had not changed in Copenhagen (10.8/13.2, $p=0.09$) but had increased in Aalborg (9.2/15.5, $p< 0.001$).

Multivariate regression models showed that baseline multinodularity was associated with an increase (>20%) in thyroid volume ($P=0.004$) while higher age and baseline thyroid enlargement were associated with individual decrease ($P< 0.001$).

36.3% of baseline solitary nodules had developed into multinodular structure (more common with higher age, in females and with goiter at baseline), while 30% had disappeared. 22.5% of baseline multinodularity had disappeared (more common with higher age and in Copenhagen) and 6.8% now had a solitary nodule. 3% of subjects without nodules had developed a solitary nodule (higher age, Aalborg, increase in thyroid volume during follow-up), and 6% had developed multinodularity (higher age, women, goiter at baseline, increase in thyroid volume during follow-up).

Conclusions: At 11 years follow-up individual changes in thyroid volume and structure were very common, with overall stable prevalence of nodules in Copenhagen but a further increase in thyroid multinodularity in the area with the lowest iodine intake (Aalborg).

P183

USEFULNESS OF ULTRASOUND ELASTOSONOGRAPHY IN PRIMARY HYPERPARATHYROIDISM

Saponaro F[1], *Loiacono V*[1], *Di Rosa G*[1], *Scutari M*[1], *Chiavistelli S*[1], *Cianferotti L*[1], *Marcocci C*[1], *Vitti P*[1], *Cetani F*[1], *Rago T*[1]

[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

Preoperative localization of parathyroid lesions is very important, particularly when minimally invasive procedures is possible to be applied. Preoperative imaging generally used B-mode conventional ultrasonography (CUS) and TC99-MIBI scintigraphy, even if they can lead to variable false positive in localization of parathyroid lesions. Ultrasound elastosonography (USE) is a new diagnostic technique that assesses hardness/elasticity of tissue that has been recently applied in the the presurgical evaluation of thyroid nodule.

The aim of this study was to investigate the usefulness of USE in the evaluation of parathyroid lesions.

Eightyone consecutive patients (13 males and 68 females) with primary hyperparathyroidism (PHPT) were prospectively enrolled to this study. In all patients we performed either CUS and USE.

Parathyroid stiffness/elasticity was classified using a USE score modified by Rago et al: score 1 high elasticity, score 2 intermediate elasticity, score 3 low elasticity.

We report the results of 43/81 patients (M=, F=) underwent parathyroidectomy (PTX). Histological diagnosis was correlated with USE score.

At histology 36 had a diagnosis of adenoma (29 chief cells adenoma and 7 oxyphyl cells adenoma), 6 of hyperplasia with prevalence of chief cells and 1 of atypical adenoma (which is a lesion with histological features worrisome of carcinoma, without clinical evidence of malignancy).

At USE score 1 was found in 32 patients with adenoma, in 5 patients with hyperplasia and in the atypical adenoma; score 2 was found in 2 adenomas and in one with hyperplasia; score 3 was found in 2 cases with adenoma.

In conclusion, a score 1 at USE characterizes the parathyroid lesions either adenoma, hyperplasia and atypical adenoma. A larger series of patients with PHPT is necessary to establish the real usefulness of USE in the diagnostic evaluation of parathyroid lesion.

P184

MICRORNA EXPRESSION PROFILE HELPS TO DISTINGUISH BENIGN NODULES FROM PAPILLARY THYROID CARCINOMAS STARTING FROM CELLS OF FINE NEEDLE ASPIRATION

Ferrarini E[1], *Patrizia A*[1], *Rago T*[1], *De Marco G*[1], *Dimida A*[1], *Molinaro A*[1], *Niccolai F*[1], *Di Coscio G*[1], *Pinchera A*[1], *Vitti P*[1], *Tonacchera M*[1]
[1]Università di Pisa, Pisa, Italy

Objective: MicroRNAs (miRNAs) are small endogenous non-coding RNAs that pair with target messengers regulating gene expression. Changes in miRNA levels occur in human cancers, including thyroid cancer. Fine needle aspiration (FNA) with cytologic evaluation is the most reliable tool for malignancy prediction in thyroid nodules, but cytologic diagnosis remains undetermined for 20% of nodules. In this study we evaluated the expression of 7 miRNAs to distinguish benign and malignant thyroid nodules.

Patients and methods: The prospective study included 141 thyroid samples obtained by FNA of nodules from 138 patients (56 benign, 43 malignant, i.e. papillary thyroid carcinoma, and 53 nodules with undetermined cytology). miRNA expression was evaluated by quantitative RT-PCR and statistical analysis of data was performed. Genetic analysis of codon 600 of BRAF gene was performed on cDNA from all samples.

Results: Using data mining techniques we obtained a criterion able to classify a nodule as benign or malignant on the basis of miRNA expression values. The decision model based on the expression of miR-146b, miR-155 and miR-221 was valid for 86/88 nodules with determined cytology (97.73%). To evaluate how much general is the criterion in correctly classifying a nodule not present in our study group, we adopted cross-validation techniques, obtaining a reliability of 78.41%. The obtained malignant/benign prediction was also valid for 31/53 nodules with undetermined cytology with 16 false positive and 6 false negative predictions. The heterozygous mutated form V600E of BRAF gene was demonstrated in 19/43 (44%) malignant thyroid nodules, in 0/56 benign thyroid nodules and in only 1/53 (1.8%) undetermined thyroid nodules.

Conclusions: The expression profiles of three miRNAs allowed to distinguish benign from malignant thyroid lesions starting from FNA, and may improve the accuracy of cytological analysis. This assay showed limitations when applied to discriminate thyroid nodules with undetermined cytology.

P185

FREQUENCY OF POLYMORPHISMS IN THE VEGF, VEGFR AND HIF GENES IN NORMAL SUBJECTS AND PATIENTS WITH NODULAR GOITER FROM AN AREA WITH MILD IODINE DEFICIENCY

Niccolai F[1], *Molinaro A*[1], *De Marco G*[1], *Agretti P*[1], *Di Cosmo C*[1], *Piaggi P*[2], *Pinchera A*[1], *Vitti P*[1], *Bocci G*[3], *Tonacchera M*[1]
[1]University of Pisa, School of Medicine, Endocrinology and Metabolism, Pisa, Italy, [2]University of Pisa, Energy and Systems Engineering, Pisa, Italy, [3]University of Pisa, Internal Medicine - Division of Pharmacology, Pisa, Italy

Introduction: Nodular goiter in patients from areas of iodine deficiency is due to the growth of follicular and endothelial cells. Numerous factors modulate angiogenesis: a potential role of different vascular-related growth factors in the pathogenesis of the thyroid nodular goiter have been proposed. The aim of our study was to examine the relationship of known polymorphisms in the VEGF, VEGF receptor (VEGFR) and HIF (hypoxia inducible factor) and the risk of nodular goiter development.

Patients and methods: We selected 116 normal subjects (41 males, mean age 48.1 years; 75 females, mean age 51 years; subjects without any thyroid disease) and 108 subjects with nodular goiter (41 males, mean age 49.6 years; 67 females, mean age 50.3 years; subjects with goiter and at least one thyroid nodule of > 1 cm of maximum size and in absence of signs of autoimmunity) from a homogeneous population living in a mild iodine deficiency geographic area. Genomic DNA was extracted from blood with standard methods. Genotyping was carried out by the TaqMan technology. We studied the following polymorphisms: VEGF+936C/T, VEGFR-604A/G and HIF-1ALFA C/T. As statistical test we used the Chi-squared test.

Results: In normal subjects the frequency of the polymorphisms was: VEGF+936 CC 78.4%, CT 19.8%, TT 1.7%; VEGFR-604 AG 44%, GG 25.8%, AA 30.2%; HIF-1ALFA CT 97.4%, TT 2.6%. In patients with nodular goiter the frequency was: VEGF+936 CC 75%, CT 21.3%, TT 3.7%; VEGFR-604 AG 55.6%, GG 16.7%, AA 27.8%; HIF-1ALFA CT 99.1%, TT 0.9%. The frequency of the studied polymorphisms was not statistically different between normal subjects and patients with nodular goiter.

Conclusions: Our study did not prove the role of VEGF, its receptor and other vascular growth factors in the development of the nodular goiter in patients coming from an area with mild iodine deficiency.

P186

CERVICAL HEMATOMA AFTER THYROID SURGERY: IS AMBULATORY SURGERY SAFE?

Ioan ME[1], *Gaillat C*[1], *Royer C*[1], *Tresallet C*[2], *Menegaux F*[2]
[1]Pitié Salpetrière University Hospital, Department of Anesthesia and Intensive Care, Paris, France, [2]Pitié Salpetrière University Hospital, Department of General, Digestive and Endocrine Surgery, Paris, France

Background: Cervical hematoma (CH) after thyroid surgery is a rare (1%) but potentially life threatening complication in case of compressive cervical hematoma (CCH). Our purpose was to evaluate in a retrospective observational study the incidence of cervical hematoma and the precise moment of occurrence in order to determine if the ambulatory thyroid surgery is safe.

Methods: From January 2002 to December 2011, 9908 patients (department data base) underwent thyroid surgery in the Department of General, Digestive and Endocrine Surgery of the Pitié Salpetrière University Hospital and were postoperatively admitted for 2 hours in post anesthesia care unit (PACU) before being discharged to conventional care unit. In 83 patients (0,83%) CH occurred and required surgical treatment (5 - 12 cases/year). Their medical files were systematically reviewed.

Results: 51 (62%) out of 83 CH were CCH and 32 (38%) non-compressive hematomas (NCH). In 24 cases CH occurred in the operating room. During the standard 2 hours surveillance in PACU, 15 CH occurred: 4 CH in the first hour and 11 CH in the 2nd hour. 45 hematomas (59%) developed after discharge from PACU: 16 cases from 2 to 6 hours after surgery, 10 cases from 6 to 24 hours after surgery, and 19 cases (23%) later than 24 hours after surgery, 5 cases during their stay in hospital and 14 cases after discharge from the hospital. The khi-2 test identified male sex, anticoagulant treatment and hypertension as risks factors for CH. In patients with CH only 15 had long-term anticoagulant treatment.

Conclusion: CH after thyroid surgery occurred in the present study with a random distribution. However, 23% of CH developed 24 hours after surgery and high-risk population is to be defined. Even if CH is a rare complication, safety of ambulatory thyroid surgery is not granted.

PO21 Case Reports 2

P187

DE QUERVAIN'S THYROIDITIS: CLINICS PLUS MINDS THERE ARE RESULTS

Antonenko M[1], Volkova N[1]
[1]Rostov State Medical University, Rostov on Don, Russian Federation

Objective: de Quervain's thyroiditis in its classic form is a simple to diagnose. The summation of a painful, tender thyroid with an elevated erythrocyte sedimentation rate (ESR), low radioiodine uptake, elevated serum thyroid hormone, symptoms improvement after glucocorticoid administration is diagnostic. However, omitting any clinical sign and previous awareness of the diagnosis could cause incorrect treatment.

Materials: woman 47 y.o. presented with elevated ESR, fatigue, diffuse neck discomfort. 8 months earlier she had been diagnosed with de Quervain's thyroiditis. The diagnosis was based on severe neck pain, elevated ESR, suppressed TSH levels, low radioiodine uptake and dramatic symptoms improvement after glucocorticoid administration. 3 months later she had recurrent episode. Diagnosis of the disease relapse was made on the same criteria. Steroids were prescribed in a higher doses. 3 months after, at the end of regimen tapering she felt worse. The thyroid gland became painful, ESR increased. This condition was accounted as recrudescence of the disease. The glucocorticoid doses were returned to original. But symptoms resolution didn't happen. At the moment of the presentation she received 5mg of prednisolone. On physical examination the patient had cushingoid habitus, the thyroid gland was tender and slightly enlarged in both lobes. There were no neck redness, acute pain during palpation. Thyroid function was normal. ESR was within 30–40 mm/h. Data of the thyroid ultrasound was consistent with lymphoma, subacute thyroiditis and Hashimoto´s thyroiditis. The fine needle thyroid aspiration showed the latter. Thus diagnosis of relapse of de Quervain's thyroiditis was mistaken, and glucocorticoids were discontinued. The reason of elevated ESR was active bronchiectatic disease. The antibiotic reponse proved it. Later the patient was diagnosed with endogenous depression.

Conclusion: The diagnosis of this disease is based primarily upon clinical manifestations. But its presence doesn't mean one cause. So the critical analysis is always needed.

P188

SURGICAL TREATMENT OF HUGE STERNAL METASTASES FROM PAPILLARY THYROID CARCINOMA: REPORT OF A CASES

Abdelrahman TEF[1], Afifi TM[2], Hassanein KM[3]
[1]Sohag University, Head and Neck Surgery Unit, Department of Surgery, Sohag, Egypt, [2]Sohag University, Cardiothoracic Surgery Department, Sohag, Egypt, [3]Sohag University, Maxillofacial, Head and Neck Surgery, Sohag, Egypt

Radioiodine therapy is currently the treatment of choice for metastasizing differentiated thyroid cancer (DTC); however, skeletal metastases are resistant to this form of therapy. The surgical removal of distant metastases from DTC offers the best chance for cure and improved quality of life. This report describes a case of aggressive sternal metastases from papillary thyroid carcinoma that were managed successfully by surgery involving total thyroidectomy followed by excision of the mass including the sternum ended by reconstruction of the chest wall with Marlex mesh. the patient recovered uneventfully. Sternal resection with Marlex mesh reconstruction of the chest wall defect proved a simple and effective method for managing sternal metastasis. Thus, the surgical resection of distant bony metastases in patients with DTC is recommended as it can be curative, as it allow for more effective radioiodine treatment.

P189

A CASE OF HYPERTHYROIDISM DUE TO FUNCTIONING BONE METASTASIS OF FOLLICULAR THYROID CARCINOMA

Synak R[1], Panholzer PJ[1], Jordan S[1], Pirich C[2]
[1]LKH Voecklabruck, Voecklabruck, Austria, [2]Paracelsus University, Salzburg, Austria

Thyrotoxicosis due to functioning metastases in differentiated thyroid cancer is exceedingly rare.

A 70-year old woman showed a multinodular goiter as well as hyperthyroidism. Ultrasound - guided fine needle aspiration biopsy was performed and resulted in strong suspicion of malignancy. A total thyroidectomy was performed in June 2009. The histopathological examination resulted in a "struma colloides nodosa", no evidence of malignancy. Post surgical examination showed a small thyroid remnant only on the left side. Tc-99m pertechnetate scintigraphy showed no visualization of thyroid tissue, however hyperthyroidism was diagnosed under levothyroxine treatment. Therefore, levothyroxine treatment was reduced in 25 µg steps until treatment came to an end. Surprisingly, hyperthyroidism still existed. The tumor marker serum thyroglobulin (Tg) concentrations were strongly elevated to >300 ng/ml. A low dose iodine -131 wholebody scintigraphy was performed and showed a positive lesion in os sacrum.

An additionally performed F18 FDG PET-CT showed a single bone lesion in the sacrum. Adjacent a computed tomography - guided needle biopsy in the osteolytic bone lesion in the sacrum was performed with histological finding of a metastasis of follicular thyroid cancer in the os sacrum.

A high dose radioiodine therapy using recombinant human thyroid-stimulating hormone (rhTSH) was performed instead of high risk surgery. The post-treatment iodine-131 whole-body scintigraphy showed positive findings in the thyroidremnant on the left cervical side and a positive uptake in the os sacrum massa lateralis left.

Anew TSH-suppressive levothyroxine treatment was successfully started. Thyroglobulin was decreased to Tg 6,1 ng/ml.

In our opinion, the noninvasive radioiodine therapy is in such cases superior to the surgical therapy. Additionally, the radioiodine therapy is a simple, safe, effective, and, economic procedure for final treatment.

P190

A RARE CASE OF AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 3 INCLUDING DIABETES TYPE 1, GRAVES´ DISEASE AND SCLERODERMA BUSCHKE

Lozanov BS[1], Lozanov LB[2], Gortcheva D[3], Kadurina M[4], Tzankov N[5]
[1]Clinical Centre of Endocrinology, Tokuda Hospital, Sofia, Bulgaria, [2]Tokuda Hospital, Dept. Endocrinol, Sofia, Bulgaria, [3]Tokuda Hospital, Sofia, Bulgaria, [4]Military Medical Academy, Dept. Dermatology, Sofia, Bulgaria, [5]Bulgarian Academy of Sciences, Sofia, Bulgaria

An woman aging 41 y. with a history of diabetes type 1 diagnosed before 17 y., subtotale thyroidectomy for Graves´ disease 19 y. ago and postoperative hypothyroidism has been admitted in the Hospital for a reason of diabetic nephropathy and renal insuficiency gr. 2. The clinical condition was worsening 3 months ago presenting ad addmission by generalized edema, high grade proteinuria and hypoalbuminaemia, ascites, bilateral hydrothorax and poor glycemic control with insulin analogues applied in intensive schemes. Hypothyroidism has been supplemented many years by 150 mcg/d levothyroxin but recently the same dose appeared insufficient. The serum TSH ad addmission was found 71 mIU/l, FT4 - 8,8 pmol/l.

The therapy applied included high dose furosemid (240 mg/d), spironolacton, human albumin infusions, betablockers, ACE inhibitors, insulin analogues (90 U/d) and the dose of LT4 enhanced up to 300 mcg/d in combination with T3 50 mc/d. We observed a remarkable improvement of the clinical state and lab. data within 2 weeks: TSH fall up to 3,1 miU/l and ft4 incresed up to 13, 9 pmol/l. Nevertheless the skin remained too tight and firm in palpation especially in the upper trunk, nack and extremities, It was suspected an concomitant disorder as Scleredema Buschke. This diagnosis was confirmed by skin biopsy which showed histological data for thickening, hyaline change of collagen and defragmentatin of elastic fibers in the deep and the middle layers of germa with accumulation of glucosaminoglycans= Scleroderma Buschke

describing in beginning of 20-th centure is proved as rare disorder of connective tissue inherited dominantly with incomplete penetrance. In 50% of cases described it was associated with diabetes type 1 depending on the duration of diabetes and diabetic microangiopathy. In our opinion It might be a component of autoimmune polyglandular syndrome type 1.

P191

UNUSUAL SHORT-TERM COMPLETE RESPONSE TO TWO REGIMENS OF CYTOTOXIC CHEMOTHERAPY IN A PATIENT WITH POORLY DIFFERENTIATED THYROID CARCINOMA

Crouzeix G[1,2], Michels J-J[3], Sevin E[4], Aide N[1], Bardet S[1], for the Tuthyref Network
[1]Centre Francois Baclesse, Nuclear Medicine and Thyroid Unit, CAEN, France, [2]Centre Hospitalo-Universitaire, Department of Endocrinology, Caen, France, [3]Centre Francois Baclesse, Department of Pathology, CAEN, France, [4]Centre Francois Baclesse, Department of Oncology, CAEN, France

Objectives: Treatment modalities for progressive iodine-refractory poorly differentiated thyroid carcinomas (PDTC) are not yet well defined. Molecular targeted therapy with multikinase inhibitors has recently shown promising results, and cytotoxic chemotherapy is generally considered of low efficacy. We report the case of a 57 yr-old woman with an advanced iodine-refractory PDTC who was treated between October 2006 and March 2011 with two different regimens of cytotoxic chemotherapy and three lines of multikinase inhibitors. The management of this patient with mediastinal nodal involvement and lung metastases was discussed several times at the French TUTHYREF web-conference.

Methods: Efficacy and adverse effects of the consecutive treatment modalities, i.e. vandetanib, doxorubicin-cisplatin combination, sorafenib, paclitaxel-carboplatin combination and sunitinib, are reported.

Results: The patient presented a complete tumor response to doxorubicin-cisplatin (10 months) and to paclitaxel-carboplatin combinations (5 months) according to RECIST and to PERCIST criteria, each time with a dramatic decrease close to nil of serum thyroglobulin level. Asthenia (grade 1), nausea (grade 1), alopecia (grade 3), and anemia (grade 1) were the main side-effects for doxorubicin-cisplatin combination. Cardiac function remained normal, and there were no infectious complications. Paclitaxel-carboplatin combination was stopped for neurotoxicity (grade 2). Conversely, she had no or limited response to kinase inhibitors, i.e. progression after 3 months of vandetanib treatment, partial response at 2 months and then progression at 4 months of sorafenib, and stable disease for 8-months with sunitinib treatment. The main adverse effects of these drugs were fatigue, weight-loss, digestive and skin toxicity, which were limited to grade 1 or 2. She died in March 2011 with pleural effusion.

Conclusions: When tumor progresses with kinase inhibitors, cytotoxic chemotherapy may be an alternative in selected cases of advanced iodine-refractory PDTC. For those rare cases, clinical management should benefit from multidisciplinary team through specialized networks.

P192

PAPILLARY THYROID CARCINOMA IN IDENTICAL TWINS

Chang H-S[1], Lee YS[1], Kim B-W[1], Park CS[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Korea, Republic of

Although most cases of follicular-derived thyroid neoplasms are sporadic, familial forms have been reported, comprising approximately 5% of thyroid cancers. Familial non-medullary thyroid cancer (FNMTC) is defined by the presence of well-differentiated thyroid cancer of follicular cell origin in two or more first-degree relatives, in the absence of other predisposing hereditary or environmental causes. FNMTC typically has an autosomal dominant pattern of inheritance with incomplete penetrance, but the susceptibility genes for FNMTC, such as the germline RET mutations for hereditary medullary thyroid cancer, has not yet been identified. Non-medullary thyroid cancer in monozygotic twins has been reported firstly in 1955 by Robinson and Orr, but these cases were rarely reported. We experienced four cases of well-differentiated thyroid cancer in identical twins.

P193

ONCE AGAIN – AMIODARONE-INDUCED THYROTOXICOSIS

Luchina EI[1], Lukashova ME[1], Meleshkevich TA[1]
[1]"Central Clinical Hospital #2 n.a. N.A. Semashko Public Corporation "Russian Railways", Endocrinology, Moscow, Russian Federation

Patient A., caucasian male 53 yr old was admitted to the cardiology department with paroxysmal atrial fibrillation. Anamnesis: over the past 15 years the patient suffered from the paroxysmal atrial fibrillation and durring the last 5 yr he had been receiving amiodarone 200 mg daily as an antiarrhythmic drug. Since the time of drug administration, annual monitoring: ultrasound (US) of the thyroid gland and thyroid status - results were normal. Examination revealed thyrotoxicosis (TSH - 0,005 mkME / ml), with the enlargement of the thyroid gland (49 ml). The patient was administered thyrostatics (Thiamazole), glucocorticoids im (cause of acute erosive gastritis) and sotalol hydrochloride in adequate doses. Within two weeks normalization of fT3 - 7, 83 pmol/l, and decrease of fT4 up to 36, 9 pmol/l were achived. The patient was then transferred to the oral glucocorticoids therapy after gastric erosions were healed. Despite initial treatment two attacks of atrial fibrillation occurred. Subsequent laboratory tests revealed elevation of fT3 - 17,78 and fT4 - 60,62. The dose of the thyrostatics and glucocorticoids was increased to the maximum tolerated, still no effect. Taking into account all the data, it was decided to hold the pulse therapy - metipred 1000 mg i/v № 3. After achieving positive dynamics (normalization of fT3, reducing of fT4), thyroidectomy was performed and hormone replacement therapy with L-thyroxine had been appointed. Thus, there was a marked resistance to thyreostatics and glucocorticoids in the presence of severe amiodarone-induced thyrotoxicosis. Candidates for receiving iodinated antiarrhythmic drugs, require more vigilant monitoring including TPO Ab and control of thyroid status during the reception of these drugs.

P194

PREOPERATIVE SERUM THYROGLOBULIN AND OTHER SUGGESTED CRITERIA MAY NOT BE VALID INDEPENDENT PREDICTORS OF MALIGNANCY IN THYROID FOLLICULAR NEOPLASMS

Bellabarba D[1], Langlois M-F[1]
[1]Faculté de Médecine, Université de Sherbrooke, Endocrinologie, Sherbrooke, Canada

Objective: Although FNA (Fine needle aspiration) is considered the main technique for the assessment of thyroid nodule, we know that it does not allow a clear distinction between a benign and a malignant follicular lesion. Several preoperative criteria have been suggested to increase the suspicion of malignancy in these cases such as age, gender, solitary nodule, size of the lesion, and thyroglobulin (Tg) levels. The latter, although controversial, has been supported by a recent publication. We report a case in which all the above mentioned criteria of suspicion were present, but were not confirmed by the final diagnosis.

Results: A 55 year-old male was referred to our thyroid clinic for a large left thyroid nodule detected during a medical examination. Patient was asymptomatic except for a slight coarse voice. The left thyroid nodule was easily palpable. On the thyroid ultrasound, it measured 4.6 x 4.4 x 2.9 cm, was hyperechoic, with abundant internal vascularisation. No microcalcifications were observed and no other nodule or lymph nodes were detected. Thyroid function tests were normal, but TG was 13,485 mg/l with negative anti-Tg antibodies. FNA indicated a follicular lesion with atypia of undetermined significance. Patient underwent total thyroidectomy and the final pathological diagnosis was that of a microfollicular adenoma of the same dimensions seen at the ultrasound, with a fine, not infiltrated, capsule.

Conclusions: Few studies have examined the importance of Tg as an independent predictive factor of malignancy in follicular neoplasm and their results have been contradictory. We also know that the two major professional thyroid associations do not recommend preoperative Tg as a specific predictor of malignancy. In our case we did the test to complete all the criteria of malig-

nancy already present. However, the final diagnosis indicating a benign lesion, infirmed all such criteria including the high titer of Tg.

P195

RADIOIODINE UPTAKE IN ABDOMINAL DERMOID CYST IN A PATIENT WITH DIFFERENTIATED THYROID CANCER (DTC)

Ruggeri RM[1], Giovinazzo S[1], Cucinotta M[2], Quartuccio N[2], Sindoni A[2], Baldari S[2], Campennì A[2]
[1]Endocrinology Unit, University of Messina, Clinical-experimental Department of Medicine and Pharmacology,, Messina, Italy, [2]Unit of Nuclear Medicine, University of Messina, Department of Radiological Sciences, Messina, Italy

Objective: Post-therapy ^{131}I whole body scan (WBS) is a sensitive procedure for diagnosing metastases from DTC. Nevertheless, a wide spectrum of potentially misleading readings has been reported. We describe a case of ^{131}I accumulation in abdominal dermoid cyst.

Case report: A 63-yr-old woman underwent near-total thyroidectomy for a large multi-nodular goiter, which proved to be a follicular carcinoma at histology. After conventional L-T4 withdrawal, the patient underwent: (a) Radioiodine Thyroid Uptake (RTU) measured 24 hours after oral administration of ^{131}I tracer activity (1.8 MBq); (b) RadioIodine Therapy (RIT) with ablative activity (3700 MBq); (c) post-dose WBS performed five days after RIT. RTU was 11%. Post-dose WBS showed thyroid remnant, lymph-nodes metastases in the mediastinum and an area of radioiodine uptake in abdomen. At the time of WBS, serum TSH was 39.5 IU/l and serum Tg was 546 ng/ml, respectively. In the absence of TgAb, Tg levels were consistent with the presence of metastases. Magnetic Resonance (MR) revealed an inhomogeneus mass at the level of the inferior abdomen. Our patient was unaware of this lesion and was asymptomatic. Patient underwent a surgical exploration with complete excision of the mass, and pathological examination was conclusive for dermoid cyst. Some months later, patient underwent a second RIT (5550 MBq) after L-T4 withdrawal. Post-dose WBS confirmed lymph-nodes metastases in the mediastinum, but did not revealed any radioiodione uptake in abdomen. At the time of the second RIT, serum TSH and Tg were 112 UI/ml and 242 ng/ml, respectively. TgAb were negative.

Conclusion: This is the first report of ^{131}I uptake in a dermoid cyst. Dermoids (often clinically silent) are not unique to a single anatomic location and may occur intra-cranially or intra-abdominally. Due to its non-negligible frequency, this malformation should be taken into account in DTC patients as a potentially pitfall at ^{131}I-WBS.

P196

NEW ONSET GRAVES' DISEASE DEVELOPED AFTER ABOUT 25 YEARS IN A PATIENT WITH SHEEHAN'S SYNDROME

Ko SH[1], Kim MH[1], Cha BY[1]
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Korea, Republic of

Background: Thyrotoxicosis occurring after hypopituitarism is very rare but not mutually exclusive. In this condition, a life-threatening adrenal crisis can occur because of increasing the turnover of cortisol. Thyrotoxicosis is a common disorder, especially in woman. Graves' disease (autoimmune hyperthyroidism) is the most common cause.

Aim: We describe that a 70-year-old woman with Graves' disease developed about 25 years after the documentation of hypopituitarism.

Case presentation: In May 2010, the patient presented to out-patient endocrinology clinic for her thyroid function. She was treated with L-thyroxine 50 µg/day and prednisolone 5 mg/day because of Sheehan's syndrome since the early 40's. At the age of 35, she suffered a massive uterine bleeding, followed by failure of lactation, amenorrhea and loss of axillary and pubic hair. The result of thyroid function test surprisingly showed increased FT4 levels: 6.14 ng/dL (n.v. 0.93~1.7) and T3 levels: 5.77 ng/mL (n.v.0.6–1.81) and suppressed TSH levels: < 0.01 µIU/ml (n.v. 0.35–5.50). She had no thyrotoxicosis clinically, no goiter and no evidence of overmedication. L-thyroxine was stopped and oral carbimazole was administrated. After 1 week, Free T4 decreased to 2.83ng/dL. She was found to have increased titer of antithyroperoxidase (anti-TPO), anti-TSH receptor (anti-TSHR) antibodies and TSHR-simulating immunoglobulin (TSI) [116.2 IU/L (n.v. < 60), +51 IU/L (n.v. -15~+15) and 250% (n.v. < 140%), respectively]. ^{99m}Tc-pertechnetate thyroid scan revealed homogenous thyroid uptake with suppressed back-ground activity. Fortunately, adrenal insufficiency was not developed.

Conclusion: Physicians have to keep in mind that thyrotoxicosis can occur at any time among patients with hypopituitarism.

P197

THYREOGLOBULIN AND CALCITONIN POSITIVITY AT FNA OF HURTHLE CELL CARCINOMA: A CASE REPORT

Altieri B[1], Capozzi A[1], Di Pizio L[1], Schirò T[1], Sun VA[1], Sorice GP[1], Fabiano MC[1], Salomone E[1], Pontecorvi A[1], Della Casa S[1]
[1]Università Cattolica del Sacro Cuore, UOC di Endocrinologia e Malattie del Metabolismo, Roma, Italy

Objective: Hurthle cell carcinoma (HCC) is a rare variant of follicular thyroid carcinoma. It represents less than 5% of all differentiated thyroid cancers and may have a benign course or become an aggressive metastatic carcinoma. We report the case of a patient affected by HCC presenting an unusual double positivity for calcitonin and thyroglobulin at first fine needle aspiration (FNA) cytology.

Methods and results: Our patient was 47-years-old and presents a progressively enlarging mass of 72mm in the right side of the neck causing difficulty in breathing. FNA showed a follicular cell pattern, nuclear pleomorphism and positive thyroglobulin and calcitonin stains. Serum calcitonin was normal (< 5pg/ml). After total thyroidectomy, histopathological examination revealed HCC. Therefore he received 131-I therapy (85 mCi) and thyrotropin suppressive therapy with levotiroxine was prescribed. He referred to us 8 years later, without follow-up controls, with a high serum thyroglobulin (569 ng/ml) and with a chest computed tomography (CT) showing several metastatic lung lesions and mediastinum lymph nodes. Histology of the lung lesions revealed metastatic HCC with positive thyroglobulin, TTF1 and galectin-3 stains. 131-I whole-body scans (WBS) was negative while Indium-111-octreotide scintigraphy (Octreoscan) confirmed lung metastases. Our patient was treated with 90Y-DOTATOC (10915 MBq) but he didn't report benefits and after 3 months, CT displayed a tumor progression. Therapy with 120mg Lanreotide was prescribed but patient died after eight months.

Conclusions: Nowadays, this is the first case of HCC presenting positivity for thyroglobulin and also calcitonin at FNA, an unusual considerable aspect which may be misleading for the initial diagnosis. Besides, since HCC metastasis often express somatostatin receptors, we confirm Octreoscan may be a promising tool for diagnosis of HCC's metastases with a negative 131-I WBS, especially when PET is not available Therefore, we need more studies to demonstrate significant benefits of treatment with somatostatin analogues.

P198

LONG-TERM FOLLOW-UP OF A SIMULTANEOUS MEDULLARY AND PAPILLARY THYROID MICROCRACINOMA: CASE REPORT

Nogueira C[1,2], Souto SB[1,2], Vinha E[1], Carvalho DM[1,2]
[1]Centro Hospitalar São João, Endocrinology, Diabetes and Metabolism, Porto, Portugal, [2]Faculty of Medicine of the University of Porto, Porto, Portugal

Introduction: The simultaneous occurrence of medullary (MTC) and papillary thyroid carcinoma (PTC) is very rare. These tumors have different cell and genetic origin and different histopathological features.

Case report: 50-year-old woman with a right thyroid nodule (13x9 mm) with rapid growing (1 cm) in 6 months was firstly seen in Surgery Department in 2000. Cytology showed a colloid nodule and she was submitted to right lobectomy. Histology revealed lesions of multinodular goiter, lymphocytic thyroiditis (LT), a MTC with 0.4 cm and foci of C cells hyperplasia, and she was referred to our Department. Total thyroidectomy and node neck dissection were performed and the histological result confirmed multinodular goiter and showed also a papillary microcarcinoma (4 mm), with no node involvement. The I-131 whole body scintigraphy one year after surgery showed no uptake. The search for RET germline mutation was negative and multiple

endocrine neoplasia type 2 was excluded. She maintains supressive treatment with levothyroxine and calcitonin, carcinoembryonic and thyroglobulin levels remain low since surgery, with no evidence of local or distant recurrence.

Discussion: PTC is the most common thyroid neoplasm and can be found as an occult tumor in surgical specimens. Many authors suggest that there is a relationship with LT and PTC and the presence of LT is associated with a better prognosis. MTC is a rare tumor and its presence in association with PTC even rarer, and there are no data in literature of the association of MTC and LT. In this case the occurrence of simultaneous PTC and MTC may be a reflection of incidental papillary microcarcinoma.

P199

WITHDRAWN

PO22 Thyroid Hormone Effects on Metabolism and Bone

P200

EFFECT OF TSH-SUPPRESSION THERAPY ON VOLUMETRIC BONE MINERAL DENSITY AND BONE GEOMETRY AT THE RADIUS AND TIBIA ASSESSED BY PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY IN WOMEN WITH DIFFERENTIATED THYROID CANCER

Antoniou J[1], Tournis S[1], Liakou C[1], Christodoulou J[1], Galanos A[1], Nikopoulou S[2], Tzavara I[3], Papaioannou N[1], Lyritis GP[1], Alevizaki M[4]
[1]Laboratory of Research of Musculoskeletal System "Th. Garofalidis", Athens University Medical School, KAT Hospital, Athens, Greece, [2]Department of Endocrinology, Elena Venizelou Hospital, Athens, Greece, [3]Department of Endocrinology, Diabetes and Metabolism, Amalia Fleming General Hospital, Athens, Greece, [4]Endocrine Unit, Department of Clinical Therapeutics, Athens University Medical School, Alexandra Hospital, Athens, Greece

The adverse effects of TSH-suppression therapy on skeletal integrity in differentiated thyroid cancer (DTC), has been widely examined. In general, most researchers support its negative impact on bone mineral density only in postmenopausal women. Our objective was to examine the effect of TSH-suppression therapy on quantitative and qualitative bone characteristics using peripheral quantitative computed tomography (pQCT) at the radius and tibia in pre- and postmenopausal women with DTC and healthy controls. Eighty women with DTC (40 pre- and 40 postmenopausal) treated with LT4 after near-total thyroidectomy for at least one year and 86 (29 and 59 respectively) healthy controls, matched for age and anthropometric characteristics, were recruited. pQCT measurements were performed at the radius (4%,_10%,_20% from the distal end- trabecular, transition, cortical respectively) and tibia (4%,_14%,_38%); DXA was performed at the hip and lumbar spine, while fasting blood samples were taken for the estimation of Ca, iPTH, 25(OH) D, 24h CaU and bone turnover markers. No differences were found between patients and controls concerning BMD values at the hip and lumbar spine. In premenopausal women there were no significant differences concerning BMC, area, and vBMD, while cortical thickness was higher at the radius in DTC patients compared with controls ($p< 0.01$). In postmenopausal women with DTC trabecular BMC, area and vBMD were lower at the radius (all $p< 0.05$), while at the tibia BMC and vBMD were lower at the transition zone (14%-$p< 0.05$). Cortical thickness was lower at the radius ($p< 0.001$) in patients compared with controls. Serum CTX was higher both in pre- and postmenopausal women with DCT ($p< 0.01$). In conclusion, TSH- suppression therapy is associated with a high bone turnover state that adversely affects trabecular and cortical bone properties only in postmenopausal women.

P201

LXR AND TR SIGNALING CROSSTALK: IMPLICATIONS IN THE CENTRAL CONTROL OF METABOLISM

Clerget-Froidevaux M-S[1], Ghaddab-Zroud R[1], Seugnet I[1], Demeneix BA[1]
[1]Muséum National d'Histoire naturelle/CNRS UMR7221, RDDM, Paris cedex, France

Thyroid hormone (TH) signaling is a key factor controlling food intake and energy expenditure. TH orchestration of energy homeostasis implicates both direct transcriptional control of key hypothalamic genes, including Trh and Mc4r, but also modulation of peripheral energy expenditure through the sympathetic nervous system.

Each of these control points represent crossroads for interactions between TR and LXR signaling. First, in terms of direct control of the Trh and Mc4r genes, as LXR and TR share the same common heterodimeric partner (RXR) and consensus positive regulatory DNA element (DR4), interactions at the transcriptional level are predicted and require investigation. Second, as intra-hypothalamic TH levels modulate fatty acid production, repercussions on LXR activity are to be expected.

By in vivo reporter assay in newborn mouse hypothalamus, we analysed whether an LXR agonist can interfere with Trh and Mc4r promoter transcription in euthyroid or hypothyroid animals. Then, to identify the gene networks controlling and integrating central metabolic signals, we performed Laser Microdissection (LMD) on specific hypothalamic sub regions (PVN, VMH, ARC), to analyse the transcriptomes of two sets of adult male mice: T3 or LXR agonist ICV treated, dissected 6 h post-treatment; untreated WT or KO $LXR^{-/-}$ mice. PVN samples of these two sets were submitted to RNAseq for differential gene expression analysis.

Our in vivo reporter assay experiments in euthyroid mice show that intra-hypothalamic injection of an LXR agonist inhibits Trh transcriptional activity, whereas, surprisingly, it has no effect in hypothyroid mice. Differentially expressed genes identified by RNAseq will be validated by Openarrays technology (Applied Biosystems).

The comparison of the different data sets will allow identification of target genes for validation and modelling of hypothalamic gene networks modulated by TR and LXR signaling.

P202

PRIMARY HYPOTHYROIDISM IN 143 PATIENTS WITH OSTEOPENIA AND OSTEOPOROSIS: THE BONE PROFILE ANALYZE

Carsote M[1], Ene C[2], Popescu M[2], Samoila R[2], Radoi V[1], Voicu G[2], Poiana C[1,2]
[1]UMPh Carol Davila, Bucharest, Romania, [2]I. Parhon, Bucharest, Romania

Introduction: The patients with treated primary hypothyroidism (PH) may associate bone loss risk but there are controversial data.

Aim: We evaluated the bone profile related to PH.

Patients and method: 143 postmenopausal women were diagnosed based on lumbar Lunar DXA with osteoporosis or osteopenia (2004 WHO criteria). There were not previously treated with osteoporotic drugs. The body mass index (BMI), and Heel Quantitative Ultrasound (Achilles) were performed. 50 patients had osteoporosis and 14 of them had PH. (group 1) 93 women had osteopenia and 30 of them had PH. (group 2) The patients with PT were under substitution therapy (from 1 year to 30 yrs), with normal TSH. The statistical analyze was performed with student ttest.

Results: The av. age of the groups were: 59.98±8.04 yrs vs. 57.41±9.94 yrs (p=0.08). The av. BMI was for group 1: 27.53±6.15 kg/m^2 (patients with PH), 28.25±8.11kg/m^2 (patients PH free) (p=0.76). The av. BMI was for group 2: 28.13±5.47 kg/m^2 (patients with PH), 28.01±4.58kg/m^2 (patients PH free) (p=0.76). The QUS Stiffness Index was for group 1: 68.67±16.69U (PH+), 68.83±13.14U (PH free) (p=0.99). The Stiffness Index was for group 2: 73.87±13.98U (PH+), 73.83±17.54U (PH free) (p=0.99). The Bone Mineral Density was for group 1: 0.81±0.08 g/cm^2 (PH+), 0.79±0.11 g/cm^2 (PH free) (p=0.5). The BMD was for group 2: 0.91±0.13 g/cm^2 (PH+), 0.94±0.05 g/cm^2 (PH free) (p=0.06). The percent of the patients with fragility fractures

was: 28.5% (osteoporosis and PH), 22.2% (osteoporosis and PH free), 10% (osteopenia and PH), 19% (osteopenia and PH free).

Conclusions: The Quantitative Ultrasound did not reveal differences in patients with or without PH and low BMD. The BMD is lower in patients with treated PH into the groups of osteopenic, and especially osteoporotic women. The fractures are more frequent in patients with PH, in osteoporosis group, but not in osteopenia group.

P203

TIME-DEPENDENT UP-REGULATION OF TYPE 2 DEIODINASE AFTER MYOCARDIAL INFARCTION.

Araujo IG[1], *Marassi MP*[1], *Silva AC*[1], *McElligott A*[2], *Paul J*[2], *Império GE*[1], *Carvalho DP*[3], *Henderson KK*[2], *Olivares EL*[1]
[1]Federal Rural University of Rio de Janeiro, Physiological Science, Seropedica, Brazil, [2]Loyola University, Chicago, United States, [3]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Triiodothyronine (T3) plays a critical role in cardiac gene expression and myocardial function. Recently, we demonstrated an acute decrease of serum T3 and thyroxine (T4) levels in an animal model of myocardial infarction (INF). The early decline in thyroid hormones was mainly attributed to the induction of type 3 deiodinase (D3) activity. In spite of persistently low T4 concentrations, serum T3 returned to control levels by 8wks post-INF. We hypothesized that an increase in type 2 deiodinase (D2) activity could be a mechanism mediating T3 normalization. Using the same model, we demonstrated herein an early and significant increase in myocardial D3 expression at 1–14 days post-INF. Importantly, D2 expression was significantly increased and the D2/D3 ratio was similar to controls by day 7. While myocardial D2 activity was not detectable, D2 activity in brown adipose tissue (BAT) was significantly increased with a positive correlation identified between D2 activity and the serum T3/T4 ratio over the 12 week study. To further characterize a mechanism underlying high BAT D2 activity, a subset of INF animals was supplemented with T4. Thyroxine replacement attenuated BAT D2 activity, suggesting hypothyroidism may contribute to the increase in D2 activity. Our findings suggest that changes in myocardial D2 and D3 expression may play an immediate and important role in the early stages of myocardial remodeling, and up-regulation of D2 activity in BAT in rats constitutes an important mechanism for serum T3 normalization in the later phases of a myocardial infarction.

P204

TRα1-MUTANT MICE MAINTAIN NORMAL BODY TEMPERATURE DESPITE DEFECTIVE VASCULAR CONTROL

Warner A[1], *Reheman A*[2], *Gottschling K*[1], *Davis B*[2], *Vennström B*[1], *Arner A*[2], *Mittag J*[1]
[1]Karolinska Institutet, Department of Cell and Molecular Biology, Stockholm, Sweden, [2]Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden

Aims: Mice heterozygous for a mutation in thyroid hormone receptor alpha 1 (TRα1+m) are a valuable animal model for receptor-mediated hypothyroidism. TRα1+m mice display hypermetabolism, caused by an overactive sympathetic nervous system stimulating the brown adipose tissue (BAT). However, despite brown fat overactivation, these animals demonstrate a lower core body temperature compared to wildtype controls. The aims of these studies were to investigate the mechanisms behind this discrepancy, and elucidate further the characteristics of thermoregulation in TRα1+m mice.

Methods: We applied infrared thermography to measure brown fat heat generation and tail heat dissipation in TRα1+m and wildtype mice. Additionally, the mice were exposed to 25°C, 30°C and 34°C (below, at, and above thermoneutrality) to determine acute thermoregulatory response. Subsequently, smooth muscle function was investigated ex vivo using organ bath-mounted segments of tail and small mesenteric arteries, as well as gene expression analysis using qPCR.

Results: The TRα1+m mice showed a significant increase of heat production from brown fat as expected; however, heat dissipation from the tail was also elevated at room temperature compared to wildtype controls. Similarly we found impaired vascular control upon acute thermal challenge in TRα1+m mice compared to wildtype controls, with increased heat loss below thermoneutrality, and lower heat dissipation above thermoneutrality. However, the ex vivo studies on isolated arteries did not reveal any defect that could explain this difference.

Conclusions: The above data demonstrates that TRα1+m mice possess a defect in vasoregulation, most likely as the consequence of a defective central thermostat rather than impairments in the peripheral vasculature. Further studies will expectantly demonstrate whether the overactivation of BAT in the TRα1+m mice is a consequence of increased heat loss through impaired vascular control, or whether the activation of brown fat causes a vascular homeostatic response in an attempt to dissipate the additional heat produced.

P205

CONCENTRATION-DEPENDENT STIMULATION OF MITOCHONDRIAL AND CELLULAR ENERGY METABOLISM BY 3,5-T2 IN HUMAN HEPG2 HEPATOCARCINOMA CELLS

Lehmphul I[1], *Vogel H*[2], *Kanzleiter T*[2], *Hoefig CS*[1], *Schürmann A*[2], *Köhrle J*[1]
[1]Charité-Universitätsmedizin Berlin, Institut für Experimentelle Endokrinologie, Berlin, Germany, [2]German Institute of Human Nutrition, Experimental Diabetology, Potsdam-Rehbrücke, Germany

Objectives: The natural probably T3-derived thyroid hormone (TH) metabolite 3,5-diiodo-L-thyronine (T2) exerts remarkable rapid anti-steatotic and metabolic actions upon administration of pharmacological doses in rodent animal experimental models, two human volunteers and various in vitro cellular models (Moreno et al. Thyroid 2008). These effects are distinct from classical T3 effects. Among direct mitochondrial actions several other rapid cellular effects have been identified. The Seahorse XF24 bioanalyzer provides a non-invasive real-time measurement in intact cells to detect TH induced changes in mitochondrial and intracellular pathways. Oxygen consumption rate (OCR) represents an indicator for mitochondrial function and extracellular acidification rate (ECAR) indicates glycolysis. Former experimental designs used Clark electrode analyses of isolated mitochondria or tissue homogenates mainly from severe hypothyroid animals. Using the bioanalyzer allows addressing TH transport across cellular membranes into mitochondria and intracellular metabolism.

Methods: HepG2 cells were treated with 10(-11)-10(-7)M T2 or T3. Classical energy substrates and mitochondrial inhibitors were employed which directly target cytochrome c oxidase (CytcOx) and enhance T2 dependent changes in mitochondrial functions. HepG2 were serum starved for 24h to estimate TH-dependent changes of basal respiration. All data are normalized to DNA content per well and to basal respiration.

Results: 10(-9)M T2 significantly increased OCR by 3% and ECAR by 8% over basal respiration. T2 effects are concentration dependent, reached a maximum after 8min and mimic T3 effects. By directly targeting the CytcOx, 10(-8)M T2 almost doubled the respiratory capacity compared to untreated HepG2 cells.

Conclusions: By directly affecting CytcOx high picomolar T2 concentrations increase at the same time extracellular proton accumulation and OCR in HepG2 cells. Non-invasive detection of cellular energetic parameters by the Seahorse XF24 bioanalyzer provides the possibility to measure changes of the mitochondrial respiratory chain in different cell systems depending on uptake, intracellular transport to mitochondria and cellular metabolism of TH.

PO23 Thyroid Hormone Action 2

P206

T3 ENHANCES GROWTH, GENE EXPRESSION, AND HORMONAL PRODUCTION IN RAT OVARIAN GRANULOSA CELL AND FOLLICLES

Misiti S[1], Verga Falzacappa C[2], Santaguida MG[2], Alfei F[1], Furno A[1], Centanni M[2]
[1]Sapienza University of Rome, Department of Experimental Medicine, Roma, Italy, [2]Sapienza University of Rome, Department of Science and Medico-Surgical Biotechnologies, Latina, Italy

Dysfuntion in thyroid homeostasis may cause ovulatory and menstrual disorders, the underlying mechanism of which is not fully understood. Thyroid dysfunction also increases morbidity and worsens outcome of pregnancy. The ovulatory and menstrual pattern is influenced by thyroid hormones directly through impact on the ovaries and indirectly through impact on SHBG, PRL, GnRH secretion and coagulation factors.

Objectves: To characterize thyroid hormone action in the ovary, analyzing the direct effect of T3 on rat granulosa cells (rGC) and follicles.

Methods: rGC and follicles isolated from rats have been treated with T3 (10–100nM) and their growth and function have been evaluated in both systems.

Results: Cell growth and MTT analyses showed an increase of 40% in rGC, while the measurements of follicles evidenced an augment of about twice the volumes. The basal production of beta estradiol was increased in rGC of 2 folds, and by 3 folds in rat follicles, as measured by chemiluminescence after 48h of T3 treatment. Aromatase activity was increased of twice the basal level by measuring E2 levels released by cultured rGC after T3 with and without Testosterone 0.5µM.

The expression of major genes involved in steroidogenesis has been analyzed by RT-PCR. StAR, Cyp17 and Aromatase genes were the most upregulated after 48h of T3 treatment.

Conclusions: Our data show that T3 effects on ovarian function is exerted at molecular, biochemical and hormonal level providing also evidences of its ability to directly target steroidogenesis.

P207

TYPE 2 DEIODINASE GENE GENOTYPE (D2 THR92ALA) INFLUENSE ON RISK OF DEVELOPMENT OF THYROID DISEASE?

Babenko AY[1], Grineva EN[1], Kostareva AA[2], Popkova DA[1], Freylichman OA[2], Solncev VN[3]
[1]Almazov Federal Heart, Blood and Endocrinology Centre, Institute of Endocrinology, Saint- Petersburg, Russian Federation, [2]Almazov Federal Heart, Blood and Endocrinology Centre, Institute of Molecular Biology and Genetics, Saint- Petersburg, Russian Federation, [3]Almazov Federal Heart, Blood and Endocrinology Centre, Group of Medical Statistic, Saint- Petersburg, Russian Federation

Genetic prediction of developments of various diseases plays an important role in modern medicine.

We identified type2 deiodinase gene genotype (D2 Thr92Ala) at 180 patients with Graves' disease (GD group (GDG)), 43 patients with papillar carcinoma of thyroid (PCT group (PCTG)) and 135 euthiroid volunteers (control group (CG)).

In the GDG, 106 (58,9%) individuals had genotype Thr92Thr, 60 (33.3%) were heterozygous (Thr92Ala), and 14 (7,8%) had genotype Ala92Ala. The frequency of Ala allele was 0.24. In the PCTG, 36 subjects had genotype Thr92Thr (84,7%), 5 (11.6%) were heterozygous, and 2 (4,7%) had genotype Ala92Ala. The frequency of Ala allele was 0.1. In the CG 53 subjects had genotype Thr92Thr (39.3%), 79 (58.5%) were heterozygous, and 3 (2.2%) had genotype Ala92Ala. The frequency of Ala allele was 0.32. The frequency of homozygotes for the Thr allele was significantly higher in the GDG in comparison with CG (58.9 vs 39.3% respectively; $P< 0.0001$). This resulted in an OR of 2,20 (95% CI 1.40–3.47, P=0.0007) for the Thr92Thr genotype in GDG, on the contrary Thr92Ala genotype has inverse relationship, the chance to get ill appears essentially less: OR of 0,36 (95% CI 0.24–0.57, $P< 0.0001$). The frequency of homozygotes for Thr allele was the highest in the PCTG (p=0,002 in comparison with GDG and p=0,0001 in comparison with CG). This resulted in an OR of 3,61 (95% CI 1.33–9.79, $P< 0.0001$) for the Thr allele in PCTG. Thr92Thr genotype influence was the most essential: an OR of 7,51 (95% CI 3.18–17.7, $P< 0.0001$) and on the contrary Thr92Ala genotype has inverse relationship, the chance to get ill appears essentially less: OR of 0,1 (95% CI 0.04–0.26, $P< 0.0001$).

It is thought that presence of a Thr92Thr genotype associated with high D2 tissue activity determines higher risk of development GD and PCT.

P208

THYROID HORMONE TRANSPORTERS DURING TESTICULAR DEVELOPMENT IN RODENTS

Rijntjes E[1], Teerds KJ[2], Wirth EK[1], Hoefig CS[1], Köhrle J[1]
[1]Charité Universitätsmedizin Berlin, CVK, Institute for Experimental Endocrinology, Berlin, Germany, [2]Wageningen University, Dept. of Animal Sciences, Human and Animal Physiology Group, Wageningen, Netherlands

Chronic dietary induced fetal-postnatal hypothyroidism results in a transient delay in Leydig cell and prolonged Sertoli cell development in the neonatal rat testis, hence the start of complete spermatogenesis is altered. In the present study we have investigated the possible role of thyroid hormone (TH) transporters and receptors and delayed onset of spermatogenesis. Hypothyroidism was induced in rats during fetal development by feeding dams an iodide-poor diet supplemented with 0.5% sodium perchlorate. Euthyroid controls received AIN-93-based rat chow.

Sertoli cells are targets for TH as they express TRα1. q-PCR analysis revealed that under hypothyroid conditions testicular expression of TRα1 is transiently increased until day 35 postpartum (pp). TRα2 followed a similar pattern, whereas TRβ levels were too low to be quantified. Testicular TH levels have then been measured using LC-MS/MS. Our first results show that T4 levels have declined by 80% in the hypothyroid testes. Strikingly testicular T3 and 3-T1AM levels were increased, while rT3 levels were similar between the hypothyroid and control groups on day 28pp. Immunohistochemistry of the testis from day 12pp up to adulthood showed staining for TH transporter Lat2 in developing and adult-type Leydig cells, independent of the TH status. Lat2 staining is absent in the seminiferous tubule. Preliminary results from a Lat2 knockout mouse model show delayed Leydig and Sertoli cell development in the early adult testis. Mct8 immunostaining proved not to be stable. Deiodinase Type 3 was found in immature type Leydig cells, but not in adult or progenitor type Leydig cells.

Conclusion: Although several TH transporter mouse models have shown that male offspring is fertile, we present indications that TH transporters play a pivotal role in the timely development of the Leydig cell population and the onset of complete spermatogenesis.

Supported by grants from EnForCé, Charité and DFG GP1208-2- TP3 to J.K.

P209

ASSOCIATION BETWEEN POST PARTUM THYROIDITIS AND THYROID HORMONE RESISTANCE IN AN ITALIAN PATIENT SHOWING A NOVEL P.V283A THRB (THYROID HORMONE RECEPTOR BETA) MUTATION

Paragliola RM[1], Concolino P[2], De Rosa A[1], Mello E[2], Zuppi C[2], Pontecorvi A[1], Capoluongo E[2], Corsello SM[1]
[1]Catholic University School of Medicine, Endocrinology, Rome, Italy, [2]Catholic University School of Medicine, Biochemistry and Clinical Biochemistry, Rome, Italy

The syndrome of resistance to thyroid hormone (RTH) is characterized by a reduced responsiveness of target tissues to thyroid hormone (TH). RTH is caused in about 90% of cases by a dominant mutation in the TH receptor beta (THRB) gene. We observed a 30 year-old RTH patient who became pregnant twice and who developed a post-partum thyroiditis (PPT) after both deliveries. Genetic test showed a new THRB heterozygous mutationPatient came to us because of hyperthyroidism with inappropriate TSH secretion (TSH: 5.9 mU/L; FT4: 29.1 pg/mL; FT3: 4.8 pg/mL). She became pregnant twice and

after both deliveries she developed a PPT: during the hyperthyroid phase an unexpected suppression of TSH was detected. After the hyperthyroid phase, she became hypothyroid, and eventually returned to her usual "euthyroid" status. To confirm the diagnosis of RTH we performed a TRH test revealing an adequate TSH response, and a pituitary MRI excluding the presence of an adenoma. After obtaining informed consent, the patient underwent genetic testing for RTH. Complete coding THRB gene sequencing, performed as previously reported, revealed the novel p.V283A (g.361470T>C; NC_000003) heterozygous mutation in exon 8 of the gene. This mutation has never been reported in literature. For this reason, in order to exclude that the p.V283A is a TRHB polymorphism, we screened 100 healthy control individuals (200 alleles) by High Resolution Melting Analysis. This screening resulted mute for the above mentioned mutation indicating a frequency less than 1%. RTH is caused in about 90% of cases by a dominant mutation in the THRB gene. In more than 85% of families with RTH, THRB mutations have been identified while in approximately 15% of families with RTH, no THRB mutations are detectable. In our patient, the THRB molecular analysis showed a novel mutation in exon 8 (p.V283A).

P210

CENTRAL HYPOTHYROIDISM AND ITS REPLACEMENT CORRELATE TO A VARIETY OF CARDIOVASCULAR RISK FACTORS IN ADULT HYPOPITUITARY PATIENTS

Hartoft-Nielsen M-L[1], Klose M[1], Klefter O[1], Marina D[1], Gavin V[1], Rasmussen AK[1], Feldt-Rasmussen U[1]
[1]Rigshospitalet, Medical Endocrinology PE 2132, Copenhagen, Denmark

Objectives: To confirm previous preliminary results, the objective of this study was in a larger cohort to test the hypothesis that thyroid hormone status has an impact on cardiovascular risk factors in adult hypopituitary patients.

Methods: Retrospective evaluation of thyroid status and cardiovascular risk markers (body mass index (BMI), fat and lean body mass (LBM) (DEXA), total -, LDL-, HDL cholesterol and triglycerides) of adult patients with hypopituitarism including growth hormone (GH) deficiency. Data from 212 patients were included (102 women, 153 adult onset). Patients were *TSH sufficient* (TSHsuf) if untreated by Levo-thyroxine and fT4 > 12 pmol/L and *TSH deficient* (TSHdef) if treated by Levo-thyroxine or fT4 ≤ 12 pmol/L. TSHdef patients were divided into tertiles according to fT4.

Results: At commencement of GH substitution, fT4 was positively associated to HDL-cholesterol (r=0.27; p< 0.001) and negatively to BMI (r= -0.16; p=0.02) independent of IGF-I SDS. Patients in the lowest 1st fT4 tertile had significantly adverse cardiovascular risk factors compared to TSHsuff patients. After 4.1 yrs (median, range 2.5 - 5.8), when T4 treatment was optimized, fT4 was no longer correlated to any of the risk factors, had a narrower range, and was without differences between the subgroups. However, ΔfT4 (follow-up - baseline) was negatively correlated to ΔBMI (r=-0.18; p= 0.02), ΔLBM (r=-0.20; p= 0.02), Δtotal- (r=-0.22; p= 0.01), and ΔLDL cholesterol (r=-0.22; p=0.01), also after adjustment for the changes in IGF-I SDS and hydrocortisone dose. ΔTotal- and ΔLDL-cholesterol varied significantly among the subgroups (p=0.01) primarily explained by differences between 1st and 3rd tertile TSHdef patients.

Conclusion: Cardiovascular risk factors were associated to fT4 in hypopituitarism. This association disappeared after optimisation of T4 replacement visualised by a narrowing of the variation in fT4. These data indicate a physiologic improvement of body composition and lipids consequent to normalisation of secondary hypothyroidism.

P211

PREVENTION OF POSTOPERATIVE HYPOCALCAEMIA AFTER TOTAL THYROIDECTOMY BY ALFACALCIDOL: A PROSPECTIVE RANDOMIZED CONTROL STUDY

Genser L[1], Trésallet C[1], Li Sun Fui S[1], Salepcioglu H[1], Hoang C[2], Leenhardt L[3], Menegaux F[1]
[1]APHP, Université Pierre et Marie Curie, Paris 6, Endocrine Surgery, Paris, France, [2]APHP, Université Pierre et Marie Curie, Paris 6, Pathology Departement, Paris, France, [3]APHP, Université Pierre et Marie Curie, Paris 6, Nuclear Medicine, Paris, France

Transient postoperative hypocalcaemia occurs in 40% of patients after total thyroïdectomy (TT). Preventive calcium and vitamin D supplementations may decrease this rate. We aimed to evaluate the effect of perioperative administration of alfacalcidol on postoperative hypocalcaemia after TT.

Materials and methods: From November 2010 to January 2011, 219 patients with a TT were included prospectively and preoperatively randomized in two groups: with alfacalcidol (AC+) 2 µg/day from the day before surgery (D-1) to postoperative day (POD) 8, or without alfacalcidol (AC-). Serum calcium and vitamin D levels were measured the day before surgery and 5 weeks later.

Results: The two groups AC+ (n=111) and AC- (n=108) were comparable for sex ratio, mean age, diagnosis of carcinoma, TT in 1 or 2 steps, associated lymph node dissection, D-1 serum calcium level and D-1 serum vitamin D level. When compared with AC- patients, mean serum calcium level was significantly higher in AC+ patients on POD1 (2.07 vs 2.03 mmol/L, p=0.05) and on POD2 (2.12 vs 2.04 mmol/L, p=0.04). The rate of severe hypocalcaemia (< 1.90mmol/L) was comparable on POD1 (11% vs 16%, NS) but significantly decreased on POD2 in AC+ group (1% vs 6%, p=0.05). Symptomatic hypocalcaemia was less frequent in the AC+ group (11% vs 22%, p=0.02). Five weeks after surgery, there were no differences between the two groups for medium serum calcium level (2.27 in each group) and serum vitamin D level (20.3 vs. 22.4 ng/mL, NS). Six months after thyroidectomy, there were no permanent hypoparathyroidism in the AC+ group and 3.7% in the AC- group (p=0.04).

Conclusion: Perioperative administration of alfacalcidol for TT reduces the rate of postoperative hypocalcaemia and its related symptoms but does not influence calcium and vitamin D serum levels 5 weeks after surgery. Alfacalcidiol seems also reduce the rate of permanent hypoparathyroidism.

P212

EXPRESSION OF TYPE 3 DEIODINASE (D3) IN THE HIPPOCAMPUS OF EPILEPTIC RATS

Nassif R[1,2], Cysneiros R[1], Scorza F[2], Bianco A[3], Ribeiro M[1]
[1]Universidade Presbiteriana Mackenzie - Ciências Biológicas, Sao Paulo, Brazil, [2]UNIFESP, Neuroscience Department, Sao Paulo, Brazil, [3]University of Miami Miller School of Medicine, Division of Endocrinology, Diabetes and Metabolism, Miami, United States

Recent studies show that thyroid disorders compromise the integrity of brain tissue, such as hippocampus and parietal cortex, influencing behavior and process of learning and memory. The deiodinase type III (D3), prevents activation of T4, converting it into reverse T3 which are considered inactive forms of the hormone. D3 is increased in critically ill patients, primarily in tissues with hypoxic-ischemic injury. Sudden death has high incidence in individuals with chronic epilepsy. Respiratory abnormalities such as apnea and hypoxia could be the major cause of death in these individuals. Following this reasoning we evaluate the effects of epilepsy on the local reduction of T3 in brain tissue. For that we studied rats with epilepsy induced by pilocarpine and quantified the expression of deiodinase type III (D3) in the hippocampal regions, using the method of Immunohistochemistry and Western Blot. D3 expression was dramatically increased in the CA3, Dentate Gyrus and Hilo when compared to control. Our data shows that epilepsy reduces local T3 by increasing the expression of D3 and could be a neuroprotective effect.

PO24 Thyroid Function Regulation Basic

P213

DEIODINASE TYPE 2 ACTIVITY AND SERUM THYROID HORMONE LEVELS AFTER SLEEP LOSS IN RATS

Rodrigues NC[1], Cruz NS[1], Nascimento CP[1], Conceição RR[1], Olivares EL[1], Silva AC[1], Carvalho DP[2], Andersen ML[3], Marassi MP[1]
[1]Federal Rural University of Rio de Janeiro, Physiological Sciences, Seropedica, Brazil, [2]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, [3]UNIFESP, Psychobiology, Sao Paulo, Brazil

Modern life shortened sleep time and the consequences of the sleep loss have been studied. Considering that thyroid function and sleep loss relation was not assessed often, the aim of this study was to analyze thyroid economy and deiodinase type 2 (D2) during paradoxical sleep deprivation (PSD) and sleep restriction (RS) and after 24 hours of rebound period. Male Wistar rats (200–250g) underwent sleep deprivation by modified multiple platform methodology. Rats were assigned in 7 groups: control (n=11); PSD for 24(n=15) and 96 hours (n=13); respective rebound groups (PSD24R24 n=12 and PSD96R24 n=14); SR for 21 days (n=14); and SR21 with rebound of 24 hours (SR21R24=15). All animals were euthanized and blood was collected for T3 and T4 analysis by electrochemiluminescence. Thyroid gland and brown adipose tissue (BAT) were used for D2 activity. To evaluate the *in vivo* NIS function, the animals received Na-125 I (250,000 dpm, i.p.) 15 min before decapitation and radioactivity of the thyroid glands was measured using a gamma counter (Wizard). The absolute and relative weights of thyroid gland increased only PSP96 compared to control. Whilst T3 increased in all groups, T4 decreased in PSD24, PSD96 and PSD96R24 compared to control. Activity of D2 only mensury in 6 groups (n=5/group), in BAT, D2 increase only in PSD 24 or 96h in relation the control Sleep loss only changed T4 in acute sleep deprivation but in chronic sleep loss T4 did not change, suggest that thyroid modulation is differ in chronic and acute sleep loss and T3 increased in all groups. D2 and T4 increased only in acute sleep deprivation but the rebound period was able to normalise this valous, suggesting that T4 decrease and T3 increase may be explained by high BAT D2 activity. The short-term radioiodide uptake was not significantly different among the groups.

P214

REGULATION OF THE NIS PROMOTER BY AMPK MODULATION

Abdulrahman RM[1], Sips HCM[1], Smit JWA[1], Hovens GCJ[1]
[1]Leiden University Medical Center, Endocrinology, Leiden, Netherlands

Background: Previously, we and others have demonstrated that AMP-activated protein kinase (AMPK) status regulates iodine uptake and expression of the sodium-iodine symporter (NIS) in FRTL-5 cells. AMPK activation reduced both Iodine uptake and NIS protein levels whereas inhibition AMPK resulted in increased iodine uptake and NIS protein levels. Although I-uptake and NIS expression by the thyrocytes have been studied extensively the mechanisms by which AMPK regulates NIS are still unknown.

Aim: To investigate if AMPK regulates NIS on the transcriptional level.

Materials and methods: AMPK was activated using AICAR (Aic) [0.5mM] and metformin(Met) [5mM] or inhibited by CompoundC(Cc) [10uM]. The effects of AMPK modulation on NIS expression in FRTL-5 cells were studied with NIS-promoter luciferase constructs harboring different regions of the promoter (Table 1).

Results: AMPK inhibition by Cc resulted in increased luciferase activity in both rNIS9 and hNIS7 after 4 days of treatment in stable and transiently transfected cells. AMPK activation by Aic and Met showed a reduction of luciferase activity in the rNIS9. However, luciferase activity of the hNIS7 construct could only be reduced with Aic after stable transfection.

Conclusion: Recently we have demonstrated that AMPK regulates iodine uptake and NIS protein expression in FRTL-5 cells. Using NIS promoter-luciferase constructs we have demonstrated that the observed effects are, at least partly, regulated on the transcriptional level.

Table 1.

NIS-promoter luciferase constructs				
promoter	From rat genome		From human genome	
	rNIS5	rNIS9	hNIS1	hNIS7
vector	PGL3 basic		PGL4.17 (Promega)	
Composition: 5' flanking region upstream the starting codon	–1 to –564 bp	(–1 to –564) + (–2264 to –2495 bp)	–40 to –1624 bp	(–40 to –1624) + (–7760 to – 10750 bp)
Known regulatory elements of the construct	AP-1, TTF-1	AP-1, TTF-1, Pax8, CREB, κB	AP-1, SP-1, TTF-1	AP-1, TTF-1, Pax8, CREB, κB

P215

THYROID PHENOTYPE IN SORTILIN KO MICE

Profilo MA[1], Lisi S[1], Botta R[1], Chiarini R[1], Altea MA[1], Leo M[1], Sisti E[1], Rocchi R[1], Latrofa F[1], Marinò M[1], Pinchera A[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy

Sortilin is a member of the Vps10p family, proteins involved in endocytosis and intracellular trafficking. In a recent study, we demonstrated that sortilin is expressed intracellularly in thyroid epithelial cells in a TSH-dependent manner. Sortilin is capable of binding to thyroglobulin (Tg) with high affinity; in thyrocytes the two proteins interact following Tg endocytosis. The process results in Tg recycling into the extracellular space, a route that is believed to serve for poorly glycosylated Tg molecules to undergo completion of glycosylation within the Golgi. We investigated the thyroid phenotype in sortilin KO mice: 14 (8 females and 6 males), 7–12 (9.5±2.3) week old sortilin1 (Sort1) $^{-/-}$ mice and 11 (4 females and 8 males), 7–13 (10.6±2.6) week old WT mice. We examined serum FT4, TSH and Tg levels and thyroid histology. FT4 serum levels did not differ between Sort1$^{-/-}$ and WT mice (P=0.9247) in females, whereas FT4 levels were significantly (P=0.0181) lower in Sort1$^{-/-}$ compared with WT mice in males. Both in females and in males serum TSH did not differ between Sort1$^{-/-}$ and WT mice (P=0.7394 in females and P=0.9473 in males). Serum Tg levels did not differ between Sort1$^{-/-}$ and WT mice regardless of the gender (P=0.2044 in females and P=0.5024 in males). No differences were observed between Sort1$^{-/-}$ and WT mice at thyroid histology. Thus, the size of thyroid follicles and the colloid content were similar in the two groups of mice and thyroid epithelial cells were not enlarged in Sort1$^{-/-}$ mice nor were the nuclei different. In conclusion, the absence of sortilin does not seem to affect thyroid hormone secretion nor seems to be a cause of goiter, but we cannot excluded that may affect thyroid function and morphology if combined with alterations of other proteins involved in thyroid hormone secretion.

P216

PHENOTYPIC ANALYSIS OF THYROID-SPECIFIC NF-KB KNOCKOUT MICE

Reale C[1,2], Guerrera D[1,2], Scudiero I[1,2], Zotti T[1,2], Vito P[1,2], Stilo R[1,2]
[1]Biogem, Ariano Irpino, Italy, [2]Università del Sannio, Benevento, Italy

The Nuclear Factor-kappa B (NF-kappaB) family of transcription factors regulates the expression of a wide range of genes controlling the immune and stress responses, inflammatory reaction, cell adhesion, and protection against apoptosis. Dysregulated NF-kappaB activity occurs in a number of chronic inflammatory diseases and certain types of cancers making NF-kappaB signaling an attractive target for the development of anti-inflammatory and anti-cancer drugs. A pivotal regulator of all inducible NF-kappaB signaling pathways is the IkappaB kinase (IKK) complex that consists of two kinases (IKKalpha and IKKbeta) and a regulatory subunit named NF-kappaB essential modulator (NEMO). NEMO deficiecy results in complete abrogation of the NF-kappaB canonical pathway.

Using the technology for the generationof conditional knockout mice, based on the use of mice strains expressing the cre recombinase under tissue specific promoters, we have generated mice deficient of NEMO (and thus

canonical NF-kappaB) in the thyroid. The phenotypic analysis of these mice is here presented.

P217

AUDIT OF PATIENT INFORMATION FOR AGRANULOCYTOSIS DUE TO ANTI THYROID DRUG (ATD) THERAPY

Richardson MN[1], *Perros P*[2]
[1]University of Newcastle upon Tyne, Medical School, Newcastle upon Tyne, United Kingdom, [2]Royal Victoria Infirmary, Endocrinology, Newcastle upon Tyne, United Kingdom

Introduction: One severe side-effect of ATDs is Agranulocytosis. Agranulocytosis manifests with sore throat, fever and mouth ulcers. Patients are advised to seek urgent full blood count should they develop any of these. TRAMP is a regional guideline that advises all patients started on ATDs should receive verbal and written information about side effects.

Aims:

- Assess whether patients are given information about side effects when started on ATDs.
- Assess patients' recall of this.
- Assess whether further patient education is required.

Method: Patients reporting to clinic receiving ATDs were included.

- Patients were interviewed using a questionnaire, about symptoms associated with Agranulocytosis
- Notes were reviewed for evidence of conversations about side effects.

Results: 8 of 33 patients remembered all 3 symptoms. 4 patients remembered no symptoms.

3 patients did not remember being told about side effects, they had no mention of any discussion in their notes or correspondence.

12 patients had no record of conversation in their notes. 15 patients had no mention in correspondence. 7 patients had no record in either.

Conclusions: There is poor compliance recording conversations in notes and letters. There are large gaps in patient's knowledge of side effects and warning symptoms.

Recommendations

1. Doctors should record in notes and correspondence, details of conversations.
2. Every time patients are seen in clinic they should be reminded of the side effects, warning symptoms, and potential severity of Agranulocytosis.

P218

EFFECTS OF METFORMIN ON THYROID FUNCTION

Hovens GCJ[1], *Abdulrahman R*[1], *Sips H*[1], *Smit JWA*[1]
[1]Leiden University Medical Center(LUMC), Dept. of Endocrinology and Metabolic Diseases, Leiden, Netherlands

Background: Metformin is generally used for treatment of type 2 diabetics where it reduces insulin resistance and hyperinsulinemia resulting in reduced diabetes-related morbidity and mortality. Recently it has also received a lot of attention for use as a potential cancer treatment and population-based studies show that metformin treatment is associated with a dose-dependent reduction in cancer risk. Previous studies in thyroid carcinoma cell-lines have demonstrated that metformin can indeed inhibit growth of several thyroid (carcinoma) cell-lines. However, the effects of metformin on differentiation (which is a cornerstone of radioactive iodine(RAI)-treatment) is largely unexplored.

Aim: To investigate the role of metformin on thyroid differentiation

Materials and methods: Metformin functions by decreasing hepatic glucose production through inhibition of the mitochondrial respiratory chain complex I resulting in the activation of the energy sensing molecule AMPK (AMP-activated protein kinase).

Therefore FRTL-5 cells were treated with the AMPK inhibitor metformin(Met) or with the AMPK activator CompoundC(Cc). The effects of metformin on thyroid function were studied by measuring iodine uptake and thyroid specific protein expression(westernblot). Furthermore, the effects of metformin on FRTL-5 cells were studied by various NIS promoter constructs.

Results: TSH induced iodine uptake in thyroid follicular cells (FRTL-5) was blocked by metformin treatment whereas CompoundC increased iodine uptake in a time dependant manner. The results in iodine uptake can at least partially be explained by in- or decreased NIS protein levels which are regulated by decreased transcription.

Conclusion: We have demonstrated that metformin reduced iodine uptake and thyroid specific protein expression in FRTL-5 cells. These findings imply that the potential of metformin as a possible treatment for thyroid cancer may be limited by a decrease in iodine uptake which would hamper conventional RAI treatment.

P219

FLAVONOID RUTIN INCREASES THYROID RADIOIODIDE UPTAKE

Gonçalves CFL[1], *Santos MCS*[1], *Carvalho DPD*[1], *Ferreira ACF*[1]
[1]Federal University of Rio de Janeiro, IBCCF - Laboratory of Endocrine Physiology, Rio de Janeiro, Brazil

Flavonoids are polyhydroxyphenolic compounds, found in vegetables that are present in human diet. Studies have suggested that these compounds could interfere with thyroid function causing goiter and hypothyroidism. Rutin (3´.4´.5.7-tetrahydroxyflavone-3-rutinoside) is a highly consumed flavonoid, found in foods, such as onions, apples and teas, and also in multivitamin compounds. The aim of the present study was to evaluate the effects of the *in vivo* treatment with rutin on thyroid function. Male Wistar rats received rutin (20 mg/Kg body weight) or vehicle (propyleneglycol) for 5 days, subcutaneously. Rutin significantly increased radioiodide uptake and thyroid mRNA levels of the Na^+/I^- symporter, thyroperoxidase, type 1 deiodinase, and thyrotropin receptor. However, serum thyroid hormones significantly decreased, without changes in serum thyrotropin (TSH). *In vitro*, rutin was able to potently inhibit TPO iodide-oxidation activity, showing an IC50 of 3.4 mM. Treatment with rutin significantly increased hypothalamus, pituitary and brown adipose tissue type 2 deiodinase activities and decreased liver type 1 deiodinase activity. We conclude that *in vivo* treatment with rutin is able to affect thyroid hormone synthesis and metabolism, reducing serum thyroid hormone concentration. Further studies are needed in order to determine whether type 2 deiodinase increase could prevent tissues from serum hypothyroidism.

P220

PAX8 CONTRIBUTES TO TSH REGULATION OF DIO1 GENE TRANSCRIPTION BY A NOVEL MECHANISM INVOLVING ITS BINDING TO THE 3'UTR REGION

Leoni SG[1], *Ruiz-Llorente S*[2], *Santisteban P*[1]
[1]Inst. Investigaciones Biomedicas de Madrid, Departamento de Fisiopatología Endocrina y del Sistema Nervioso, Madrid, Spain, [2]Memorial Sloan-Kettering Cancer Center, New York, United States

It has been described that TSH regulates DIO1 (deiodinase type 1) expression, however the mechanisms involved in this regulation is not yet clarified. The screening for Pax8 binding sites along the genome of rat thyrocites, previously done by our group using ChIP-Seq and expression arrays, allowed us to identify a Pax8 binding site on the 3´UTR region of DIO1 gene. This binding was confirmed by EMSA analysis in rat FRTL5 and human NTHY-ORI cells and also, that it is increased by TSH treatment. The **aim** of this work was to better understand the regulatory mechanism of DIO1 expression in thyroid cells.

Using a reporter vector containing DIO1 3´UTR (pGL3luc-Dio1 3´UTR), and its reverse control, we show that neither TSH (added to FRTL5 cells medium) nor Pax8 (co-transfected in HeLa cells) had any effect on 3´UTR activity. However, TSH increased the activity of DIO1 promoter (pGL-4luc-Dio1 promoter) while Pax8 had no effect in co-transfection assays. Nevertheless, Pax8 seems to be essential for DIO1 expression, as the silencing of Pax8 in thyroid cells leads to an inhibition of DIO1 mRNA levels. Then, we suggest the existence of a novel mechanism by which Pax8 binding to DIO1 DNA on 3´UTR region is regulating DIO1 gene transcription. Experiments in progress, with new vector constructs containing DIO1 promoter linked to its 3´UTR will elucidate the role of this new Pax8 binding motif on DIO1 transcriptional regulation in thyroid cells.

Supported by of Grants BFU-2010-16025, RETIC RD06/0020/0060 and S2011/BMD-2328 TIRONET

P221

TRANSCRIPTION FACTOR NKX2.5 REGULATES H2O2 GENERATION AND IODIDE UPTAKE IN PCCL3 CELLS

Cardoso LC[1], *Penha RCC*[2], *Carvalho DP*[2], *Ferreira ACF*[2]
[1]UFF, Departamento de Patologia, Niterói, Brazil, [2]UFRJ, Instituto de Biofísica Carlos Chagas Filho, Rio de Janeiro, Brazil

Objetives: DUOX1 is the main source of H2O2 in rat thyroid cell line (PPCL3) an essential cofactor for thyroid hormones biosynthesis. NKX2.5 is expressed during thyroid embryogenesis (E8.5–12) and positively modulates Tg and TPO promoters. We have previously shown that DUOX2 promoter activity is also stimulated by NKX2.5. Moreover, mutations in NKX2.5 are related to thyroid digenesis and cardiac defects. Despite that, little is known about the role of this factor on thyroid H2O2 generation and iodide uptake. Herein, we have investigated if NKX2.5 is able to modulate DUOX1, DUOX maturation factor (DUOXA1) expression, H2O2 generation and iodide uptake in PCCL3 cells.

Methods: PCCL3 (1.5 x10^5) cells were cultured in HAM's F12 medium, penicillin, bovine fetal serum. Plasmids encoding mouse NKX2.5 were transfected in PCCL3 cells and, 24 h later, cells were collected for DUOX1 and DUOXA1 RNAm detection (qPCR). GUS gene was used as internal control. Thyroid H2O2 extracellular generation was evaluated by Amplex red assay and radioiodide uptake was evaluated 45min after ^{125}I addition.

Results: We have found an increase in DUOX1 and DUOXA1 mRNA levels in cells transfected with NKX2.5. Moreover, H2O2 extracellular generation was also stimulated in the presence of NKX2.5 while iodide uptake was decreased.

Conclusion: Our data suggest that NKX2.5 is able to regulate H2O2 generation in PCCL3 cells, probably due to induction of DUOX1 and DUOXA1 expression. Since increased H2O2 levels could lead to increased oxidative stress to thyroid cells, the decrease in radioiodide uptake found in cells transfected with NKX 2.5 might be related to oxidative damage to NIS or to a direct effect of NKX2.5 regulating NIS expression.

P222

THE FOLLICLE THYROID CELL LINE PCCL3 DIFFERENTIALLY RESPONDS TO LAMININ AND TO POLY-LAMININ, A POLYMERIC FORM OF LAMININ ASSEMBLED AT ACIDIC PH

Palmero CY[1], *Carvalho DPD*[1], *Merlmestein CS*[1], *Coelho-Sampaio T*[1], *Miranda-Alves L*[1], *Nasciutti LE*[1]
[1]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

The extracellular matrix protein laminin forms polymers both *in vivo* and *in vitro*. Acidification of pH leads to the formation of an artificial polymer with biomimetical properties, named polylaminin (polyLM). Follicle cells in the thyroid are in close contact with laminin, but their response to this important extracellular signal is still poorly understood. PCCL3 cells cultivated on glass, regular laminin (LM) or laminin previously polymerized in acidic pH (polyLM) showed distinct cell morphologies and propensities to proliferate, as well as differences in the organization of their actin cytoskeleton. While on polyLM cells displayed a typical epithelial morphology and organized actin fibers radially, on LM they spread irregularly on the substrate, lost cell contacts and produced thick actin fibers, which expanded the whole width of the cytoplasm. Iodide uptake equally decreased in response to both laminin substrates in comparison to glass. When we analyzed NIS expression in PCCL3 cells cultivated on laminin substrates we observer that both laminin substrates decreased the NIS expression. By immunocytochemistry, we demonstrated that when PCCL3 cultivated on the glass showed a NIS distribution punctual in plasma membrane, on poly-LM the NIS was observed mainly in perinuclear compartment, and on LM NIS was observed more diffusely throughout the cytoplasm. Finally, polyLM was shown to specifically favor the maintenance of cell polarity in culture. In this study we demonstrated that PCCL3 cells can discriminate between LM and polyLM and that they respond to the latter by better preserving their phenotype as in the thyroid tissue.

PO25 Clinical Thyroid Autoimmunity 2

P223

AGE-RELATED FEATURES OF ASSOCIATIVE BONDS BETWEEN IMMUNOGLOBULINS TO LYMPHOTROPIC VIRUS AND IMMUNE RESPONSE COMPONENTS IN WOMEN WITH AUTOIMMUNE THYROIDITIS

Karachentcev Y[1,2], *Goncharova O*[2], *Kravchun N*[1], *Iliyna I*[1]
[1]PI «V. Danilevsky Institute of Endocrine Pathology Problems at AMS of Ukraine », AMS of Ukraine, Kharkov, Ukraine, [2]Kharkov Medical Academy of Postgraduate Education, of Endocrinology and Pediatric Endocrinology, Kharkov, Ukraine

Today, role of latent viral infection in initiation of autoimmune thyroiditis (AIT)is being actively discussed. Since there is a significant increase in frequency of AIT among postmenopausal women, age-related differences in role of virus in it must be of interest.

Aim: to establish correlation between immunoglobulins (Ig) to cytomegalovirus (CMV) and herpes simplex virus (VSH) and components of cellular and humoral immunity in women with AIT in reproductive and postmenopausal ages.

Materials and methods: Investigated IgG to CMV and VSH in women with AIT in menopausal (51,4±0,46 years, n=26) and reproductive (31,4±0,82 year, n=29) periods and in control group without thyroid pathology at age of 50,8±0,69 (n=10) and 31,8±1,0 (n=9). In women with AIT investigated also CD3, CD4, CD8, CD16, CD21, CD95, ATTG and ATTPO. Correlation analysis was performed by Pearson method.

Results: Levels of IgG to CMV and to VSG in women with AIT didn´t exceed control data (IgG-CMV in reproduction were 2,36±0,19 vs. 2,55±0,48 in control; in postmenopause 2,46±0,21 vs. 2,92±0,28; in control at a rate of < 0,268 g/l; IgG VSH in reproduction were 3,85±0,04 vs. 4,11±0,03 in control; in postmenopause 3,72±0,06 vs. 3,87±0,05 at a rate of < 0,170 g/l), although they were elevated in all of the women surveyed. Valid correlation between IgG-CMV and cellular immune components was found only in reproduction: with CD4+ (r=-0,572, p< 0,01), CD8+ (r=0,415, p < 0,01), IRI (r=0,319, p< 0,05), CD16+ (r=0,419, p< 0,01). Whereas, valid correlation was determined between IgG-VSH in menopause with CD4+ (r=0,412, p< 0,05), IRI (r=0,392, p< 0,05), CD21+ (r=0,616, p< 0.01) and in reproduction with CD3+ (r=0,499, p< 0,01) and CD21+ (r=0,420, p< 0,05). None of the viruses showed an associative bond with antithyroid antibodies.

Conclusion: In women with AIT availability bonds exist between CMV and HSV and only cellular immunity. Age factor plays significant role in nature of these bonds.

P224

EVALUATION OF CD4+CD161+CD196+ AND CD4+IL-17+ TH17 CELLS IN THE PERIPHERAL BLOOD OF YOUNG PATIENTS WITH GRAVES' DISEASE AND HASHIMOTO'S THYROIDITIS

Bossowski A[1], *Moniuszko M*[2], *Dąbrowska M*[3], *Jeznach M*[2], *Rusak M*[3], *Bossowska A*[4], *Sawicka B*[1], *Borysewicz-Sańczyk H*[1], *Bodzenta-Łukaszyk A*[2]
[1]Medical University in Bialystok, Dep. of Pediatrics, Endocrinology, Diabetology with Cardiology Subdivision, Bialystok, Poland, [2]Medical University in Bialystok, Department of Allergology and Internal Medicine, Bialystok, Poland, [3]Medical University in Bialystok, Dep. of Hematology Diagnostic, Bialystok, Poland, [4]Internal Affairs and Administration Ministry Hospital in Białystok, Department of Cardiology, Bialystok, Poland

Objectives: Up till now, altered balance of Th1 and Th2 immune cells has been postulated to play an important role in the pathogenesis of autoimmune thyroid diseases (AITD). However, recent studies on thyroid diseases suggest a new role for Th17 (T helper 17) cells that have been classified as a new lineage, distinct from Th1, Th2 and Treg cells. Despite wide interest, role of

Th17 cells in the pathogenesis of inflammatory and autoimmune diseases is still debated. Th17 cells can be characetrized by several surface markers, i.e. CCR6 (CD196), IL-23R, IL-12Rbeta2 and CD161.

The aim of the study was to estimate the frequencies of circulating CD4+CD161+CD196+ and CD4+IL-17+ Th17 cells in patients with Graves' disease (GD, n=20, mean age ± SEM 15.3±2.6 years), Hashimoto's thyroiditis (HT, n=20, mean age ± SEM 16±2.5 yrs) and in healthy controls (C, n=20, mean age ± SEM 16.3±3 yrs).

Methods: Polychromatic flow cytometry and several fluorochrome-conjugated monoclonal antibodies were applied to delineate Th17 cells with either CD4+CD161+CD196+ or CD4+IL-17+ phenotype. Thyroid binding inhibiting immunoglobulins (TBII), anti-thyroperoxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies were measured in all samples using electrochemiluminescence "ECLIA" with Cobas analyzer (Roche Diagnostics, Poland).

Results: In untreated HT children we observed a tendency to increased frequencies of CD4+CD161+CD196+ (8.9±3.5 vs 7.7±2.8, p< 0.05) and CD4+IL-17+ Th17 (3.7±2.7 vs 2.5±1.4, p< 0.01) lymphocytes in comparison to the healthy controls. In untreated GD children we didn't reveal such abnormalities in the population of these cells compared to controls. In cases with HT, positive correlation between percentage of CD4+CD161+CD196+ T cells and serum level of anti-TPO antibodies (r=0.65, p< 0.01) was detected.

Conclusions: We conclude that the increase percentage of Th17 cells in children with Hashimoto's thyroiditis can suggest their role in initiation and development of immune processes in this endocrinopathy.

P225

CHARACTERISTICS OF THE AUTOIMMUNE THYROIDITIS IN PATIENTS WITH DIABETES MELLITUS OF THE 1, 2 TYPE

Kravchun NA[1], *Chernjavskay IV*[1]
[1]Institute of Problems of Endocrine Pathology n.a. V.Y. Danylevskogo of AMS of Ukraine, Department of Pharmacotherapy of Endocrine Diseases, Kharkov, Ukraine

Aim: to study the particularities of the autoimmune thyroiditis (AIT) in patients with diabetes mellitus (DM) 1, the 2 type.

Methods: two groups of patients were examined: the 1st - 25 patients with AIT and DM, 1 type, the 2nd - 30 - with AIT and DM, 2 type, by the decompensation of the carbohydrate metabolism. The subpopulation lymphocyte composition was studied by the immunoperoxidase method while the levels of IL-6, leptin - by the immunoenzyme method. There were made the calculations of immunoregulatory index (IRI).

Results: The 2nd group at the elder age (p< 0,05) have higher figures of BWI (p< 0,01) and levels of TG, ß-lp, TG (p< 0,01). The levels of TG were compared (3,2 ± 12 and 2,68 ± 14 ME/ml). The level of AT to TG was higher than by the 2nd group of patients and amounts 2,2 ± 0,24 and 1,6 ± 0,15 (p< 0,01). The elevation of IRI level was observed among the 2nd group (considering the reduction of the cytotoxic T-lymphocyte) - 4,0 and 2,2, IL-6 - 22,8 [14,2;32] and 5,6 [5,3;1] pg/ml and leptin - 32,4 [26,4;44,2] and 15,5 [1;9,8] pg/ml.

Regarding the data of ultrasound investigation the focal changes in the tissue of the thyroid gland were diagnosed more frequently among the 2nd group of patients, (74,8% and by 1,1%).

Conclusions:

1. Elevation of AT to TG takes place among the patients with AIT and DM, 2 type.
2. In cases the conspicuous metabolic changes by DM, 2 type and obesity, cytokine imbalance notified at the elevation of IL-levels - 6 and leptin and indicates the activation of the immune system.

The elevation of the immunoregulatory index among the patients with of the DM, 2 type contributes to the progress of the autoimmune process.

P226

AUTOIMMUNE THYROIDITIS IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS IN ARMENIA: ASSOCIATION WITH GENDER, AGE, DIABETES DURATION AND PUBERTY

Navasardyan LV[1], *Aghajanova YM*[1], *Arakelyan LM*[1], *Bayburdyan GM*[1], *Hakobyan SV*[1], *Kalantaryan LG*[1]
[1]Yerevan State Medical University, Endocrinology, Yerevan, Armenia

Objectives: The prevalence of positive thyroid antibodies in children with type 1 diabetes (T1DM) varies considerably between 3–50% in different countries. The aim of this study was to investigate the prevalence of autoimmune thyroiditis in a large cohort of T1DM children and adolescents in Armenia, whether the sex, age and diabetes duration influence on prevalence of AIT.

Materials and methods: Since 2009, 225 children and adolescents with T1DM from 325 registered on Armenia were included in this investigation. Thyroid-stimulating hormone (TSH), anti-peroxidase-antibody (Anti-TPO) levels were measured, age, DM duration, thyroid ultrasound signs were documented. A total of 51,6% of these patients were boys (0–18 years), the range of diabetes duration was from 0–15 years. TSH values >4,0µU/ml and an Anti-TPO titer exceeding 34U/ml were considered to be elevated. AIT was diagnosed in case of both elevated TSH and Anti-TPO or elevated TSH and thyroid ultrasound changes (enlargement, typical patterns of hypoechogenicity, diffuse changes, parenchymal hypervascularity).

Results: A total of 30 (13,3%) patients had T1DM with AIT, and females were dominant (63.4%-19 patients) over males (36.6%-11 patients), compared T1DM patients without AIT (46.1% of patients were girls). The highest prevalence of AIT (40%) was registered in patients with diabetes duration from 0.5–5 years, then 26.6%-at the onset of diabetes, 20%-in patients with 6–10 years of diabetes duration, 13.3%-in patients with diabetes duration more than 10 years. The highest prevalence of AIT was detected in 10–15 years children and adolescents (pubertal age).

Conclusions: AIT seems to be particularly common in girls with type 1 DM in the second decade of life with diabetes duration from 0.5–5 years in Armenia. Yearly TSH and Anti-TPO examination, ultrasound of thyroid gland is suggested to be part of routine tests in T1DM population, especially in girls during puberty, to make a precocious diagnosis of AIT.

P227

DOES FAMILY AND PERSONAL HYSTORY OF AUTOIMMUNE AND THYROID DISEASES INFLUENCE GRAVES DISEASE PRESENTATION AND EVOLUTION?

Martin CS[1,2], *Predescu A*[1], *Fica S*[1,2]
[1]Elias Hospital, Endocrinology, Bucharest, Romania, [2]"Carol Davila" University of Medicine and Pharmacy, Endocrinology, Bucharest, Romania

Objective: Graves´ disease (GD) is the most common form of thyrotoxicosis, currently viewed as an autoimmune disease of unknown cause. Both genetic and environmental factors contribute to susceptibility of GD. There is a strong familial predisposition in that about 15% of patients with GD have a close relative with the same disorder. In this study we evaluated wether positive family and personal history of autoimmune or thyroid diseases influence the first presentation or the clinicoparaclinical evolution of GD patients.

Design: prospective observational study.

Patients: 98 consecutive untreated patients with GD, at the first episode of hyperthyroidism, mean age 43 years, 80, 6% females were included. We evaluated the clinical and biochemical severity of hyperthyroidism at diagnosis, and recorded the personal and family history of autoimmune and thyroid diseases; patients were started on antithyroid drugs (ATD), followed-up with regular visits and dose/ duration of treatment recorded.

Results: 9,2% had family history of autoimmune diseases (FHAD), 19,4% family history of thyroid disorders (FHTD), 10,2% personal history of autoimmune diseases (PHAD) and 14,3% personal history of thyroid diseases (PHTD). The GD patients with FHAD had similar FT4 and TT3 at diagnosis, but significantly lower FT4 (p=0,001) and TT3 (p=0,002) at the first visit after the initiation of ATD and they needed a shorter time until TSH return to

normal (p=0,05) compared to the group without FHAD; the GD patients with PHAD had a lower FT4, FT4/TT3 ratio (p=0,009) at diagnosis and needed a lower medium doze of ATD(mg/day) until TSH returned to normal (p=0,016) compared to the GD group without PHAD.

Conclusion: Our study supports the hypothesis that positive family or personal history of autoimmune diseases may be associated in GD patients to a less severe presentation and a better short term prognosis.

P228

ANAEMIA IN INDIAN SUBJECTS WITH AUTOIMMUNE THYROID DISEASE: COULD IT BE A SURROGATE MARKER FOR AUTO IMMUNE GASTRITIS?

Varthakavi PK[1], *Lathia TB*[1], *Joshi AS*[1], *Nishtala S*[2], *Bhagwat NM*[1], *Chadha MD*[1], *Dholye JP*[1], *Rathi P*[2], *Kamat SM*[1]
[1]T.N. Medical College & BYL Nair Ch. Hospital, Endocrinology, Mumbai, India, [2]T.N. Medical College & BYL Nair Ch. Hospital, Gastroenterology, Mumbai, India

Background: Nutritional Anemia is highly prevalent in India. It may co exist with and impact the quality-of-life of patients with thyroid disorders.

Autoimmune thyroid disorders(AITD), may be associated with Autoimmune gastritis(AIG) which is characterized by Parietal cell antibodies, atrophic body gastritis and hypergastrinemia. AIG is associated with achlorhydria, pernicious anaemia(PA) and iron deficiency.

Aim:

1. To determine the prevalence of AIG in patients with AITD in Mumbai, India.
2. To diagnose and characterize anemia in this population.

Methods: 69 consecutive patients (7 M/ 62 F mean age 37.5 years) with serologically proven AITD and seronegative for H.Pylori and 20 nonanaemic, age and gender matched controls were recruited for the study. Venous blood was collected for estimation of serum gastrin and antiparietal cell antibodies(APCA), haemogram, Iron studies, and assays of Vitamin B12 and folic acid.

Results: 15/69 patients (21.73%) were positive for APCA. 66% of APCA positive and 23.63% of APCA negative patients had hypergastrinemia

Conclusions: The prevalence of AIG is 21.73%. Patients with AIG, had lower Ferritin, Serum Iron and transferrin saturation suggesting iron deficiency compared to controls and patients without AIG.

AIG may unmask Iron deficiency, and this may be the earliest manifestation of Atrophic body gastritis

---

P229

THYROID DISORDERS IN CUSHING'S SYNDROME

Manetti L[1], *Raffaelli V*[1], *Scattina I*[1], *Lupi I*[1], *Cosci C*[1], *Gasperi M*[2], *Cosottini M*[3], *Iannelli A*[3], *Bogazzi F*[1], *Martino E*[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy,
[2]University of Molise, Chair of Endocrinology, Campobasso, Italy,
[3]University of Pisa, Department of Neurosciences, Pisa, Italy

Cushing's syndrome (CS) is characterized by abnormalities of immune function. Moreover autoimmune disease, including thyroid disorders, improve during active CS. It is also known that hypercortisolism can affect thyroid function both at the hypothalamic-pituitary both at the thyroid-level.

Objective of this longitudinal study was to evaluate the prevalence of autoimmune thyroid diseases and positive thyroid antibodies in patients with CS and the possible association with nodular goiter.

One hundred thirty-two patients with CS were enrolled in the study. Eighty-nine patients were affected by an ACTH-secreting pituitary adenoma, 4 had an ectopic ACTH secretion and 39 had an adrenal adenoma. Free thyroid hormones (fT4, fT3), TSH, antithyroglobulin (TgAb), antithyroperoxidase (TPOAb) and thyroid ultrasound were performed in all patients at baseline and after the cure.

At the last observation, after surgery and/or radiotherapy or medical treatment, 97 patients were in remission of disease (71%) and 35 had persistence/recurrence of hypercortisolism (29%). Follow up period ranged from 11 to 180 months. Serum TSH concentrations were significantly lower during hypercortisolism than in remission (0.82±0.83 *vs* 1.30±0.90 mg/ml, p< 0.001). The prevalence of positive TgAb titre was significantly higher in remission CS (15.5%) than in active phase (8.4%), while positive TPOAb titre was similar in the two groups (8%) The prevalence of Hashimoto's thyroiditis (HT) was similar in patients with remission (9.3%) and in active phase (11.4%). In summary, 15 CS patients were affected by autoimmune thyroid disease (Graves' disease and HT), 46 had non-toxic nodular/multinodular goiter, 4 patients had toxic nodular/multinodular goiter (mild or severe), 4 patients a non-nodular goiter and 4 patients a thyroid cancer.

In conclusion, patients with CS showed a high prevalence of thyroid disorders. Moreover, patients successfully treated for CS have an increased prevalence of thyroid autoimmunity.

P230

THYROID FUNCTION IN EUTHYROID PATIENTS WITH HASHIMOTO´S THYROIDITIS IS DIFFERENT THAN IN HEALTHY SUBJECTS

Zaletel K[1], *Žitko-Krhin M*[1], *Gaberšček S*[1], *Grabnar I*[2], *Hojker S*[1]
[1]University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

Objectives: It is believed that thyroid function in patients with euthyroid Hashimoto´s thyroiditis (EuHT) is not affected and therefore we usually do not treat those patients. The aim of our study was to compare thyroid function tests and serum fT4/fT3 ratio between patients with EuHT and healthy subjects (HS).

Methods: We included 509 EuHT patients and 564 HS, evaluated at our thyroid department in the period between March 2009 and February 2010. Among EuHT 52 were males and 457 were females aged between 15 and 88 (mean, 47.5±16.9 years). HS group included 137 males and 427 females and their age was between 15 and 85 (mean, 42.5±17.7 years). EuHT was diagnosed in patients with positive thyroid peroxidase antibodies and/or thyroglobulin antibodies and with characteristic hypoechoic thyroid ultrasound pattern. HS were negative for thyroid antibodies and on ultrasound thyroid appeared isoechoic. In all subjects we measured TSH, fT4, fT3 and all values were within normal range (0.35–5.5 mU/L, 11.5–22.7 pmol/L and 3.5–6.5 pmol/L, respectively). Additionally, fT4/fT3 ratio was calculated.

Results: In EuHT, TSH level was significantly higher than in HS (median, 3.158 and 2.110 mU/L, respectively, p< 0.01). The fT4 level was significantly lower in EuHT compared with HS (median, 13.8 and 14.8 pmol/L, respectively, p< 0.01). Interestingly, only in subjects with TSH below 0.7 mU/L the fT4 level did not differ between EuHT and HS. There was no significant dif-

Table for Abstract P228.

Parameter	Controls N=20	APCA negative normal gastrin N=41	APCA negative high gastrin N=13	APCA positive high gastrin N=10	APCA positive normal gastrin N=5
S.Gastrin *	25.75 (3.7)	27.01 (2.05)	99.3 (9.71)	101.52 (12.81)	24.96 (1.54)
Haemoglobin#	12.6 (0.25)	10.75 (0.29)	10.5 (0.57)	10.19 (0.31)	10.7 (0.35)
MCV	82.8 (1.0)	79.17 (1.39)	74.01 (2.8)	78.45 (1.99)	78 (2.29)
S. Iron*	80.8 (1.1)	71.58 (1.65)	70 (2.6)	66.5 (1.67)	66.1 (2.91)
TIBC #	404.5 (9.01)	437.56 (7.48)	446.36 (14.26)	447 (11.74)	420 (16.43)
% Saturation*	19.9 (0.74)	16.72 (0.63)	15.84 (1.12)	15.19 (0.77)	14.9 (0.25)
Ferritin #	33.95 (6.5)	21.85 (2.95)	10.9 (3.52)	12.95 (1.99)	5.125 (1.42)
Vitamin B12	248 (19.1)	265.6 (18.15)	282.2 (27.7)	331.9 (36.22)	226 (16.96)
Folic Acid	6.92 (0.8)	7.45 (0.89)	7.05 (1.65)	12.06 (2.13)	9.06 (1.80)

ference in fT3 level between the two groups. Accordingly, the fT4/fT3 ratio was significantly lower in EuHT than in HS (median, 2.73 and 2.89, respectively, p< 0.01). Only when TSH was below 1.4 mU/L the fT4/fT3 ratio did not differ significantly between EuHT and HS.

Conclusions: Although considered euthyroid, patients with EuHT differ significantly from subjects with healthy thyroid with respect to TSH, fT4 and fT4/fT3 ratio.

PO26 Environmental Factors and Drugs Affecting Thyroid Function 1

P231

THYROID DISORDERS IN ADULT POPULATION OF UKRAINE AFTER THE CHERNOBYL NPP ACCIDENT

Kaminskyi OV[1], *Afanasyev DY*[1], *Kovalenko OM*[1]
[1]National Research Center for Radiation Medicine of NAMS of Ukraine, Department of Radio-Induced General and Endocrine Disease, Kiew, Ukraine

Objectives: After the March 2011 nuclear accident in Fukushima there is a strong concern towards the consequences of man-made disasters such as the Chernobyl NPP accident (ChNPPA) (1986). We present some new data on thyroid disease in ChNPPA survivors in Ukraine under the environmental iodine deficiency.

Methods: The incidence of thyroid disease was analyzed in 7588 ChNPPA emergency workers engaged in activities in 1993–2010. Data were compared to the indices of official statistics from the entire population of Ukraine (the control group). Additionally 379 emergency workers and 556 persons from the control group were involved in verification study with application of thyroid ultrasound and assay of serum thyrotropin, thyroid hormones and thyroid antibodies.

Results: Nodular goiter and chronic autoimmune thyroiditis were found being most frequent thyroid diseases in the ChNPPA emergency workers vs. the entire population i.e. 24% vs. 0.53% ($p \leq 0.01$) and 14.5% vs. 0.35% ($p \leq 0.01$). Prevalence of autoimmune thyroiditis among the ChNPPA emergency workers is increasing since 1997 being stable in the control group. High prevalence of nodular goiter (24.2%) and autoimmune thyroiditis (23.7%) in emergency workers was confirmed by the additional study results debating at that the official statistics data in control group. Namely the nodular goiter was found in 20.6% and autoimmune thyroiditis - in 17.8% of Ukrainian population in general.

Conclusions: Thyroid diseases after the ChNPPA in population of Ukraine arise not only due to the impact of ionizing radiation but also are predetermined by environmental iodine deficiency predisposing to active accumulation of excessive iodine by the hypertrophied thyrocytes.

Radiation accidents are unpredictable and the respective risk is always present here. Therefore adequate and proper iodine prophylaxis is desirable for population of the iodine-deficient regions aiming among other the prevention of excessive thyroid accumulation of iodine after possible nuclear accident and prophylaxis of thyroid disease.

P232

SURVEY OF THE MANAGEMENT OF AMIODARONE INDUCED THYROTOXICOSIS

Taylor P[1], *Raghavan R*[2], *Bhake R*[3], *Vaidya B*[4], *Martino E*[5], *Bartelena L*[6], *Dayan C*[1], *Bradley K*[2]
[1]Cardiff University, Centre for Endocrine and Diabetes Sciences, Cardiff, United Kingdom, [2]Bristol Royal Infirmary, Department of Endocrinology, Bristol, United Kingdom, [3]University of Bristol, HWLINE, Bristol, United Kingdom, [4]Peninsula Medical School, Department of Endocrinology, Royal Devon and Exeter Hospital, Exeter, United Kingdom, [5]University of Pisa, Department of Endocrinology, Pisa, Italy, [6]University of Insubria, Department of Cilnical Medicine, Varese, Italy

Objectives: AIT is difficult to manage and requires considerable clinical acumen; at present there are no formal UK guidelines for the differentiation between type 1 and type 2 AIT and their management.

Methods: We conducted an online survey of members of the Society for Endocrinology, UK and the British Thyroid Association to collate current UK opinion regarding the current management of AIT.

Results: 179 endocrinologists (21.2%, n=38 were trainees) took part. Overall a consensus was reached on recommending use of TPO antibodies and thyroid gland morphology in differentiating type-1 and type-2 AIT. Radioiodine uptake, colour flow doppler sonography and Technetium scintigraphy are currently used in similar proportions with radioiodine uptake being marginally preferred. In type-1 AIT, thionamides were the initial treatment of choice (80%) with 71% opting for thionamides alone and 9% opting for combination therapy with glucocorticoids. This is lower than the European Thyroid Association (ETA) 2004 survey where 98% of respondents would use thionamides either alone or in combination with glucocorticoids/potassium perchlorate. 12% of respondents adopted a wait-and-see policy simply compared to 1% in the ETA survey. The use of potassium perchlorate by UK endocrinologists was far lower (3% vs. 31%) than our continental colleagues.

In type-2 AIT the majority of clinicians in our survey (69.4%) would use glucocorticoids; 36.6% opted for glucocorticoids alone, with 32.8% selecting combined glucocorticoid and thionamide therapy. Surprisingly 21% (n=29, consultants=27/29) would initially use thionamides alone. This is markedly different from the ETA survey where 100% of respondents would give glucocorticoids either alone or in combination with thionamides.

Conclusions: Our survey highlights that the treatment of AIT in the UK varies from that of the previous European view (especially higher threshold for initiating treatment and less use of potassium perchlorate). Clear UK/European guidelines would be helpful in standardising and agreeing current best practice.

P233

HOW IS IODINE SUPPLY MAINTAINED DESPITE LOW DIETARY IODINE INTAKE?

Smyth PPA[1,2], *Burns R*[1], *Huang R-J*[2], *Hoffman T*[3], *O'Dowd C*[2]
[1]University College Dublin, School of Medicine, Dublin, Ireland, [2]National University of Ireland (Galway), School of Physics, Galway, Ireland, [3]Johannes Gutenberg Univ of Mainz, Inst. of Inorganic and Analytical Chemistry, Mainz, Germany

Dietary iodine status in a population is conventionally established by measuring urinary iodine excretion (UI) in a group of schoolchildren. However there is a debate whether this group accurately reflects requirements of the population at risk from iodine deficiency disorders (IDD), namely pregnant mothers. In spite of lower dietary iodine intake and borderline UI there was little evidence of (IDD) in a population with minimal iodised salt availability (< 5% of salt iodised). We have previously shown that while iodine is in the main supplied from dietary sources, living near the sea in a seaweed abundant environment and therefore exposed to gaseous I2 ingestion by respiration may confer advantages in terms of iodine intake. This communication examines if this environment equally affects the iodine intake of adults and schoolchildren. Atmospheric I2 measured by gas chromatography-mass spectrometry (GC-MS) was greatest over the seaweed mass (Median 186: range 110-301PPT) compared to inland values of 15-18PPT. Iodine intake was assessed by measuring urinary iodine (UI) excretion by persulphate digestion. UI was measured in schoolchildren(Median age,12 years) and adults living in a coastal area of Galway on the West coast of Ireland. Highest values for UI

were observed in schoolchildren (Median UI 145µg/L; n=46). The greatest number of UI values > 150 µg/L (45.6%) was also observed in this group. In contrast, the median UI in the adult cohort (n=98) was 84ug/L with only 5.9% > 150 ug/L. These findings suggest that intake of seaweed derived gaseous I2 may preferentially influence iodine intake in children perhaps reflecting the the much greater inhalation dose coefficient (DC) in younger age groups. The findings, in addition to indicating a role for respiration in determining iodine intake, support the concept that schoolchildren may not adequately reflect the iodine intake of adult populations at risk of IDD.

P234

THYROID DISORDERS IN PATIENTS HEMATOLOGICAL MALIGNANCIES

Nonchev BI[1], Goranova-Marinova V[2], Pavlov P[3], Orbetzova M[1], Goranov S[2]
[1]Medical University, Endocrinology, Plovdiv, Bulgaria, [2]Medical University, Hematology, Plovdiv, Bulgaria, [3]Medical University, Central Clinical Laboratory, Plovdiv, Bulgaria

Background: There are few reports in the literature focused on the prevalence and characteristics of thyroid disorders in patients with hematological malignancies. Furthermore, some of the major treatment modalities for these diseases as alpha-interferons and Thyrosine-Kinase Inhibitors affect the thyroid functional state by various mechanisms.

Aim: To study the parameters of thyroid function, morphology and autoimmunity in patients with hematological malignancies.

Patients and methods: 62 patients were analyzed, male/female = 1/1.06, mean age 59y (20–76). Thyrosine kinase inhibitors were applied in 25 (40.3%) patients with chronic myeloid leukemia; interferon-alfa in 37 patients with the following underlying hematological diseases: 15 (24.2%) - Essential thrombocytemia, 8 (12.8%) - Hairy cell leukemia, 5 (8.1%) - Polycytaemia vera, 4 (6.5%) - Mycosis fungoides, 4 (6.5%) - Chronic myeloid leukemia, 1 (1.6%) - Multiple myeloma. Mean time since diagnosis was 32.8 mo (5–68). The following thyroid markers were analyzed: TSH, FT3, FT4, TAB, TPO-Ab -(hemiluminescent immune analysis), TRAB (ELISA), ultrasonography.

Results and discussion: Abnormal thyroid tests were found in 20.75% (n=11) of the studied group. Autoimmune thyroiditis was the most frequent thyroid pathology. No predictive significance was found for the diagnosis, duration and phase of the disease, type and duration of therapy. The prognosis of the patients with hematological malignancies is significantly improved in the last decade. Changes in thyroid functional tests should be taken into consideration in their complex evaluation. The data from the analysis reveal the need of further investigation.

P235

IODINE DEFICIENCY IN EASTERN UKRAINE

Mamenko M[1], Belykh N[1], Shleyenkova G[1], Sherbakova M[1]
[1]Luhansk State Medical University, Department of Postgraduate Education in Pediatrics, Luhansk, Ukraine

Background: Iodine deficiency disorders (IDD) result from inadequate thyroid hormone production. IDD are one of the most common human diseases. Ukraine does not yet have a national program for control of iodine deficiency and there are no recent data on the severity of the iodine deficiency disorders (IDD) in some parts of the country.

Objctive: The aim of the present study was to assess current IDD status in Eastern Ukraine.

Methods: 1-st target group: school children 6–12-y-old (n=934). Methodology for selection: school-based 30-cluster survey (proportionate to population size). Salt iodine content: by rapid test kits. Dietary iodine intake in population: urinary iodine concentration (UIC) (Sandell-Kolthoff reaction). Thyroid size: by ultrasonography; compared to normative value, presented as a function of age, sex and body surface area (WHO, 2001 & 2007). 2-nd target group: infants.

Methodology: TSH screening (n=46235). Epidemiological criteria: WHO/ICCIDD, 2001, 2007.

Results: 18% of household salt samples were iodized in adequate level. Recommended by WHO/ICCIDD rate of iodized salt usage to prevent IDD is 90–95%. The median UIC in school children was 83µg/liter (mild level of iodine deficiency 50,0–99,0µg/liter). The goiter prevalence was 27,7% (normative data WHO, 2001) and 48,7% (normative data WHO, 2007). Transient neonatal hyperthyrotropinemia rate was 20,5% (moderate level of iodine deficiency 20,0–39,9%).

Conclusions: In Eastern Ukraine school children are mildly iodine deficient. But the prevalence of goiter corresponds to the moderate level of IDD. Coexisting deficiencies of iodine and iron and severe environmental conditions at the industrial cities can impair thyroid function. High rate of transient neonatal hyperthyrotropinemia proves iodine deficiency in population. Ukraine needs a national program for control of iodine deficiency.

P236

DRUG-INDUCED THYROIDITIS BY NEW TREATMENTS SUCH AS ANTI-TUMOR NECROSIS FACTOR (TNF)

Favre L[1], Ducry J[1], Portmann L[1]
[1]University Hospital CHUV, Service d'endocrinologie, diabétologie et métabolisme, Lausanne, Switzerland

The introduction of new biological immunosuppressive agents may cause various insults to the thyroid gland with diagnostic pitfalls. We report two unusual cases of subacute thyroiditis caused by anti-TNF therapy.

Case 1: A 49-year-old woman was treated during 4 months with golimumab (Simponi) for spondylarthropathy. A few days after the last injection she experienced fatigue, palpitations and episodes of fever. Hyperthyroidism was present, the thyroid gland was normal by palpation while ultrasound showed a heterogeneous mildly enlarged thyroid (19 ml) with hypoechogenic areas and no hypervascularisation. Autoantibodies were negative and thyroglobulin was elevated. The scintigraphy revealed decreased uptake of Tc-99m. The hyperthyroid state resolved spontaneouly followed by a transient phase of mild hypothyroidism, treated by levothyroxin for two months. Four months later the patient was euthyroid, while echography showed a small thyroid (4 ml).

Case 2: Six months after introduction of adalimumab (Humira) for spondylarthropathy, a 22-year-old woman reported tiredness and cold sensitivity. Hypothyroidism was present without thyroid antibodies. The thyroid gland was normal on palpation, echography revealed a swollen heterogeneous gland with hypoechoic areas and normal vascularization. Levothyroxine administration normalized thyroid function.

Discussion: The diagnosis of drug-induced subacute thyroiditis may be ascertained considering the absence of thyroid autoimmunity and the chronology between anti-TNF administration and the beginning of the thyroid dysfunction. The spontaneous resolution after cessation of the treatment is typical of such thyroiditis in case 1. As long as the effects of anti-TNF on thyroid hormone metabolism remain unclear and the very low prevalence of thyroid dysfunction, an early diagnosis of such thyroiditis is challenging as the symptoms of any thyroid dysfunction may be incorrectly attributed to the primary disease or treatment. It is therefore critical to be aware of such uncommon side effectc and to have a low threshold for screening for thyroid dysfunction.

P237

IODINE STATUS AND THYROID FUNCTION IN HIMALAYAN MOUNTAIN POPULATIONS

Chandola-Saklani A[1], Kathait A[1,2], Farswan A[3], Yadav N[1], Kumar D[1]
[1]Apeejay Stya University, Biosciences & Clinical Research, Gurgaon, India, [2]HNBG Central University, Dept of Biotechnology, Srinagar Garhwal, India, [3]Govt PG College, Dept of Zoology, Agastya Muni, Rudraprayag, India

Objective: Himalayan mountains are known to be deficient in iodine, and, Universal Salt Iodisation program (USI) of Govt of India was launched in 1986 in the region. In this paper attempt was made to assess dietary iodine intake (SI), urinary iodine excretion (UIE), circulating thyroid hormones and prevalence of iodine deficiency disorders (IDD) in populations residing in remote Himalayan region with a view to study the impact of Indian salt iodisation program.

Method: Twenty villages were surveyed in two major river valleys viz., Alaknanda(A) & Pinder(P) in Chamoli district of Uttarakhand hill State during 2006–2011. Periodic Health camps and door to door surveys were conducted in association with Health Directorate. Questionnaire based, and, visual observations on IDD were made including palpation after informed consent involving

10–15% population at random. Subset samples of dietary salt, Urine and blood were collected for estimation of serum T4, T3 (RIA), TSH & FT4 (ELISA), UIE (WHO-photometric assay) and dietary SI (WHO-titrimetric).

Results: Indicate an overall TGR of 0.00, 0.002; mentally retarded 0.21, 0.15%; Strabismus 4.52±1.23, 0.29±0.13; Spastic diplegia 0.12±0.08, 0.04; deaf/mute 0.14, 0.17±0.07% of surveyed population in A & P valleys respectively. Circulating thyroid hormone levels were found in normal range (TSH 3.41±0.31µIU/ml, T4 124.29±3.74 ng/ml, T3 0.82±0.05 ng/ml, FT4 1.06±0.09 ng/dl) which is in harmony with the low incidence of IDD observed.

However, despite decades of USI, 70–90% population in the villages was still utilizing uniodized crystal salt '*Gara'*. This is reflected in lower UIE values observed (median 88.89, 71.26 µg/L) in the same populations, only 23% being iodine sufficient with 77% ranging from severe to mild(WHO).

Conclusion: The striking finding of these observations is the normal thyroid function and low prevalence of IDD in the face of continued iodine deficiency questioning the efficacy of USI program in the region and its utility.

P238

MULTIPLE PESTICIDES EXPOSURE OF GREENHOUSES WORKERS AND THYROID PARAMETERS

Simescu MM[1], *Podia Igna CC*[2], *Nicolaescu E*[3], *Caragheorgheopol A*[4], *Ion I*[5], *Ion AC*[5], *Neagu C*[6], *Negru M*[6], *Pribu M*[6], *Kochanska Dziurowicz A*[7], *Stanjek-Cichoracka A*[7]

[1]National Institute of Endocrinology, Endocrinology, Bucharest, Romania, [2]Astra Clinic, Endocrinology, Sibiu, Romania, [3]SC SIMEDIS CONSULT SRL, Bucharest, Romania, [4]National Institute of Endocrinology, Bucharest, Romania, [5]Politechnic University, Bucharest, Romania, [6]National Institute of Public Health, Bucharest, Romania, [7]Department of Isotopic Diagnostics, Sosnowiec, Poland

Objective: The persistence of high prevalence of thyroid pathology, despite the correction of iodine deficiency in our population, determined the evaluation of impact of factors different than iodine intake on the thyroid gland as environmental endocrine disruptors. We studied the potential correlation between pesticide exposure and parameters of the function, autoimmunity and morphology of the thyroid in a group of greenhouses workers (GHW) exposed to multiple uncontrolled pesticides across agricultural season.

Materials and methods: 108 GHW, aged 18–78 y.o, with normal iodine intake, from a plain village, were enrolled voluntary in this study. They were exposed to multiple pesticides, as confirmed by toxicological investigations. In biological samples (urine, blood) collected across 2 agricultural seasons were determined thyroid parameters (TSH; free T4; antibody to thyroid peroxidase and thyroid echography) and pesticide concentrations for chlorpyrifos (CPF), its metabolite trichlopyridinol (TCP), dimetoat, cypermetrin and carbofurane. Urinary iodine concentration (UIC) was determined in 104 schoolchildren.

Results: Median TSH 1.72±2.71 mcUI/mL, range 0.051 - 14.97; TSH higher than 4.2 in 13,92% of subjects. Median FT4 16.68 pmol/l. Positive ATPO in 18,51% of subjects. Thyroid nodules were found in 35,51% and echographic pattern suggestive for chronic thyroiditis in 14,81% of subjects. Median UIC was 135,20±59,28 µg/l. TCP was detectable in 12,5%-100% (mean 1µg/l-57,28µg/l) of samples, in different time season exposure. Carbofurane in serum was present in 50%-85,7% (mean0,125 µg/ml- 0,24 µg/ml) of samples. Cypermetrin and dimetoat concentration in the majority of samples was under the quantification limit.

Conclusions: The incidence of thyroid pathology in studied group, in conditions of normal iodine intake, was at the upper limit of known epidemiology of thyroid disease. The most frequently encountered pesticides were chlorpyrifos and carbofurane in the same samples which can have an additive effect. There are data that thyroid gland may be a sensitive target for CPF.

PO27 Graves' Orbitopathy Clinical 2

P239

IS RECOMBINANT HUMAN TSH A TRIGGER FOR GRAVES´ ORBITOPATHY?

Daumerie C[1], *Boschi A*[2], *Perros P*[3]

[1]Université catholique de Louvain, Clin. Univ. St-Luc, Endocrinology, Brussels, Belgium, [2]Université catholique de Louvain, Clin. Univ. St-Luc, Ophthalmology, Brussels, Belgium, [3]Royal Victoria Infirmary, Endocrinology, Newcastle Upon Tyne, United Kingdom

The pathogenesis of Graves' Orbitopathy (GO) remains unknown. The hypothesis of a causal relationship between autoimmunity against the TSH receptor (TSHR) and GO is supported by clinical studies. Radioiodine treatment is associated with worsening or new onset of GO, possibly via antigen shedding or by inducing hypothyroidism. Coexistence thyroid cancer with Graves' disease (GD) and GO is rare.

Here we report three cases of reactivation of GO in patients who underwent treatment with recombinant human TSH (rhTSH) and radioiodine ablation. In each case a thyroidectomy was performed to treat the GD and an incidental thyroid cancer was discovered. In all three cases, reactivation of GO was observed three to six weeks after administration of rhTSH, despite maintaining euthyroidism, which was unaccompanied by a rise in serum TSHR antibodies after radioiodine and despite steroids in one of the three patients.

These observations suggest that binding of either TSH or TSHR-Ab to the TSH receptor, independently of thyroid status, may be causally related to deterioration of GO. Clinicians should be aware of a possible association between rhTSH administration and reactivation of GO, which should be taken into account before prescribing rhTSH in patients with GO. Prophylactic steroids may need to be considered for patients at high risk of exacerbation of GO.

P240

HIGH PREVALENCE OF SUBCLINICAL EXTRAOCULAR MUSCLES ALTERATIONS IN GRAVES' DISEASE PATIENTS WITHOUT CLINICALLY EVIDENT GRAVES'ORBITOPATHY

Boi F[1], *Vacca R*[1], *Zucca I*[2], *Cuccu A*[2], *Fossarello M*[2], *Marini S*[3], *Mariotti S*[1]

[1]Endocrinology Unit, University of Cagliari, Department of Medical Sciences, Monserrato - Cagliari, Italy, [2]Ophthalmology Unit, University of Cagliari, Department of Surgical Sciences, Cagliari, Italy, [3]Radiology Unit, University of Cagliari, Department of Medical Sciences, Monserrato - Cagliari, Italy

Aim: To evaluate the extraocular muscles involvement in Graves' disease (GD) patients without clinically evident Graves' orbitopathy (GO).

Patients and methods: Fifty three GD patients without clinically evident GO and diplopia were studied. All cases underwent eye examination: intraocular pressure in upward gaze, cover test, ocular motility and red filter test to identify latent diplopia. Orbital ultrasound (US) was employed to measure extraocular muscle thickness (n.v. < 4 mm). Thyroid function (serum FT3, FT4 and TSH) and thyroid autoantibodies (TPOAb, TgAb and anti-TSH receptor, TRAb) were also performed. At the time of the enrollment, 6/53 (11%) patients were over hyperthyroid, 15/53 (28%) were subclinical hyperthyroid and the remaining 32/53 (61%) were euthyroid under anti-thyroid drug therapy or after thyroid definitive cure.

Results: Overall, 24/53 (45%) patients displayed both one or more thickened muscles at US and one or more ocular test alterations; 16/53 (30%) shown ocular test alterations and 8/53 (15%) displayed only US alterations. The remaining 5/53 (10%) did not display any alteration. As expected, similarly to how observed in clinically evident GO, the more frequent altered test was increased intraocular pressure in upward gaze (75%) followed by diplopia with red filter test (55%) and ocular motility alterations (33%). There were no significant differences between hyperthyroid and euthyroid patients in the prevalence of ocular tests alterations (15/21, 72% *vs* 25/32, 78%, p=0.7) and US alterations (11/21, 52% *vs* 21/32, 66%, p=0.3) respectively. An higher prevalence of both US and ocular tests alterations was observed in positive TRAb (33/36, 91%) *vs* negative TRAb (10/14, 71%, p=0.08) patients.

Conclusions: This preliminary study shows high prevalence of subclinical extraocular muscles alterations in GD patients without clinically evident GO, unrelated to thyroid function. Further investigations are needed to confirm the clinical relevance of this observation.

P241

METHYLPREDNISOLONE-INDUCED HEPATITIS DURING THYROID ORBITOPATHY TREATMENT CONDUCTED IN ACCORDANCE WITH EUGOGO RECOMMENDATIONS

Poullot A-G[1], Fisch A-L[2,3], Speux A[4], Fénichel P[2], Sadoul J-L[5]
[1]CHU de Nice, Endocrinology, Nice, France, [2]CHU de Nice, Endocrinologie, Nice, France, [3]CHU de Nice, Ophtalmologie, Nice, France, [4]CHU de Nice, Pharmacovigilance, Nice, France, [5]CHU de Nice, Endocrinology, Nice Cedex, France

EUGOGO recommend that active thyroid orbitopathy (TO) deserves 12 weekly methylprednisolone pulses (MPP), with a cumulative dose < 8 g, in order to minimize adverse effects (AE).

Case report: A 67 years old lady diagnosed with autoimmune thyroiditis received Levothyroxine (25 µg increased subsequently to 125 µg) for mild hypothyroidism. She did well for 6 years. She then experienced diplopia and peri-ocular pain during eye-movements. Active TO (Mourits score: 4) was diagnosed given clinical features, MRI findings, and sligthly elevated TSH-receptor antibodies. Weekly MPP (8 X 500 mg, 8 X 250 mg) were scheduled. Before the first MPP, on 125 µg of Levothyroxine, FT4 and TSH levels were within normal limits, as were liver enzymes and serology for B and C viral hepatitis. Liver enzymes increased slightly between the 7th and 8th MPP (ASAT 1.5 upper limit of normal [ULN], ALAT 2,3 ULN, GammaGT 0.8 ULN). Therefore, the 9th MPP was reduced to 125 mg. After a 3 weeks pause, overt hepatitis was documented : ASAT 15.3 ULN, ALAT 24.3 ULN, GammaGT 4.3 ULN; and MPP were stopped. Hepatitis peaked 4 weeks later : ASAT 16.6 ULN, ALAT 27.2 ULN, GammaGT 5.1 ULN, Bilirubin 1.0 ULN. There were no clinical or biological features of hepatic insufficiency. Liver ultrasound was normal while searches for various viral or auto-immune hepatitis were negative. Liver biopsy was denied by the patient. Complete biological resolution of hepatitis occured 9 weeks after the last MPP.

Comments: MPP imputability for this AE, although not proved, seems sounded. Thus, even with the reduced dose regimen proposed by EUGOGO, hepatitis might sill occur. Baseline assessment (including viral and auto-immune hepatitis clues) and a carefull monitoring of liver function is absolutely warranted during and after MPP use for TO treatment.

P242

COMPARISON OF COURSE OF CHANGES IN LEVELS OF TSH-RECEPTOR ANTIBODIES (TRAB) AND COURSE OF GRAVES´ORBITOPATHY (GO) IN 160 PATIENTS WITH GRAVES´DISEASE AFTER TWO DIFFERENT ABLATIVE REGIMENS: (SUB)TOTAL THYROIDECTOMY VERSUS RADIOIODINE

Grussendorf M[1], Bacher K[1], Cordes A[1], Feldmann B[1]
[1]Endokrinologie im Zentrum, Stuttgart, Germany

Comparative studies on the outcome of different ablative therapies in patients with Graves' disease are scarce.

Methods: Data from 80 patients with Graves´disease who had undergone (sub)total thytroidectomy (T-group) were evaluated retrospectively and compared with data from 80 similar patients before and after radioiodine therapy (R-Group).

Results: Results are presented as percentages of the total patient groups (T-group/R-group):

1. Data at first Graves´diagnosis (V1): distribution of
   TRAb levels: < 1 U/l: 7/25%, 1,1–5 U/l: 37/47%, 5,1–15U/l: 24/19%,>15U/l: 32/9%
   Thyroid volume: < 24ml: 14/27%, 25–50ml: 52/58%, >50ml: 34/15%
   GO-severity-score (GO-SS): 0: 48/84%, 1–3: 23/11%, 4–6: 19/4%, >6: 10/1%
2. Data at last investigation before ablative therapy (V2): distribution of
   TRAb levels: < 1 U/l: 8/31%, 1,1–5 U/l: 44/38%, 5,1–15 U/l: 26/19%,>15 U/l: 22/12%
   GO-SS: 0:41/82%, 1–3: 23/11%, 4–6: 28/6%, >6: 8/1%
3. Data at 6 months after ablative therapy (V3): distribution of
   TRAb levels (in relation to values at V2): < -10 U/l: 16/0%, -10 - -2 U/l: 35/10%, -2 - +2 U/l: 49/30%, +2 - +10: 0/10%, >+10:0/50%
   Thyroid volume: 0ml: 53/0%, 0,5–3ml: 36/14%, 4–10ml:9/22%, 11–24ml: 2/45%, 25–50ml: 0/20%, >50ml: 0/0%
   course of GO-SS (in relation to values at V2): < -4: 4/2%, -4 - -2: 20/8%, -1 - +1: 68/82%, +2 - +4: 8/5%, >+4: 0/3%
4. Data at 12 months after ablative therapy (V4): distribution of TRAb levels (in relation to V2): < -10 U/l: 22/10%, -10 --2: 40/14%, -2 - +2: 38/38%, +2 - +10: 0/17%, >+10 U/l: 0/21%
   course of GO-SS (in relation to V2): < -4: 4/2%, -4 - -1: 19/5%, -1 - +1: 64/84%, +1 - +4: 11/7%, >+4: 2/2%

Conclusion: We found a highly significant increase in TRAb levels after radioiodine-therapy and a clear decrease after thyroidectomy; course of GO-SS was not significantly different in both groups.

P243

COMPARISON OF EARLY TOTAL THYROIDECTOMY WITH ANTITHYROID TREATMENT IN PATIENTS WITH MODERATE TO SEVERELY ACTIVE GRAVES' ORBITOPATHY, A RANDOMIZED PROSPECTIVE TRIAL

Erdoğan MF[1], Demir Ö[1], Ersoy RÜ[2], Gül K[2], Ünlütürk U[1], Aydoğan Bİ[1], Üç ZA[3], Mete T[4], Ertek S[5], Çakır B[2], Aral Y[3], Güler S[4], Erdoğan G[5], Ankara Thyroid Study Group
[1]Ankara University, Endocrinology and Metabolic Diseases, Ankara, Turkey, [2]Ankara Atatürk Training and Research Hospital, Endocrinology and Metabolic Diseases, Ankara, Turkey, [3]Ankara Training and Research Hospital, Endocrinology and Metabolic Diseases, Ankara, Turkey, [4]Ankara Numune Training and Research Hospital, Endocrinology and Metabolic Diseases, Ankara, Turkey, [5]Ufuk University, Endocrinology and Metabolic Diseases, Ankara, Turkey

Objectives: We aimed to compare early total thyroidectomy with the anti-thyroid treatment regimens, in patients with moderate to severely active Graves' orbitopathy (GO) prospectively.

Methods: The inclusion criteria: Hyperthyroidism and GO developed in the last six months, thyroid volume ≥15 mL, no previous treatment except local interventions for GO. GO activity has been defined as clinical activity score (CAS) ≥3 and carrying at least one of the following criteria; Proptosis ≥21 mm in one eye, ≥2 mm difference between two eyes, presence of diplopia, lid aperture ≥9 mm. Initially, all the patients were made euthyroid (TSH 0.4–1 mIU/L). Pulse methylprednisolone of total 4.5 gr were given intravenously to all patients before randomization. In the first group, patients were sent to total thyroidectomy. Second group of patients were followed with anti-thyroid drugs and with the addition of levothyroxine, when necessary. TSH levels were kept within 0.4–1 mIU/L.

Results: 14 patients were randomized to total thyroidectomy (TT) group and 20 patients were randomized to medical antihyroid treatment (AT) group. There were no difference between the two groups with respect to age, gender, smoking habit, duration of hyperthyroidism and GO, thyroid volume, TSH, free T4, anti-TPO, anti-Tg and TRAb levels initially. When the TT group was compared with AT group, thyroid antibodies were significantly decreased in TT group while there was no significant difference with respect to proptosis, lid aperture, CAS and diplopia between groups. However in TT group additional pulse methylprednisolone treatment was given to 3 (21%) patients and urgent orbital decompression was applied to 2 (14%) of those patients. Hyperthyroidism reocurred in 3 patients in AT group.

Conclusion: Although the significant decrease of thyroid autoantibodies were achieved in TT group, this was not reflected as an beneficial effect on the course of GO during the 24 months mean follow-up period.

P244

FEATURES OF GRAVES' OPHTHALMOPATHY IN TYPE 2 DIABETIC PATIENTS

Le Moli R[1], Muscia V[1], Castoro C[1], Squatrito S[1], Vigneri R[1]
[1]University of Catania, Biomedicine, Clinical and Molecular, Catania, Italy

Aim: Graves' ophthalmopathy (GO) is an autoimmune disease. Oxidative reactive species (ROSs) are increased in patients with Graves' disease (GD) and GO in respect to patients with only GD. Hyperglycemia and ROSs are linked and ROSs are one of the major causes of chronic diabetic complications. We studied the clinical features of GO in DT2 patients.

Subjects and methods: 90 consecutive GO patients, 30 with DT2 (group 1, G-1) and 60 without (G-2) were mached according to age, sex and smoking abit, at ratio one G-1 vs two G-2. In all patients we evaluated: the clinical activity score (CAS), soft tissue (ST), eyelid aperture (E), proptosis (P), diplopia and oftalmological examination. GO was defined severe in case of optic nerve damage (DON). Twelve patients with active GO and DON (11 G-1 and 1 G-2) and 15 patients with moderate active GO (MGO) (7 G-1 and 8 G-2) were treated with intravenous steroids (IVMP).

Results: Thyroid function, autoimmunity markers, CAS, duration of hyperthyroidism and eyes simptoms were not different between G-1 and G-2 patients. Data were as follows:

DT2 and smoking were determinants of severe GO (OR:14, 95% CI 4.1–28; 5, 95% CI 1.7–18), DT2 was determinant of diplopia, GO asimmetry and GO onset before iperthyroidism OR:1.8 (95% CI=1.1–2.9); 6.4, (1.9–22); 9, (9–27).

Conclusions: DT2 is an important determinant of GO severity and response to IVMP therapy.

P245

OPHTHALMOPATHY INDUCED BY BILATERAL CAROTID CAVERNOUS FISTULA IN A PATIENT WITH GRAVES' DISEASE

Suk J[1]
[1]Maryknoll Hospital, Department of Internal Medicine, Busan, Korea, Republic of

Graves' disease (GD) can lead to spcific eye afflictions including proptosis, periorbital swelling, conjunctival injection, chemosis and opthalmoplegia, which then become a condition called Graves' opthalmopathy (GO) or thyroid-associated opthalmopathy (TAO). A carotid cavernous fistula (CCF) is an abnormal vascular communication between carotid artery and cavernous sinus. Due to the similarities of clinical signs, CCF is considered in the differential diagnosis of TAO, especially when the eye involvement is unilateral or asymmetric. We would like to present an interesting case of bilateral ophthalmopathy induced by CCF in a GD patient. A 54-year-old man with a 6-year-history of GD presented with bilateral exophthalmos and conjunctival injection for two months. The orbital CT scan findings were consistent with CCF, and an angiography revealed bilateral CCF. He received a bilateral coil embolization for the CCF and his ophthalmic signs were immediately improved. We recommend orbital imaging to exclude other coexisting diseases in patients who are suspected of TAO, especiaaly when the diagnosis is uncertain or when determining whether medical or surgical intervention is appropriate.

PO28 Thyroid Cancer Diagnostics Clinical 3

P246

ULTRASONOGRAPHIC FEATURES PREDICTING RECURRENT LARYNGEAL NERVE INVOLVEMENT IN THYROID CANCER

Kim B-W[1], Chang H-S[1], Park CS[1]
[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Departments of Surgery, Seoul, Korea, Republic of

Background: The recurrent laryngeal nerve (RLN) is vulnerable to invasion by thyroid cancer due to its anatomical location. The aim of this study was to identify preoperative ultrasonographic (US) features that are able to predict RLN invasion in thyroid cancer patients.

Materials and methods: Between May 2009 and April 2011 among 1636 patients who underwent surgical treatment due to thyroid cancer, 150 patients with thyroid cancer bound to the thyroid posterior capsule except the tracheal side were enrolled. We assessed US features of papillary thyroid carcinoma (PTC) and whether the RLNs were invaded or not. Features were evaluated by one board certified radiologist, including tumor margin status, internal echogenicity, relationship between the tumor and posterior capsule, and transverse and longitudinal locations of the tumor.

Results: The rate of RLN invasion was 20% in 150 PTC bound to the posterior capsule and the RLNs were completely enveloped by the tumor in 3 of 150 cases (2.0%). We found a statistically significant association between RLN invasion and US features of PTC (tumor margin status in US, internal echogenicity, relationship between the tumor and posterior capsule, and transverse and longitudinal locations of the tumor.

Conclusion: In PTC, if a tumor is bound to the posterior thyroid capsule, independent factors in predicting RLN invasion were poorly defined edge, coarse and strong echo, destroyed capsule, being located in the upper one third in the longitudinal view, and being located in the medial one half in the transverse view. When these US features are found preoperatively, surgeons should pay attention to the possibility of RLN invasion by the tumor during the operation.

P247

DIFFERENTIATED CARCINOMA IN DYSEMBRIOGENETIC THYROID LESIONS

Sturniolo G[1], Violi MA[1], Presti S[1], Moleti M[1], Di Bella B[1], Di Mauro F[1], Trimarchi F[1], Vermiglio F[1]
[1]Università degli Studi di Messina, Clinico-Sperimentale di Medicina e Farmacologia, Messina, Italy

The prevalence of differentiated thyroid carcinoma (DTC) in lingual thyroid (LT) and thyroglossal duct cysts (TDC) is around 1%. Nowadays, almost 250 cases of DTC were reported in TDC and less than 60 cases in LT. Here we report 4 cases of neoplasia in LT (1/4) and TDC (3/4) in a consecutive series of 1025 DTC patients (0.4%).

Case 1: D.F. 63 year-old woman with thyroid follicular carcinoma in ectopic gland located at her tongue's basis. March 2009: the lesion, infiltrating surrounding tissues, presented insular-like areas (T3N1Mx). July 2009 and 2010: two radiometabolic treatment (cumulative dose of 224 mCi of ^{131}I) with

Table 1 for Abstract P244.

	number	DON (%)	MGO (%)	Mild GO (%)	Asimmetrical GO (%)	Before Thyro Toxic GO (%)	Motility Impairment (%)	Diplopia (%)	Response to IVMP MGO/ DON (%)
G-1 (with DT2)	30	36.6	36.7	26.7	30	15.4	53.3	50.0	48.2/45
G-2 (without DT2)	60	1.7*	40.0	58.3*	5*	0*	10.0*	17.0*	*87.5/100

*=p<0.05

no evidence of local/distant metastases and undetectable serum thyroglobulin (Tg), following the last radioiodine administration.

Case 2: B.B. 37 year-old woman with TDC. October 2001: Exeresis of a thyroid papillary carcinoma (PC) in TDC infiltrating soft local tissues (T3NxMx). December 2001: Total thyroidectomy (tTx) with histologic finding of benign adenomatous goiter. 2002–2008: five radiometabolic treatment (cumulative dose of 500 mCi of ^{131}I) due to iodine uptaking lung metastases. September 2009: persistence of elevated Tg levels (56.1 ng/ml) following recombinant human TSH stimulation. Proposal of further radiometabolic treatments refused.

Case 3: B.S. 42 year-old man. November 2001: PC of thyroglossal duct infiltrating the surrounding fibro-adipose tissue with lymphatic and intravascular diffusion. March 2002: tTx with evidence of 2 foci of PC (T3bN0Mx). July 2002: 100 mCi of ^{131}I, Tg undetectable and WBS negative.

Case 4: D.B. 21 year-old woman with a PC follicular variant in TDC. July 2010: tTx with histologic evidence of benign macrofollicular goiter.

Conclusions: The higher prevalence of DTC (also in form of aggressive variants) in dysembrogenetic than in orthotopic thyroid tissue (0.4 vs 0.004%) argues in favor of a close monitoring of all the dysembriogenetic thyroid lesions.

P248

REGULATION OF TIGHT JUNCTION PROTEINS DURING THE EPITHELIAL-MESENCHYMAL TRANSITION IN THYROID CANCER: THE ROLE OF THE SLUG TRANSCRIPTION FACTOR

Colato C[1], Monzani F[2], Brazzarola P[3], Martignoni G[1], Chilosi M[1], Ferdeghini M[1]
[1]University of Verona, Pathology and Diagnostics, Verona, Italy, [2]University of Pisa, Internal Medicine, Pisa, Italy, [3]University of Verona, Surgery and Oncology, Verona, Italy

Objectives: Acquisition of epithelial-mesenchymal transition (EMT) by cancer cells is associated with disrupted epithelial integrity, local invasion, and metastasis.

The tight junction (TJ) is a key structure that determines epithelial cell polarity and disappears during EMT. The Snail superfamily transcription factors, already firmly established as repressors of E-Cadherin, have been recently recognized as an important regulators of EMT. Actually, Snail has also been shown to be able to downregulate the TJ proteins Claudins/Occludin whereas Slug appears to act as repressor of Claudin-1 expression. Tubulin is a multifunctional cytoskeletal protein involved in cell movement, intracellular transport, and mitosis.

Few knowledge is available about the expression of EMT regulators in thyroid cancer.

In this study, we examined the expression pattern of Slug (Cell Signaling), Claudin-1/7 (Zymed) and βIII-Tubulin (Covance) in a panel of well-differentiated and anaplastic thyroid carcinomas by immunohistochemistry.

Methods: 5 anaplastic thyroid carcinomas (ATC), 12 papillary thyroid carcinomas (PTC) including 3 tall cell variants, and 12 normal thyroids (NT) were analyzed. Unequivocal nuclear staining for Slug, membranous staining for Claudins and cytoplasmic staining for βIII-Tubulin were considered for interpretation.

Results: All cases of ATCs showed strong nuclear immunoreactivity for Slug (4 cases diffuse, 1 case focal). Slug expression was associated with absence of Claudin-1/7 and ectopic expression of βIII-Tubulin. None of the NTs and PTCs were immunoreactive for Slug ($p < 0.0001$). As expected, all PTCs were positive for Claudin-1/7 with heterogeneous and variable staining for βIII-Tubulin.

Conclusions: The EMT regulator Slug is expressed in ATC and is associated with absence of Claudin-1 and -7 and up-regulation of βIII-Tubulin, suggesting the role of EMT in this cancer. These observations support the recent insights into the relationship between alterations in cell polarity proteins and EMT in cancer, opening new avenues for their potential use as therapeutic targets to prevent tumour progression.

P249

PREOPERATIVE MALIGNANCY RISK PREDICTION IN THYROID NODULES WITH "FOLLICULAR NEOPLASM" CYTOLOGY

Lanshchakov K[1], Belousov P[2], Vanushko V[3], Beltsevich D[3], Fadeev V[3], Rumyantsev P[3], Abdulkhabirova F[3], Platonova N[3], Troshina E[3]
[1]Endocrinology Research Center, Endocrine Surgery, Moscow, Russian Federation, [2]Moscow State University, Moscow, Russian Federation, [3]Endocrinology Research Center, Moscow, Russian Federation

Fine-needle aspiration cytology (FNAC) - «gold standard» in thyroid nodules differentiated diagnostics but it has obvious "grey zone" unable to distinguish benign and malignant pathology occurring 15 to 30% observations. In order to investigate additional tools to predict thyroid nodule malignancy three promising carcinoma-associated serum antigens (ANKRD30A/NY-BR-1, HYDIN2/KIAA1864, RGS5) were chosen from pretested panel of 19 well-known and candidate affinity-purified recombinant His6-tagged cancer-associated antigens using a dot-blot ELISA-based analysis. Three selected antigens were confirmed as true-negative in 36 healthy controls.

Materials and methods: Analysis of three potential anticancer-antigens (ANKRD30A/NY-BR-1, HYDIN2/KIAA1864 и RGS5) in blood was conduct preoperatively in 48 patients with FNAC of "follicular neoplasm". US of nodules didn't revealed any suspicion for carcinoma. Avoiding the immunological false-positive cross-reactivity all patients were confirmed HIV, HIC, HIB negative. Patient's age varied from 22 to 69 years (mean 45±13.2). F:M ratio - 39:9 (4,3:1). Size of tumors varied from 1 to 6.4 cm (mean 2.8±1.2). All patients underwent surgery with subsequent histology examination. If all three anticancer-antigens were undetected in blood serum the result considered as negative. When at least one antigen has been detected result interpreted as positive.

Results: Positive results were obtained in 15 of 26 differentiated thyroid carcinomas (10/18 - papillary and 5/8 - follicular). Only in one of twenty two patients with benign disease the result was false-positive (1/11 - NG, 0/11 - FA). Diagnostic efficacy of preoperative testing with three antigens panel was assessed with ROC-curve analysis (AUC=0.78). Sensitivity 0.42 (95%CI 0.26–0.59), specificity 0.92 (95%CI 0.70–0.99).

Conclusions: The panel of three exstudied antigens couldn't be recommend to predict thyroid malignancy with negative predictive value 0.3 (95%CI 0.19–0.53) in uncertain 'grey zone'. Nevertheless its high positive predictive value 0.94 (0.7–0.99) should be further investigated as preoperative marker of low-risk of malignancy in thyroid nodule disclosed as "follicular neoplasm".

P250

USEFULNESS OF ELASTOSONOGRAPHY AS AN ADDITIONAL DIAGNOSTIC TOOL FOR THYROID NODULES

Filieri C[1], Rossi M[1], Trasforini G[1], Beccati MD[2], Rossi R[1], Zatelli MC[1,3], degli Uberti E[1,3]
[1]University of Ferrara, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy, [2]S. Anna Hospital, Ferrara, Cytopathology, Ferrara, Italy, [3]LTTA, University of Ferrara, Ferrara, Italy

Fine needle aspiration biopsy (FNAB) represents the gold standard in the management of thyroid nodules. Despite its high sensitivity and specificity, thyroid cytology displays indeterminate results in 20–40% of cases. Elastosonography (ES) is a new dynamic technique for the differential diagnosis of thyroid nodules. The aim of this study was to investigate the potential diagnostic value of ES in detecting malignant thyroid nodules.

Sixty five patients with thyroid nodules detected at ultrasonography (US) underwent ES, FNAB and genetic analysis for BRAF and RET/PTC mutations. All patients underwent total thyroidectomy due to malignant cytology or to positive genetic analysis. ES results were correlated with cytological and histological results.

Among the 6 cytologically benign lesions (TIR 2), 4 solid nodules with ES score 3–5 were PTC at final histology; 2 nodules showing prevalent ES score 1–2 were diagnosed as 1 PTC and 1 goiter at histology.

Among the 31 cytologically indeterminate lesions (TIR 3), 26 anelastic nodules (score 3–5) included 20 PTC at histology; all 5 elastic nodules (score 1–2) were benign lesions.

Among the 28 cytologically malignant lesions (TIR 4), only 2 nodules were prevalently elastic (ES score 1–2) and were benign at final histology; all the other 26 solid lesions (score 3–5) were PTC.

ES displayed a 96% sensitivity, a 54% specificity, a 89% positive and a 78% negative predictive value for malignant lesions. ES features significantly correlated with malignancy at histology ($p < 0.01$). Histological diagnosis of malignancy correlated with ES pattern of suspicious malignancy in 66% of TIR 2, 84% of TIR 3 and 93% of TIR 4, respectively.

Therefore, ES may represent an additional helpful tool for the diagnosis of thyroid cancer and may be useful in selecting patients who are candidates for surgery, in particular in nodules with indeterminate cytology, together with US, cytology and molecular analysis.

P251

FDG-PET/CT IN HIGH RISK DIFFERENTIATED THYROID CANCER

Yang JH[1], Nakabashi CCD[1,2], Camacho CP[1,2], Andreoni DM[1,2], Padovani RP[1,2], Malouf EZ[1,2], Ikejiri ES[1,2], Mamone MCC[1,2], Abrahão M[3], Hojaij FC[3], Hidal JT[1,2], Osawa A[4], Yamaga LYI[4], Wagner J[4], Maciel RMB[1,2], Biscolla RPM[1,2]

[1]Federal University of São Paulo, Endocrinology, São Paulo, Brazil, [2]Thyroid Diseases Center, Instituto Israelita de Ensino e Pesquisa Albert Einstein and Federal University of São Paulo, São Paulo, Brazil, [3]Federal University of Sao Paulo, Otorhinolaryngology, Head and Neck Surgery, São Paulo, Brazil, [4]Hospital Israelita Albert Einstein, Imaging Department, São Paulo, Brazil

Objective: The study aims to evaluate the clinical impact of FDG-PET/CT in the management of high risk differentiated thyroid cancer (DTC).

Methods: Forty two patients with high risk DTC underwent FDG-PET/CT between February/2008 and December/2011. They were divided in 3 groups:

GROUP 1/n=6: negative Whole Body Scan (WBS) and elevated serum thyroglobulin (sTg) or anti thyroglobulin antibody, without identified metastases at conventional imaging (CI);

GROUP 2/n=16: negative WBS and elevated sTg, with known or suspected focus at CI;

GROUP 3/n=20: patients with metastases and the scan was performed to determine extention of disease. There was suspicion of tumor undifferentiation with undetectable sTg/n=8; suspicious lesions not feasible to US-guided FNA/n=6; extension of cervical disease/n=2; positive WBS and elevated sTg, without focus/n=4.

Results:

GROUP 1: There were no FDG avid lesions. Low levels of sTg (medium 5.5 ng/mL;3.6–7.4) and microscopic disease might explain lack of FDG uptake, since the scan has limitations to detect minimal disease.

GROUP 2: In 12/16 patients the imaging disclosed 20 foci/5 organs. Although no additional lesions were revealed, FDG-PET/CT results had cleared up 10 suspicious lesions (8 patients) that would demand an invasive procedure for differential diagnosis: cervical(1)/mediastinal(3)/retropharyngeal(1)/infiltrating trachea (1)/lungs(3)/lumbar vertebrae(1). FDG-PET/CT positive findings combined with clinical data outlined surgery procedure in 07 patients.

GROUP 3: FDG uptake was observed in 3/8 patients with suspected tumor undifferentiation: pharynx infiltrating mass/sTg=5.0ng/mL and diffuse macronodular lung pattern/sTg=156 ng/mL. The third patient presented a scapula focal uptake/sTg=0.7 ng/mL, but surgery wasn´t undertaken due to low risk of fracture or nerve compression injure. In 3/8, FDG-PET/CT was helpful to elucidate lymph nodes not feasible to US-guided FNA. No true positive images were obtained in four patients with positive WBS, elevated sTg and no recurrence focus at CI.

Conclusion: FDG-PET/CT is a valuable tool in clinic management and follow up of DTC.

P252

ROLE OF ULTRASONOGRAPHY, CLINICAL PROFILE, CYTOLOGY AND BRAF V600E MUTATION EVALUATION IN DETECTING MALIGNANT THYROID NODULES

Zatelli MC[1,2], Rossi M[1], Buratto M[1], Bruni S[3], Filieri C[1], Tagliati F[1], Trasforini G[1], Rossi R[1], Beccati MD[4], degli Uberti E[1,2]

[1]University of Ferrara, Section of Endocrinology, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy, [2]University of Ferrara, LTTA, Ferrara, Italy, [3]S. Anna Hospital, Section of Endocrinology, Ferrara, Italy, [4]S. Anna Hospital, Cytopathology, Ferrara, Italy

Ultrasound (US)-guided fine-needle aspiration biopsy (FNAB) is the most reliable nonsurgical test for distinguishing benign from malignant thyroid nodules. However, there is no consensus on which nodules should undergo FNAB. We evaluated the utility of US-guided FNAB in the diagnostic assessment of nodules with or without clinical/US features suggestive for malignancy and investigated the additional contribution of BRAF V600E mutation analysis in the detection of differentiated thyroid cancer.

Thyroid cytoaspirates from 2421 nodules ≥ 4 mm in diameter performed in 1856 patients underwent cytological evaluation and biomolecular analysis. Cytology showed high positive predictive value and specificity for the diagnosis of malignant lesions. BRAF V600E mutation was found in 115 samples, 80 of which were also cytologically diagnosed as papillary thyroid cancer. BRAF mutation analysis significantly enhanced the diagnostic value of cytology, increasing FNAB diagnostic sensitivity for malignant nodules by ~28%. MicroPTC (63% of diagnosed PTC) showed a high prevalence of multifocality, extrathyroidal extension and lymph node metastases, underlining the malignant potential of thyroid microcarcinomas. Each investigated US/clinical characteristic of suspected malignancy correlated with the presence of a thyroid cancer in thyroid nodules with diameter ≥ 4 mm. These data indicate that nodules ≥ 4 mm may underlie a thyroid cancer independently of US/clinical characteristic of suspected malignancy, suggesting the need to perform FNAB. The diagnostic sensitivity for thyroid cancer is significantly increased by BRAF V600E mutation analysis, indicating that the screening for BRAF mutation in FNAB samples has a relevant diagnostic potential.

P253

PROGNOSTIC VALUE OF POST-OPERATIVE NECK ULTRASOUND FOR PREDICTING RECURRENCES IN DIFFERENTIATED THYROID CANCER PATIENTS WITH INITIAL LYMPH NODES INVOLVEMENT

Lepoutre-Lussey C[1], Maddah D[1], Golmard J-L[2], Le Henaff V[1], Hoang C[3], Trésallet C[4], Ménégaux F[4], Aurengo A[1], Leenhardt L[1]

[1]Hôpital Pitié-Salpêtrière, Service de Médecine Nucléaire, Paris, France, [2]Hôpital Pitié-Salpêtrière, Service de Biostatistiques et Unité de Recherche Clinique, Paris, France, [3]Hôpital Pitié-Salpêtrière, Service D'anatomopathologie, Paris, France, [4]Hôpital Pitié-Salpêtrière, Service de Chirurgie Endocrinienne, Paris, France

Objectives: To evaluate the value of post-operative cervical ultrasound (POCUS) for predicting local recurrences (LR) in differentiated thyroid cancer (DTC) patients with initial lymph node metastases (N1).

Methods: We retrospectively analysed data of 659 N1-DTC patients treated by surgery and radioiodine therapy in our institution from 1997 to 2010. The survival without LR was estimated with the method of Kaplan-Meier and the prognostic value of POCUS was studied in univariate and multivariate Cox model-based analyses.

Results: 136 patients presented with a LR (20.6%). Among these patients, LR occurred during the first year and within 3 years in 42% and 83% of cases respectively. Sensitivity of POCUS in detecting precocious LR occurring during the first year was 86,1%. During the first year of follow-up, 37% of the patients with abnormal POCUS were re-operated. An abnormal POCUS result, an elevation of stimulated thyroglobulin level and a cervical uptake outside the thyroid bed on post radioiodine therapeutic whole body scan (WBS) were significantly associated with LR ($p < 0.0001$). In a multivariate analysis, only an

abnormal POCUS result and an elevated stimulated thyroglobulin level were predictive of LR (p< 0.0001).

Conclusion: The POCUS procedure is useful to detect persistent disease and precocious LR in N1-DTC patients who are classified as moderate and high risk DTC groups. It is a strong and independent predictor of the LR risk. POCUS is helpful for individual risk stratification. Prospective randomized studies are needed to confirm the impact of the POCUS procedure on the decision of reintervention.

P254

EFFECT OF PROPHYLACTIC CENTRAL LYMPH NODE DISSECTION ON POSTOPERATIVE STIMULATED THYROGLOBULIN LEVELS AND ON DISEASE PERSISTENCE AND RECURRENCE IN LYMPH NODE NEGATIVE PATIENTS WITH PAPILLARY THYROID CARCINOMA

Aydoğan Bİ[1], Ünlütürk U[1], Taşkıran B[2], Can F[3], Yüksel B[3], Özkan E[4], Erdoğan MF[1], Güllü S[1], Emral R[1], Başkal N[1], Çorapçıoğlu D[1], Şahin M[1], Küçük Ö[4], Uysal AR[1]

[1]Ankara University School of Medicine, Endocrinology and Metabolism, Ankara, Turkey, [2]Yunus Emre State Hospital, Endocrinology and Metabolism, Ankara, Turkey, [3]Ankara University School of Medicine, Internal Medicine, Ankara, Turkey, [4]Ankara University School of Medicine, Nuclear Medicine, Ankara, Turkey

Background: The effect of prophylactic central lymph node dissection (CLND) on PTC recurrence remains controversial. It was suggested that prophylactic CLND may decrease postoperative off-T4-stimulated thyroglobulin levels at the time of remnant ablation (RA-Tg) which may be useful in predicting the risk of disease persistence and recurrence.

Objective: The aim of this study was to evaluate the effect of prophylactic CLND on RA-Tg and on disease recurrence in lymph node negative patients with PTC

Method: The data from 157 node negative PTC patients [median age 43 yr (16–75), 130 females and 27 males] were evaluated. Tumor sizes were classified according to the TNM classification. The node positive and/or metastatic cases were excluded. RA-Tg levels, type of the surgical procedure, tumor size, recurrence or residual disease were analyzed.

Results: The median follow up was 54 months (12–372). Patients who underwent total thyroidectomy (TTx) were classified as group-1 (n=136), and who underwent TTx and CLND as group-2 (n=21). 89 cases in group-1 (66.4%) and 15 (71.4%) cases in group-2 had T1 tumors, whereas T2 was seen in 14.2% (n=19) and 19.1% (n=4), and T3–4 in 19% (n=26) and 9.5% (n=2) of the patients, respectively. While disease recurrence or persistence was observed in 22 patients (16%) in group-1, none of the patients in group-2 had recurrence or persistence. Median RA-Tg levels were significantly higher in group-1 than group-2 [2.0ng/ml (0–456) vs. 0.7ng/ml (0–88), p=0.048]. Median RA-Tg levels were also significantly higher in patients who experienced disease persistence or recurrence [21 ng/ml (0.9–456) vs. 1.0 ng/ml (0–249), p< 0.001]. PTC recurrence or persistence were also significantly higher in group-1(p=0.046).

Conclusions: The levels of RA-Tg may be useful in predicting the risk for persistent/recurrent disease. Moreover, performing routine CLND in node negative PTC patients might decrease RA-Tg levels and reduce disease recurrence.

P255

THE RELATIONSHIP OF PREOPERATIVE TSH LEVELS AND COEXISTING AUTOIMMUNE THYROID DISEASE WITH TUMOR STAGE AT THE DIAGNOSIS AND RECURRENCE IN DIFFERENTIATED THYROID CARCINOMA PATIENTS

Taşkıran B[1], Aydoğan Bİ[1], Ünlütürk U[1], Öztürk B[2], Bali E[3], Güllü S[1], Erdoğan MF[1], Emral R[1], Başkal N[1], Çorapçıoğlu D[1], Şahin M[1], Özkan E[3], Küçük Ö[3], Uysal AR[1]

[1]Ankara University School of Medicine, Endocrinology and Metabolism, Ankara, Turkey, [2]Ankara University School of Medicine, Internal Medicine, Ankara, Turkey, [3]Ankara University School of Medicine, Nuclear Medicine, Ankara, Turkey

Background: The risk factors for developing disease recurrence in differentiated thyroid carcinoma (DTC) are not well known. An association between TSH levels and tumor growth was demonstrated in several studies. It was also suggested in some studies that coexisting autoimmune thyroid disease (AITD) may increase the risk of DTC and can also modify prognosis.

Objective: To assess the relationship of preoperative TSH levels and/or presence of AITD with tumor stage and recurrence risk.

Method: Retrospective data from 217 DTC patients [median 42 yr (16–82), 173 females and 44 males] were evaluated. Seven of 217 patients were diagnosed with follicular, and 209 with papillary thyroid carcinoma and the remaining patient with mixed DTC. Preoperative TSH levels, the coexistence of AITD, postoperative TNM classifications, 3-level risk stratification of tumor recurrence(ATA 2009 guidelines), AITD was assessed histopathologically.

Results: The median follow up of the patients was 51 months (12–372). According to the TNM classification 76% of the patients had stage-I, 6% had stage-II, 4.2% had stage-III and 13.8% had stage-IV disease. The mean preoperative TSH level was 1.7±2.1 22.1% of the patients had AITD. Mean TSH level of patients with AITD was 2.05±1.45 (1.86, 0.16–5.6). Groups were not significantly different (p>0,05). 49.8% of the patients were in the low-, 33.2% in the intermediate-, and the remaining 17% were in the high-risk group for tumor recurrence. The coexistence of AITD was not associated with TNM stage, disease specific risk groups or residual tumor and recurrence. There was also no association between the preoperative TSH levels, the TNM stage, disease specific risk groups and the presence of a residual disease or tumor recurrence.

Conclusions: Although AITD was prevalent in DTC patients, there was no relationship between preoperative TSH levels or coexisting AITD with tumor stage at the diagnosis and recurrence.

P256

WHOLE-BODY DIFFUSION MRI AND SKELETAL LESIONS IN THYROID CANCER: DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS

Locati LD[1], Potepan P[2], Granata R[1], Gianluca A[3], Civelli EM[2], Bossi P[1], Montin E[2], Licitra LF[1]

[1]Fondazione IRCCS Istituto Nazionale dei Tumori, Medical Oncology, Milan, Italy, [2]Fondazione IRCCS Istituto Nazionale dei Tumori, Radiology, Milan, Italy, [3]Fondazione IRCCS Istituto Nazionale dei Tumori, Radiology-Nuclear Medicine, Milan, Italy

Background: Bone metastases affect at least 40–50% of patients with metastatic thyroid cancer (TC). ^{99m}Tc scintigraphy is employed to assess bone lesions, although it lacks of accuracy. MRI is able to capture both bone and bone marrow involvement. Whole-body diffusion imaging (WB-DWI) is an accurate tool for detection and therapy monitoring of bone metastases. We investigated the role of WB-DWI in TC: i) sensitivity and specificity; ii) evaluation of response during TKIs.

Material and methods: Baseline radiological records of patients with known metastatic TC submitted to WB-DWI were reviewed. False-positive was a positive imaging not confirmed by histopathology or/and another imaging or by two imaging exams. False-negative was a negative finding with a positivity on another imaging plus histopathology or two imaging methods.

Results: Since 2010, nine MTC (5M/4F) and five RAI-resistant DTC (3M/2F) patients were considered. Results are listed in Table 1.

Table 1.

	WB-DWI	Bone scan	Bone CT
Number of exams	14	12	12
True-positive	10	8	8
True-negative	4	4	4
False-positive	0	1 (MTC)	0
False-negative	0	1 (DTC)	1 (MTC)
Sensitivity%	100	88	88
Specificity%	100	80	100
Accuracy%	100	86	92

WB-DWI was employed in three patients (2 MTC/1 DTC) to assess the response during a TKI: cystic evolution was observed in the responding lesions (apart from the histotype); other lesions appeared as stable or dimensional enlarged, suggestive of lack of response.

Conclusions: WB-DWI seems to be the best method to identify bone lesions from TC, potentially addressing unmet clinical and therapeutic needs for bone lesion response.

P257

PATTERN OF NODAL SPREAD ACCORDING TO TUMOR LOCATION OF PAPILLARY THYROID CARCINOMA

Jeong W-J[1], *Hong SN*[1], *Kim YW*[1], *Sung M-W*[2], *Kim KH*[2], *Ahn S-H*[1]
[1]Seoul National University Bundang Hospital, Department of Otorhinolaryngology - Head & Neck Surgery, Seongnam, Korea, Republic of, [2]Seoul National University Hospital, Department of Otorhinolaryngology - Head & Neck Surgery, Seoul, Korea, Republic of

Background: Management of lateral neck metastasis in papillary thyroid carcinoma is still a controversial issue, especially regarding dissection of level II. Prediction of level II metastasis according to node positivity in adjacent neck levels has been elucidated, but that in regard to primary tumor characteristics, especially tumor location within the thyroid gland has not been properly investigated. We sought to investigate the pattern of nodal spread in regard to primary tumor size and location, and correlate with level II metastasis.

Materials and methods: The study was performed in a tertiary referral center for known papillary thyroid cancer with proven lateral neck metastasis. All underwent comprehensive neck dissection of levels II-V and central compartment neck dissection. Thyroid dimensions and tumor attributes were calculated from axial and coronal CT scans and USG, which were then compared with pathological data from neck dissection.

Results: Total 67 cases were identified and eligible for evaluation. The rate of level II node metastasis was 64.1%. In 39 cases with tumors involving or nearly adjacent to the superior pole, the rate of level II node involvement was 79.5%, compared to 42.9% for the 28 cases in the middle to lower portion of the thyroid gland. The rate of level II nodal metastasis for tumors confined in level III (12 cases), spanning between levels III and IV (41 cases), and confined in level IV (14 cases) were 75.0%, 68.3%, and 42.9%, respectively. Level II metastasis rate for tumors spanning the whole thyroid gland (7 cases) was 85.7%.

Conclusions: Tumor location within the thyroid gland is associated with level II metastasis in cases with proven lateral neck metastasis. Tumors involving the superior pole, those confined in level III, and those spanning the whole gland have a high chance of metastasis to level II nodes.

PO29 Thyroid Cancer Therapeutics Clinical 3

P258

LONG TERM IMPACT OF RADIOIODINE TREATMENT FOR DIFFERENTIATED THYROID CARCINOMA ON PERIPHERAL BLOOD CELL COUNT

Kneer K[1], *Luster M*[1], *Bommer M*[2], *Ohlhauser D*[1]
[1]Uniklinikum Ulm, Nuklearmedizin, Ulm, Germany, [2]Uniklinikum Ulm, Innere Medizin III, Ulm, Germany

Objectives: Dose related bone marrow suppression after multiple radioiodine (RAI) therapies is not well described. Furthermore the impact of RAI treatment after four years or more hasn't been studied yet. In this retrospective trial, we examined whether there are persistent changes in blood count after multiple RAI treatments. We considered leukocytes as a whole, erythrocytes, platelets, hemoglobin and hematocrit.

Methods: We analysed in this retrospective study documents of 210 consecutive patients. The following parameters were studied: gender (female: 147, male: 63), age at diagnosis (range 11,2 - 81,0 years, mean = 49,9 years), histology, TNM-stage, time interval after first treatment (range 4 - 14 years, mean = 6 years), cumulative administered activity (range 2,8 - 67,1 GBq, mean = 10,6 GBq), presence of metastases and changes of blood count. Before each RAI administration a automated complete blood count (CBC) had been determined.

Results: In 191 of 210 cases the treatment was successful as defined complete remission. Considering the latest available blood count of each patient, we found pathological results in 77 of 210 patients. Leukopenia in 21, thrombocytopenia in five, changes in erythrocyte levels in 38 patients. Most of the changes of blood count were transient. We found only 4 patients demonstrating persistent blood count changes (one acute myelogenous leukemia, one chronic lymphocytic leukemia, two multiple myeloma) The administered activity of this four patients range from 4,8 to 62,9 GBq (mean administered activity = 33,0 GBq).

Conclusions: Persistent changes in blood count after multiple RAI treatment are rare and most likely correlate with the administered dose. Changes in blood count were especially found with combined bone and pulmonal metastases. In general RAI treatment may be considered safe modality with regards to persistent changes in CBC.

P259

VALUE OF FIRST THYROGLOBULIN AS A PROGNOSTIC FACTOR IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

Zakavi SR[1], *Ayati A*[1], *Mousavi Z*[2], *Ayati NK*[1]
[1]Nuclear Medicine Research Center/ Mashhad University of Medical Sciences, Mashhad, Iran, Islamic Republic of, [2]Endocrine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, Islamic Republic of

Aim: Risk categorization of the patients with well differentiated thyroid cancer (DTC)is the most important step in management of the patients. We evaluated the prognostic effect of the first thyroglobulin (fTg) level in patient with DTC.

Methods: 228 patients (178 women, 50 men, 38.6±15.1 years) with DTC underwent measurement of fTg, anti-Tg antibody(TgA) and TSH before radio-iodine therapy in off T4 state. 30 patients excluded from the study due to elevated TgA. All patients underwent radio-iodine therapy and suppressive therapy and followed for at least for 12 months. One year later all patients underwent whole body iodine scan(WBIS) and measurement of Tg and TgA under endogenous TSH stimulation. Complete remission was defined as negative WBIS with off T4-Tg< 2ng/ml, negative TgA and normal neck ultrasonography.

Results: Papillary, follicular and Hurthle cell carcinoma was seen in 180,13 and 5 patients respectively. According to TNM staging, 63.5%, 9.6%, 7.6% and 19.3% of the patients were in stage I, II, III and IV respectively. The

mean TSH level was 75.9± 57.0 U/ml and mean fTg level was 217.6±906 ng/ml. At the end of the follow up, 58.1% of the patients had complete remission. The mean fTg level was 28.5±65.8 versus 479.6±1359.2 ng/ml in patients with complete remission and persistent disease respectively (P=0.003). The mean age, TSH level, TgA level and mean largest diameter of the tumor were not significantly different between the two groups. Cox regression analysis showed that fTg, male sex and higher TNM stage are the most important predictors of survival in these patients.

Conclusion: First thyroglobulin concentration, is higher in patients with persistent disease than in patients with complete remission and can be used as one of the most important prognostic factors in patients with DTC.

P260

FOLLOW-UP IN PATIENTS WITH ANTIBODY INTERFERENCE IN TG MEASUREMENT: A CONSENSUS STATEMENT

Verburg FA[1], *Luster M*[2], *Chiovato C*[3], *Chiovato L*[4], *Duntas L*[5], *Elisei R*[6], *Feldt-Rasmussen U*[7], *Rimmele H*[8], *Seregni E*[9], *Smit JW*[10], *Theimer C*[11], *Giovanella L*[12]

[1]University Hospital Aachen, Nuclear Medicine, Aachen, Germany, [2]University Hospital Ulm, Nuclear Medicine, Ulm, Germany, [3]Azienda Ospedaliera-Universitaria Pisana, Endocrine Outpatient Clinic, Pisa, Italy, [4]University of Pavia Hospital, Department of Internal Medicine and Endocrinology, Pavia, Italy, [5]Evgenidion Hospital, University of Athens Medical School, Endocrine Unit, Athens, Greece, [6]Department of Endocrinology, University Hospital Pisa, Pisa, Italy, [7]Rigshospitalet, Endocrinology, Copenhagen, Italy, [8]Ohne Schilddruese Leben e.V., Berlin, Germany, [9]Instituto di Tumori, Endocrinology, Milan, Italy, [10]Leiden University Medical Center, Endocrinology, Leiden, Netherlands, [11]Thermo Fisher Scientific, Inc., Hennigsdorf, Germany, [12]Oncology Institute of Southern Switzerland, Department of Nuclear Medicine and PET Centre, Bellinzona, Switzerland

Background: Although the presence of anti-thyroglobulin antibodies (TgAb) represents a significant problem in the follow-up of differentiated thyroid cancer (DTC) patients, the various guidelines on the management of DTC that have been published in recent years contain no paragraphs concerning the methods to be used for detecting such antibody related interference in Tg measurement or how to mange TgAb-positive patients, in whom Tg cannot be used reliably as a tumor-marker.

Aim: A group of European experts involved in the care of DTC patients gathered for a dedicated conference in Berlin, Germany, on November 6, 2011, to form a consensus opinion on how to proceed with treatment and follow-up in TgAb positive DTC patients based on the available evidence in the literature. Here we will report on the consensus opinions that were reached regarding technical and clinical issues.

Result: The current literature does not provide enough data for giving solid answers and useful recommendations in the care of TgAb positive DTC patients. This consensus statement provides an overview of the available evidence and the resulting consensus recommendations. Where not enough evidence was available, a thorough discussion by a group of physician-scientists, all of whom have a distinguished track-record in thyroid cancer care, was held to arrive at a consensus expert opinion. The questions and answers discussed were then summarized into an algorithm for the management of TgAb positive patients.

Conclusion: We were able to define 25 consensus expert recommendations and a resulting algorithm for the care of TgAb positive DTC patients.

P261

LIFE EXPECTANCY IS NORMAL IN PATIENTS WITH UICC/AJCC TNM STAGE I, II AND III DIFFERENTIATED THYROID CANCER, BUT CLEARLY REDUCED IN STAGE IV DISEASE

Verburg FA[1,2], *Maeder U*[3], *Tanase K*[2], *Thies ED*[2], *Diessl S*[2], *Buck AK*[2], *Reiners C*[2], *Luster M*[4]

[1]University Hospital Aachen, Nuclear Medicine, Aachen, Germany, [2]University Hospital Wuerzburg, Nuclear Medicine, Wuerzburg, Germany, [3]University Hospital Wuerzburg, Comprehensive Cancer Center Mainfranken, Wuerzburg, Germany, [4]University Hospital Ulm, Nuclear Medicine, Ulm, Germany

Objective: Differentiated thyroid carcinoma (DTC) generally has a good prognosis. As yet it is however not yet clear whether life expectancy is impaired in these patients and if so, to what extent. The aim of this study was to determine how the all-cause mortality rate in DTC patients compares to that of the general population.

Design: Database study.

Patients: The study sample comprised 2011 DTC patients treated in our hospital from 1980–2011. All patients received total thyroidectomy with subsequent I-131 ablation except for those patients with an isolated papillary microcarcinoma. Survival data for the general German population were obtained from the German Federal Statistics Agency and matched to our DTC population for age and sex.

Results: All-cause mortality was not significantly reduced compared to expected mortality in patients with stage I, II or III disease according to version 7 of the UICC/AJCC TNM system (86% of patients). However, those with extensive perithyroidal invasion (stage IVa and IVb), those with lateral lymph node metastases of 45 years and over at diagnosis (stage IVa) and those with distant metastases of 45 years and over (stage IVc) had a clearly lower survival (relative cumulative relative survival rate (observed:expected) for stage IVc after 20 years: 0.295; 95% confidence interval 0.033–0.556).

Conclusion: life expectancy is not significantly reduced in over 85% of DTC patients; only patients with TNM stage IVa, IVb and IVc disease showed a clearly lower life expectancy.

P262

PREDICTIVE VALUE FOR DISEASE PERSISTENCE OR EARLY PROGRESSION OF SERUM THYROGLOBULIN LEVELS AT TIME OF ^{131}I REMNANT ABLATION USING RECOMBINANT TSH

Melo M[1,2], *Costa G*[3], *Ribeiro C*[1], *Carrilho F*[1], *Martins MJ*[4], *Gaspar da Rocha A*[2], *Soares P*[2,5], *Carvalheiro M*[1]

[1]University Hospital of Coimbra, Department of Endocrinology, Diabetes and Metabolism, Coimbra, Portugal, [2]Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP), Porto, Portugal, [3]University Hospital of Coimbra, Department of Nuclear Medicine, Coimbra, Portugal, [4]University Hospital of Coimbra, Department of Pathology, Coimbra, Portugal, [5]Medical Faculty, University of Porto, Department of Pathology, Porto, Portugal

Introduction: Endogenously-stimulated thyroglobulin (Tg) levels measured just before ablation demonstrated to have predictive value for disease-free remission. Little is known about the significance of Tg levels at ablation when rhTSH is used.

Objectives: To investigate the prognostic value of Tg levels at ^{131}I remnant ablation after rhTSH stimulation.

Methods: One hundred forty one consecutive patients treated for a thyroid carcinoma - 113(80.1%) papillary, 25(17.7%) follicular and 3(2.1%) poorly differentiated - with no initial evidence of distant metastasis (pT1-3, Nx-1, Mx) were included. All patients had a total thyroidectomy followed by ablation with 100mCi ^{131}I after rhTSH stimulation. Tg and Tg-Antibodies (Tg-Abs) were measured three days after the second rhTSH administration (day 2 after radioiodine). The minimum follow-up time was 12 months (mean=24.3±9.3). Protocol included neck ultrasound, TSH and fT4 at 3 months after ablation and stimulated Tg, Tg-Abs, TSH and neck ultrasound at 9–15 months. Patients were considered as disease-free if they had no uptake outside thyroid bed in

postablation whole-body scan, normal neck ultrasound and stimulated Tg< 1ng/mL. Patients with Tg-Abs were excluded. ROC curve analysis was used to assess Tg predictive value.

Results: Eight patients were excluded due to the presence of Tg-Abs. At the end of follow-up, 97(72.9%) were considered as free of disease. In the group with persistence/progression of disease, 13 had proven lymph node metastasis, 7 displayed distant metastasis, 3 developed local recurrence, 3 showed radioiodine uptake outside the thyroid bed and 7 only presented elevated Tg levels. Tg levels were able to predict disease persistence/early progression (AUC=0.78, SE=0.049; $p< 0.001$). The Tg cut-off value with the highest accuracy was 7.2ng/mL (Sensitivity=80.0%, Specificity=61.7%, Positive Predictive Value=43.8%, Negative Predictive Value=89.2%).

Conclusions: Thyroglobulin measured at ablation with rhTSH preparation was able to predict absence of disease persistence or early recurrence. Thus, this measurement seems useful in predicting early disease-free remission.

P263

EFFECTS OF PILOCARPINE ON SALIVARY GLAND FUNCTION AFTER POSTOPERATIVE RADIOIODINE THERAPY FOR DIFFERENTIATED THYROID CANCER

Lim J-Y[1], Choi J-S[1], Kim Y-M[1]
[1]Department of Otorhinolaryngology, Inha University College of Medicine, Incheon, Korea, Republic of

Objectives: The aim of this study was to investigate the effect of pilocarpine on salivary gland function in patients with postoperative ^{131}I therapy-induced salivary dysfunction using a visual analog symptom scale and quantitative analysis of salivary flow rate, as well as salivary gland scintigraphy.

Materials and methods: Fifty patients who had RI-induced salivary dysfunction (sialadenitis, xerostomia, or hypogeusia) after treatment of ^{131}I for postoperative ablation of differentiated thyroid cancer were enrolled. 25 patients were assigned randomly to the pilocarpine treatment group, which received 5mg pilocarpine tid in addition to traditional conservative treatment such as hydration, sucking on sour candies or lemons, and massaging the affected gland, and 25 patients were assigned to the control group with only conservative treatment. Salivary dysfunction was graded according to a visual analog symptom scale before and 3 month after treatment. Salivary flow rate was measured and quantitative salivary gland scintigraphy was performed for analysis of salivary parenchymal function.

Results: There were no statistical differences in the mean age and the mean dose of ^{131}I administered between 2 groups. The salivary symptom scale on sialadenitis was significantly improved in the treatment group compared to the control group. But pilocarpine treated group showed no significant improvement of the function parameter by salivary flow rate as well as quantitative salivary scintigraphy compared to the control group.

Conclusions: Pilocarpine treatment reduced the occurrence of symptoms on salivary dysfunction. Salivary flow rate and scintigraphic parameters were not statistically different between the pilocarpine treated and control group, which suggest that adding pilocarpine to traditional sialogogues may not improve the parenchymal damage to salivary gland.

P264

PROGNOSTIC IMPLICATIONS OF THE NUMBER AND RATIO OF METASTATIC LATERAL NODES IN PAPILLARY THYROID CARCINOMA

Koo MY[1], Lee SK[2], Bae SY[2], Choi MY[2], Choe J-H[2], Kim J-H[2], Kim JS[2]
[1]National Police Hospital, Surgery, Seoul, Korea, Republic of,
[2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Surgery, Seoul, Korea, Republic of

Purpose: The purpose of this study was to examine the effect of the number of involved lateral nodes and the ratio of metastatic nodes in papillary thyroid carcinoma with lateral lymph node metastasis.

Methods: From January 2000 to December 2010, 345 papillary thyroid carcinoma patients underwent concurrent total thyroidectomy and central lymph node dissection with modified lateral lymph node dissection. All of the patients were diagnosed with lateral lymph node metastasis before or during surgery.

Results: The cohort had a mean age of 43 years (range 12–75), and 283 (80%) of the patients were female. There was a weak quantitative relationship between the number of CLN and LLN metastases ($P = 0.000$, $\delta = 0.305$) and the metastatic ratio ($P = 0.000$, $\delta = 0.319$). Metastasis of more than 4 involved lymph nodes was associated with a larger median tumor size, a higher median number of CLN metastases, a higher median ratio of CLN metastases, and a higher median off-T4 Tg level ($P = 0.000$). Additionally, micropapillary carcinoma was more frequent in PTC with less than 4 involved lateral nodes ($P = 0.000$). A comparative analysis of the metastatic LLN ratio also showed similar results. A metastatic LLN ratio above 16% was associated with a larger median tumor size, a higher median number of CLN metastases, a higher median ratio of CLN metastases, and a higher median off-T4 Tg level ($P = 0.000$). Additionally, micropapillary carcinoma was more frequent in patients with more than 16% of the LLNs involved ($P = 0.000$).

Conclusion: In this study, the number and ratio of involved LLNs were associated with clinical characteristics and with the off-T4 Tg level in PTC patients.

P265

PROGNOSTIC VALUE OF STIMULATED THYROGLOBULIN PRIOR ^{131}I ABLATION IN DIFFERENTIATED THYROID CARCINOMA: A PROSPECTIVE STUDY

Scheffel RS[1], Zanella AB[1], Dora JM[1], Maia AL[1]
[1]Hospital de Clínicas de Porto Alegre, Thyroid Section, Endocrine Division, Porto Alegre, Brazil

Background: Thyroglobulin (Tg) is a specific marker of thyroid tissue and Tg levels before ^{131}I ablation (Tg-ablation) had been suggested as a prognostic marker in patients with differentiated thyroid carcinoma (DTC).

Objectives: To evaluate whether Tg-ablation adds in risk stratification of DTC.

Methods: Patients with DTC followed at our Institution who underwent total thyroidectomy and ^{131}I ablation. Tg-ablation was measured under stimulated TSH condition (endogenous hypothyroidism). Patients with positive antithyroglobulin antibodies were excluded. Persistent disease was defined as clinical or imaging evidence of tumor and/or serum Tg under TSH stimulation >1ng/mL. The Tg-ablation performance was evaluated using the receiver operator characteristics (ROC) curve. Multiple logistic regression analysis was performed using persistent disease as dependent variable and age, sex, histological subtype, TNM stage, Tg-ablation as independent variables.

Results: One hundred and ninety patients were included; of them, 154 (81.1%) were women and 161 (84.7%) had papillary thyroid carcinoma. The TNM stage were as follow: 93 (48.9%) patients were in stage I, 19 (10%) in stage II, 19 (10%) in stage III and 29 (15.3%) in stage IV. After a median follow-up of 48.5 months (IQR 28–74), 74 (38.9%) patients showed persistent disease. The ROC curve resulted in an AUC of 0.84 (95%CI 0.78–0.90) and the best cut-off point was 7.0ng/mL (sensibility of 80%, specificity of 77%). Among patients with Tg-ablation (≤ 7ng/mL), only 14.4% had persistent disease, contrasting with 68.6% in the group with Tg-ablation >7ng/mL. Remarkable, none of the patients with Tg-ablation undetectable (< 1ng/mL) showed persistent disease. Multiple logistic regression analysis identified Tg-ablation >7.0ng/dL (OR 12.4, CI95% 4.4–43.2; P< 0,001) and male sex (OR 6.6; CI95% 1.89–23.08; P=0.03) as independent prognostic factors for persistent disease.

Conclusion: Tg-ablation level is an independent prognostic factor for persistent disease and might be used on defining the best therapeutic approach for DTC patients.

P266

WITHDRAWN

P267

SIDE EFFECTS OF TYROSINE KINASE INHIBITORS (TKI) APPLIED IN THYROID CANCER (TC) PATIENTS – ONE CENTER EXPERIENCE

Krajewska JA[1], *Kukulska A*[1], *Paliczka-Cieslik E*[1], *Handkiewicz-Junak D*[1], *Gawlik T*[1], *Olczyk T*[1], *Kropinska A*[1], *Skoczylas A*[1], *Michalik B*[1], *Jarzab B*[1]
[1]M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Nuclear Medicine and Endocrine Oncology Department, Gliwice, Poland

TKI are now being evaluated and their efficacy in prolongation of TC progression free survival has been documented. However, problem of their tolerability is raised as their side effects potentially limit their clinical use. Only drugs which were known to inhibit VEGFR were considered. In the study we decided to evaluate adverse effects in patients treated in our center within the prospective clinical trials phase II and III.

Objectives: The aim of the study was an analysis of frequency and severity of side effects related to TKI in TC patients. Thus, we retrospectively reevaluated side effects on the basis of Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The comparison of the drugs was not aimed.

Methods: 37 therapies with TKI due to advanced TC were assessed. 19 subjects were given vandetanib, 15 - lenvatinib, 3 - axitinib. Median treatment duration was 26.7 months (range: 4.0 - 62.2). The drug was discontinued due to TC progression in 9 subjects, adverse events in 5 and for other reasons in 4. Adverse events leading to treatment withdrawal were: weight loss (1), lymphopenia (1), QTC prolongation (1), tracheo-esophageal fistula (1) and purulent meningitis (1).

Results: Frequency and severity of the most common treatment-related side effects are shown in the table 1.

Conclusion: Despite frequent treatment-related side effects the tolerability of tyrosine kinase inhibitors in advanced TC patients was acceptable (most adverse reactions G1-G2). Only in 13.5% cases treatment discontinuation was required.

Table 1.

	G1	G2	G3	Total	Treatable	Dose reduction
Skin reactions	16	8	2	26 (70.3%)	yes	no
Arterial hypertension	3	7	17	27 (73.0%)	yes	1
Diarrhea	7	9	4	20 (54.1%)	yes	4
Weight loss	4	13	3	20 (54.1%)	yes	5
Stomatitis	15	1	-	16 (43.2%)	yes	no

P268

PROS AND CONS OF PROPHYLACTIC CENTRAL COMPARTMENT LYMPH NODE DISSECTION IN DIFFERENTIATED THYROID CANCER PATIENTS

Valerio L[1], *Viola D*[1], *Materazzi G*[2], *Miccoli P*[2], *Basolo F*[2], *Sensi E*[2], *Faviana P*[2], *Molinaro E*[1], *Agate L*[1], *Pinchera A*[1], *Elisei R*[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy, [2]University of Pisa, Department of Surgery, Pisa, Italy

The clinical benefit of the prophylactic central compartment lymph node dissection (CCL) in differentiated thyroid cancer (DTC) is still controversial. This treatment seems to reduce DTC recurrence rates and the need of performing a reoperation. The risk of a higher rate of surgical complications represents the major concern.

The aim of the present prospective study was to evaluate the pros and cons of PCCLD and the outcome of DTC patients treated with either total thyroidectomy (TTx) or TTx+CCL.

A total of 169 DTC patients with no preoperative evidence of lymphnode metastases (N1) were randomly assigned to TTx, (Group-A, n=84) or TTx+CCL, (Group-B, n=85).

The two groups did not differ for their epidemiological and clinical features. As expected the Group-B showed a higher prevalence of N1 (47.1% vs 7.1%) while no differences were observed for other pathological features (i.e multifocality, tumoral capsular infiltration, histological variants etc). After a mean follow-up of 3.5 years, no difference was observed in the outcome of the 2 groups of patients. At the present, reoperation was not needed in any patient. However, a statistically significant higher number of ^{131}I courses was administered to Group-A (p=0.0009). Furthermore, a statistically significant higher prevalence of permanent hypoparathyroidism was observed in Group-B (p=0.046).

In conclusion, this study showed that the short term outcome of DTC patients treated with either TTx or TTx+CCL was very similar. However, the patients treated with TTx have to undergo a higher number of ^{131}I courses than those treated with TTx+CCL. Conversely, those treated with TTx+CCL have a higher number of permanent hypoparathyroidism. A longer term follow-up is needed to verify the prevalence of recurrences in the 2 groups.

P269

METASTATIC THYROID CANCER (TC) UNRESPONSIVE TO CONVENTIONAL THERAPY AND OTHER THYROSINE KINASES INHIBITORS (TKI) TREATED WITH SUNITINIB "OFF-LABEL"

Cappagli V[1], *Bottici V*[1], *Molinaro E*[1], *Agate L*[1], *Viola D*[1], *Valerio L*[1], *Mazzeo S*[2], *Battaglia V*[2], *Contillo Pontillo B*[2], *Dal Canto L*[3], *Vitti P*[1], *Pinchera A*[1], *Elisei R*[1], *Ribechini A*[4]
[1]University of Pisa, Endocrinology and Metabolism, Pisa, Italy, [2]University of Pisa, University Radiodiagnostic, Pisa, Italy, [3]AOUP, Pharmacy, Pisa, Italy, [4]University of Pisa, Thoracic Surgery-Section of Thoracic Endoscopy, Pisa, Italy

Objective: We evaluated the clinical benefits of sunitinib in patients (pts) with metastatic TC, refractory to other conventional therapies and to other TKI, not eligible for clinical trials and with a progressive disease.

Patients: We enrolled 4 pts (3 females,1 male) with the above mentioned features:1 papillary, 2 follicular and 1 medullary. Pts mean age was 55 years. They were followed from 1 to 18 months after starting the treatment. To evaluate the response to sunitinib we performed a CT scan, a biochemical evaluation (serum thyroglobulin [Tg] or calcitonin [Ct]) and a performance status (PS) evaluation after 1 and every 3 months.

Results: According to RECIST criteria, after one month, 3 pts showed an evident stabilization of the disease (SD) and 1 pt showed a partial response (PR). In all cases a clinical improvement of PS was referred. A stabilization or a decrease of Tg or Ct was also found. During the follow-up, 2/3 SD pts and the pt with PR showed a durable disease stabilization for 4, 9 and 17 months after the first control. The other SD pt, despite the initial good response, required the therapy discontinuation due to severe adverse events (i.e. pulmonary abscess). In all pts, after the starting dose of 50 mg orally/die for 4 weeks followed by 2 weeks off, we adopted an alternative schedule (1 week "off" and 1 week "on") to better control the side effects. With this schedule, 3/4 pts could continue the treatment until now.

Conclusions: We observed an overall clinical benefit in 4/4 pts (100%) which was durable in 3/4 pts for a relatively long term period. The side effects could be managed with a new schedule of administration of the drug. It is desirable that sunitinib could become a "first choice" drug in advanced and progressive TC.

PO30 Thyroid Cancer Pathogenesis Clincial/Translational

P270

ASSOCIATION OF PAPILLARY CARCINOMA, AND SOME OF ITS BASIC FEATURES WITH THE PRESENCE OF HASHIMOTO´S THYROIDITIS

Semenov A[1], Chernikov R[1], Vorobyov S[1], Bubnov A[1], Slepcov I[1], Uspenskaya A[1], Makarin V[1], Timofeeva N[1], Chinchuk I[1], Novokshonov K[1], Karelina J[1], Rusakov V[1], Fedorov E[1], Kulyash A[1]
[1]St. Petersburg Branch Pirogov National Medical & Surgical Center, Endocrine Surgery Department, St. Petersburg, Russian Federation

Objective: The aim of the study was to evaluate the relationship of Hashimoto´s thyroiditis (HT) with the underlying disease according to morphological studies.

Results: Patients with papillary carcinoma accounted for 43.0% all 3112 patients operated. Of these 36.7% had HT which was in 30.3% a focal one and in 6.4% - diffuse. The remaining patients had HT in 17.2% (13.4% focal). The difference was significant ($\chi2$=141,2; p< 0,0000001). The relative risk of papillary thyroid carcinoma to thyroiditis Hashimoto was 1.66.

Of the 1338 patients operated with a papillary carcinoma proved or found via histological examination 433 (32.4%) had multifocal tumor. At the same time multiple primary tumors occurred in 40.7% of cases with Hashimoto thyroiditis and 27.7% with no background HT (the difference was significant: $\chi2$=24,1; p=0,00000045). It was also noted a significant difference ($\chi2$=5,9; p=0,0076) in the likelihood of multifocal process in patients with focal and diffuse nature of the thyroiditis - 43.3% and 28.6% respectively. In 406 (30.6%) patients with papillary carcinoma of the capsule invasion was observed tumors (including extrathyroid extension). Invasion of the gland capsule was significantly more prevalent in HT background (33.3% vs 28,7%; $\chi2$=3,1; p=0,00387), in this case was a marked difference in the probability depending on the type of thyroiditis; rate of invasion was 38.8% for patients with focal thyroiditis and for patients with diffuse was 7,1% ($\chi2$=30,8; p< 0,0000001). The relative risk of invasion by the nature of focal thyroiditis was significant and amounted to 5.37.

Conclusions: There is marked association of papillary carcinoma, and some of its basic features with the presence of HT, mainly its focal form. Probably, there are common etiological factors underlying both diseases. Those results suggest avoiding operations of less than total thyroidectomy volume in cases with ultrasound features of Hashimoto thyroiditis.

P271

PREVALENCE AND INFLUENCE OF OBESITY IN DIFFERENTIATED THYROID CARCINOMA

Castagna MG[1], Ciuoli C[1], Theodoropoulou A[1], Brusco L[1], Maino F[1], Belardini V[1], Serafini A[1], Memmo S[1], Pacini F[1]
[1]University of Siena, Siena, Italy, Section of Endocrinology and Metabolism, Department of Internal Medicine, Endocrinology and Metabolism and Biochemistry, Siena, Italy

Introduction: An association between obesity and an increased relative risk of thyroid cancer has been reported in the literature.

Aim: to evaluate 1) the prevalence of obesity in thyroid cancer and 2) the impact of obesity on the clinical features and outcome of differentiated thyroid carcinoma (DTC).

Patients and methods: 615 consecutive patients (surgical series) submitted to thyroidectomy for benign or malignant thyroid disease and 524 patients followed for DTC (DTC series) were retrospectively studied. Body Mass Index (BMI) obtained at the time of thyroid surgery, was correlated with histological results and, in DTC patients, with pathological tumor features at diagnosis and clinical outcome.

Results: In the surgical series (n=615) the prevalence of overweight/obesity in thyroid cancer (154/265, 41.8%) was not different to the prevalence of overweight/obesity in benign thyroid nodules (215/350, 61.4%, p=0.40). In particular, thyroid cancer was found in 111/246 (45.1%) normal weight, in 82/179 (45.8%) overweight and in 72/190 (37.8%) obese patients, without difference between the 3 groups (p=0.21). Regarding the DTC series (n=524), no difference was found in the pathological features (tumor size, multifocality, extracapsular invasion, lymph nodes or distant metastases) between normal weight and overweight/obese patients. No association was also demonstrated between BMI and recurrent (0.8% in normal weight, 1.1% in overweight, 1.8% in obese) or persistent disease (13.3% in normal weight, 12.8% in overweight, 17.9% in obese) at the last follow-up (median 4 years, range 1.5–21.6 years).

Conclusions: Our results do not demonstrate an increased risk of thyroid cancer in obese patients and, in patients with DTC, do not support an association between obesity and aggressive thyroid cancer features at diagnosis or worst outcome.

P272

2D-DIGE PROTEOMIC ANALYSIS IS A USEFUL TOOL IN THE SEARCH OF NEW BIOMARKERS IN THE EPITHELIAL THYROID TUMORS WITH DIFFERENT DEGREES OF MALIGNANCY

Mato E[1,2], Barceló S[3], González C[1,2], Aulinas A[2], Bell O[1,2], Moral A[4], Pérez JL[4], de Leiva A[1,2]
[1]Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Barcelona, Spain, [2]Hospital Sant Pau, Autonomous University, Endocrinology Department, Barcelona, Spain, [3]Instituto Aragonés de Ciencias de la Salud (ICS), Unidad Mixta de Investigación, Proteomics Unit, Zaragoza, Spain, [4]Hospital Sant Pau, Autonomous University, General Surgery, Barcelona, Spain

Introduction: Proteomic approaches are useful tools to identify differential protein expression between thyroid tumours with different histopatological patterns (differentiated tumours with a good prognosis *versus* tumours that present an aggressive behaviour and readily metastasize).

Aim of this project was to apply two-dimensional difference gel electrophoresis (2D-DIGE) in order to identify new proteins pattern, which define patients with a worse prognosis. In addition, to find new targets that permit testing new treatments. This approach permits us to compare hundreds of proteins in a single experiment under quantitative and reproducible conditions.

Methods: We analyzed PTC(n=5), FTC(n=4), ATC(n=3) and adenomas(n=4). These tumours were classified according the (AJCC). The protein samples were covalently labelled with different fluorochromes, mixed, and fractionated in a single 2D-gel. The significant spots were cut. Tripsine digestion, extraction of the peptides, and then measurement of their masses by MALDI-TOF/MSMS and peptide mass fingerprint (Aldente(Expasy)). The data analysis were performed by software packages DeCyder5.02(Amersham Biosciences) for the normalization, the co-detection of the spots by DIA(DeCyderDifferential In-Gel Analysis) and finally, the volume relationship for each of the spots were processed by BVA(DeCyder Biological Variation Analysis) that detect and calculate the relative changes observed in all gels. The data were organized by biological function, using curate protein family and subfamily classification using Panther software.

Results: Proteomic profiling revealed that 208 protein spots were present in the gels with a statistical significance (ANOVA p< 0,05). These were selected for analysis and 120 were successfully identified. Most of them were included in clusters defined by: metabolic, communicative, developmental, molecular structure, catalytic activity and binding proteins. Differential pattern expression was detected on thyroid tissue with a different degree of malignancy.

Summary: 2D-DIGE analysis showed proteins are differentially expressed in the thyroid tumours and could be a key in the knowledge of dedifferentiation process in these tumours.

P273

ANAPLASTIC AND POORLY DIFFERENTIATED THYROID CARCINOMA SHOW A LOW PREVALENCE OF KNOWN GENETIC ALTERATIONS

Alessia T[1], Romei C[1], Molinaro E[1], Agate L[1], Cosci B[1], Vivaldi A[1], Giani C[1], Pieruzzi L[1], Lorusso L[1], Elisei R[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy

Objectives: Molecular mechanisms responsible for the development of Anaplastic Thyroid Cancer (ATC) and poorly Differentiated Thyroid cancer (PDTC) are not well defined although many genes (i.e. BRAF, RAS, beta-catenin, PIK3CA, TP53, AXIN1, PTEN and APC) have been found to be altered. The purpose of this study was to define the prevalence of genetic alterations in ATC and PDTC.

Methods: Our series consisted of 14 cases of ATC and 13 cases of PDTC. Fresh tumoral thyroid tissues (n=22) and fine-needle aspirated material (n=5) were used for DNA extraction. Somatic mutations were analyzed by direct sequencing.

Results: In the group of ATC, genetic screening allowed the identification of 2 cases with the BRAFV600E mutation, 2 cases with a somatic mutation in exon 8 of p53 gene (R273N and R267W) and a complex mutation of the PTEN gene (one base pair deletion at codon 119 followed by a heterozygous mutation Q97R). In PDTC we found the AKTQ17K mutation in one case, a PIK3CAH1047R mutation in one case and the BRAFV600E mutation in another case. No mutations of the RAS and beta-catenin genes were found. In addition to mutations with transforming activity we identified the T1493T polymorphism of the APC gene in 6/8 cases (4 homozygous and 2 heterozygous) of PDTC, in 8/11 cases (4 homozygotes and 4 heterozygotes) of ATC. We also found the p53 gene polymorphisms (R213R) in 1 ATC case.

Conclusions: These data show a quite low prevalence (5/14, 35%) of mutations in ATC. In particular only 2 cases (14%) with p53 mutations have been found. An even lower prevalence (3/13, 23%) of mutations was observed in PDTC. In this group there were no mutations of the p53 gene. Finally, the prevalence of the APC polymorphism was not different from the prevalence of the same polymorphisms in healthy controls (n=200).

P274

DIFFERENCIATED THYROID CANCER COEXISTENT WITH CHRONIC THYROIDITIS (HASHIMOTO'S THYROIDITIS) A STUDY ON GENDER DIFFERENCES

Mitsuhashi T[1], Tomemori T[1], Watanabe R[1], Hiruma K[1], Sakitani E[1], Sugisaki H[1], Yanagi Y[1]
[1]Tokyo Metropolitan Cancer and Infectious Diseases Center KOMAGOME Hospital, Otorhinolaryngology Head and Neck Oncology, Tokyo, Japan

Introduction: It is suggested that there is some relationship between chronic thyroiditis (Hashimoto´s thyroiditis) and differentiated thyroid cancer (papillary carcinoma in particular) by clinical or immunohistochemical gene study. Many studies have reported an increased risk of malignancy in Hashimoto´s thyroiditis (HT). We found some reports of more than 30% prevalence, but unfortunately the most of reports are retrospective studies. In late years pilot case-control study to identify the association of HT and differenciated thyroid cancer (DTC) begins to be performed, but the results do not yet appear.

HT affects almost 5% of the population and is more common in women, M to F=1 to 10 ~ 20. In addition, prevalence of thyroid cancer is female preponderance epidemiologically, M to F=almost 1 to 2. However, there is much number of the male DTC patients with HT unexpectedly.

Objectives: We studied the difference of ratios that the DTC patient contracts a disease in HT between men and women.

Material and methods: We reviewed 189 thyroid cancer cases that we made treatment (operation in principle) in our department by March 2012 since April 1996. We diagnosed TgAb or TPOAb either positive case as HT.

Results: 58 are male, and 131 female (M to F=1 to 2.26). Average age : 59 years old.

51 (29.0%) of 176 DTC were HT. In this HT group, papillary carcinoma (PTC) 46, follicular carcinoma (FTC) 5, sex ratio M to F=1 to 4.67. On the other hand, in non-HT group (125 cases), PTC 104, FTC 21, M to F=1 to 1.91. The proportion of PTC to FTC (9.2 to 1) in HT group clearly exceeded that in non-HT group, 5 to 1. All cases of male HT group were PTC.

Conclusions: As for PTC of a man, it was suggested deep association with HT.

P275

EXOME WIDE ANALYSIS IN 5 PAPILLARY THYROID CARCINOMAS

Frasca F[1], Nicolosi ML[1], Gianì F[1], Vella V[2], Cattonaro F[3], Morgante M[3], Vigneri R[1]
[1]University of Catania, Clinical and Molecular Biomedicine, Endocrinology Unit, Catania, Italy, [2]University of Enna 'Kore', Scienze Motorie, Enna, Italy, [3]University of Udine, Istituto di Genomica Applicata, Parco Scientifico e Tecnologico, Udine, Italy

Background: Recent progresses in molecular biology have improved the understanding of the pathogenesis of cancer. For the thyroid, the most important genetic alterations occurring in Papillary Thyroid Carcinomas (PTCs) including BRAF mutations, RET and TRK rearrangements and RAS mutations have been identified. However, a considerable proportion of PTCs displays no one of these known alterations. Hence, a certain number of PTC-specific genetic alterations is still unknown. DNA sequencing is today the standard method for the genetic analysis of biological samples. New technologies, such as Illumina Genome Analyzer, today allow the whole-genome sequencing, including analyses of individual human genomes.

Aim: The aim of this study is to carry out a pilot investigation to identify potential mutations in the whole coding genome (exome) of 5 PTC samples and their normal counterpart through the Illumina Genome sequencing.

Method: The study was carried out in collaboration with IGA (Istituto di Genomica Applicata) in Udine. Total mRNA was extracted from fresh frozen thyroid cancer tissue and normal counterpart and used for reverse transcription to obtain cDNA to be subjected to sequencing. Therefore the whole transcriptome sequencing of this PTC was obtained and compared to that of the normal counterpart.

Results: The PTC tissue, compared to the normal paired thyroid tissue, showed the non synonym mutations in the following expressed genes: PDE4DIP (Arg-His), JUND (Leu-Arg), CHST15 (Leu-Pro), PNKD(Arg-His), USMG5 (Thr-Lys), SVIL (Stp-Glu), CREB3 (Glu-Gly) and KANK2 (Phe-Ser).

Conclusions and perspectives: Mutations found in these genes may be an important because of the role of these genes in many cell functions. Some of these mutations were reported in other type of tumors, suggesting that they are important also in thyroid tumor initiation and/or progression. These results, however, require functional investigations and need to be replicated in other PTC specimens.

P276

DNA METHYLATION OF CBX7 GENE IN PAPILLARY THYROID CARCINOMA

Chung K-W[1], *Park S-Y*[2], *Lee EK*[2], *Lee YJ*[2], *Kim SK*[2], *Kim TS*[2], *Jung YS*[2], *Kim TH*[2], *Ryu JS*[2]

[1]Asan Meical Center, Ulsan University, College of Medicine, Division of Endocrine Sdurgery, Department of Surgery, Seoul, Korea, Republic of, [2]National Cancer Center, Center for Thyroid Cancer, Goyang, Korea, Republic of

Objectives: Various molecular prognostic factors are studied in papillary thyroid carcinoma (PTC). DNA methylation is one of main mechanism to control expression of these genes. We investigated DNA methylation status of MIG6, CBX7 and FOXA2, which are known to be associated with prognosis of PTC. We also investigated association of DNA methylation and known prognostic markers including BRAF mutation.

Methods: 58 paraffin embedded PTC tissues and normal adjacent thyroid tissues were collected from archives. Methylation specific high resolution melting analysis (MS-HRM) was performed to validate DNA methylation status of target genes using cell lines. Then methylation specific PCR was performed to find DNA methylation of target genes using DNAs from paraffin embedded tissues. Significant association between DNA methylation and clinicopathological factors were defines as p value was less than 0.05.

Results: We failed to find suspicious DNA methylation site in MIG6 and FOXA2 genes. However, CBX7 gene was methylated in cell lines by HRM analysis. CBX7 DNA was methylated in twelve out of fifty-eight (20.7%) PTC tissues. All normal tissues were unmethylated. CBX7 DNA was also methylated in BCPAP, FRO and FTC133 cell lines while TPC1 and FRTL5 (rat normal thyrocyte) cell lines. CBX7 expression was not observed in methylated cell lines and CBX7 expression was restored after treatment of 5' AZA. Methylation of CBX7 were not associated with known prognostic factors. However, BRAF mutation is more frequently found in CBX7 methylated PTCS. (10/10 vs. 36/48, p=0.023)

Conclusions: CBX7 expression in PTC is regulated by CBX7 DNA methylation. CBX7 methylation is associated with BRAF mutation.

P277

MATRIX METALLOPROTEINASE-9 (MMP-9) AND TISSUE INHIBITOR OF METALLOPROTEINASE-1 (TIMP-1) OVEREXPRESSION IN PAPILLARY THYROID CARCINOMA: IMPLICATIONS FOR CLINICAL DISEASE PRESENTATION

Romitti M[1], *Ceolin L*[1], *Ferreira CV*[1], *Cavalcante S*[1], *Wajner SM*[1], *Meurer L*[2], *Brasil BA*[2], *Maia AL*[1]

[1]Hospital de Clínicas de Porto Alegre/ Universidade Federal do Rio Grande do Sul, Endocrinology Service, Porto Alegre, Brazil, [2]Hospital de Clínicas de Porto Alegre, Pathology, Porto Alegre, Brazil

The matrix metalloproteinases (MMPs) constitute a large group of enzymes that degrade components of the extracellular matrix and basement membrane. Recent studies have demonstrated overexpression of these enzymes and their tissue inhibitors (TIMP-1 and TIMP-2) in several carcinomas, suggesting role of these molecules on clinical disease presentation.

Objective: To evaluate the expression of MMP-9 and TIMP-1 in papillary thyroid carcinomas (PTC) samples and correlate with clinical parameters.

Methods: PTC and surrounding thyroid tissue paraffin-embedded blocks were collected from 54 patients. Immunohistochemical analyzes were performed using human antibodies against MMP-9 and TIMP-1 proteins. The expression levels were evaluated by Image-Pro Plus software and expressed as Integrated Optical Density (IOD). $BRAF^{V600E}$ mutation was identified by direct sequencing. Clinical data were retrospectively reviewed in medical records.

Results: Fifty-four patients aged 43.8±15.5 years were enrolled and 77.5% were female. Local or distant metastasis at diagnosis were present in 60.3% and 8.5% of cases, respectively. The $BRAF^{V600E}$ mutation was identified in 21% (n=12) of samples. As compared with surrounding thyroid tissue, increased MMP-9 expression was observed in 88% of PTC samples (31.79(22.61–35.46) vs. 133.4(80.10–181.55); p< 0.001). No association was found among MMP-9 expression and age at diagnosis, tumor size, local or distant metastasis (all p>0.05). Increased expression of TIMP-1 was present in the majority of PTC samples (98%) (148.21(96.76–231.12) vs. 20.59(19.51–29.42); p< 0.001). Interestingly, TIMP-1 levels were positively correlated with age at diagnosis (r=0.31; p=0.024) and small tumors (< 1.0cm;(p=0.013). No associations were observed among the levels of MMP-9 or TIMP-1 with $BRAF^{V600E}$ mutation.

Conclusion: The induction of MMP-9 and TIMP-1 indicate a possible role of MMP signaling pathway in PTC pathogenesis. The association of increased TIMP-1 expression with late onset and small tumors may suggest a potential role of this molecule as a marker of low PTC aggressiveness.

P278

PAPILLARY THYROID CARCINOMA WITH SIZE OF UP TO 10 MM – A DIFFERENT CLINICAL ENTITY?

Stanicic J[1], *Jukic T*[1], *Dabelic N*[1], *Granic R*[1], *Kusic Z*[1]

[1]University Hospital Centre Sestre Milosrdnice, Dpt of Oncology and Nuclear Medicine, Zagreb, Croatia

Introduction: Thyroid cancer incidence has been increasing in Croatia, as well as throughout the world during the last decades. The bulk of this increase is made out of papillary thyroid carcinomas with size of ≤10 mm, probably because of increasing use of ultrasonography in thyroid diagnostics.

Objectives: The aim of our study is to determine the differences between PTC patients divided into different groups by the size of their tumors (≤10 mm, 11–20 mm, 21–40 mm and >40 mm).

Subjects and Methods: A total of 1266 patients were included in the study treated at our department from 1987 to 2011. Clinical features analyzed in this study include patient age at the time of diagnosis, patient sex, presence of local and distant metastases and presence of thyroid capsule involvement.

Results:

Patients with tumors smaller with size up to 10 mm tended to have fewer local and distant metastases, and less frequent thyroid capsule involvement. However, these patients tended to be older and even more predominantly female than patients with larger tumors.

Conclusions: The anomaly in behavior of tumors with size of up to 10 mm consisted in them being discovered at a significantly more advanced age than larger tumors, which can, at least partially, be explained by women of more advanced age having more frequent thyroid check-ups. However, it also suggests that at least a part of these tumors are not precursors of larger tumors and that they might follow a different clinical path.

Table for Abstract P278.

Tm size (mm)	N of patients	F/M ratio	Age (median)	Age (mean+95% CI)	Thyroid capsule involvement	LN metastases	Distant metastases
≤10	536	5.78	51	49.87 (48.75–50.99)	12.38%	18.64%	0.86%
11–20	349	3.65	46	46.57 (46.04–47.09)	20.83%	30.70%	4.44%
21–40	181	3.89	48	46.92 (46.11–47.73)	34.74%	32.95%	9.49%
>40	55	1.20	53	52.34 (50.82–53.87)	64.00%	40.00%	11.54%

P279

SOMATOMETRIC PARAMETERS AND DAILY HABITS AS RISK FACTORS FOR THYROID CANCER DEVELOPMENT

Mathiopoulou L[1], *Boudina M*[1], *Chrisoulidou A*[1], *Mandanas S*[1], *Panagiotou G*[1], *Doumala E*[1], *Iliadou P*[1], *Tziomalos K*[1], *Pazaitou- Panayiotou K*[1]
[1]Theagenio Cancer Hospital, Endocrinology and Endocrine Oncology, Thessaloniki, Greece

Objective: The number of newly diagnosed thyroid cancers has more than doubled during the last 3 decades. One possible explanation for this trend is increased detection through more widespread use of ultrasound and image-guided biopsy. Data indicate that the increased incidence has occurred across all tumor sizes and stages, suggesting that more intense scrutiny is not solely responsible for this trend. The aim of the present study was to determine whether other factors, like components of metabolic syndrome and several daily habits, can influence thyroid cancer risk and its histology.

Methods: 315 patients operated for thyroid cancer and 127 healthy controls were included in the study. Data regarding age, sex, height (cm), weight (kg), waist and hip circumference, waist to hip ratio (WHR) and body mass index (BMI) were collected from all patients and controls. Moreover, patients' information including history of type 2 diabetes, lipid profile, hypertension as well as daily habits such as smoking, alcohol and coffee consumption were recorded. Specific histologic characteristics regarding tumor size, lymph nodes metastases, invasive characteristics of the tumor and extrathyroidal extension were also collected. Data analysis was performed with the statistical package SPSS (version 17.0). All data were analyzed anonymously.

Results:

a) Patients proved to be taller than controls (height 164.3±7.9cm vs. 162.3±7.6 cm, p=0.015)

b) WHR was found to be higher in patients compared to controls (0.88±0.09 vs. 0.86±0.06, p=0.026)

c) Coffee consumption seems to protect from thyroid cancer development (1.3±1.1 in patients vs. 1.6±1.1 in the control group, p=0.013).

d) Tumor size was positively correlated with age, body weight, WHR, waist circumference (p value 0,010- 0,034- 0,013- 0,013 respectively).

Conclusions: Somatometric parameters as well as daily habits represent risk factors for the development of thyroid cancer and can influence its histology.

P280

EYA-SIX TRANSCRIPTIONAL SIGNAL PATHWAY IS INVOLVED IN THYROID CANCER TUMORIGENESIS

Riesco-Eizaguirre G[1], *Miranda S*[2], *Mendiola M*[3], *Hardisson D*[3], *Nistal M*[3], *Santisteban P*[4]
[1]Hospital La Paz, Endocrinology, Madrid, Spain, [2]Instituto de Investigaciones Biomédicas de Madrid, Fisiopatología Endocrina y del Sistema Nervioso, Madrid, Spain, [3]Hospital La Paz, Madrid, Spain, [4]Instituto de Investigaciones Biomédicas de Madrid, Madrid, Spain

The transcriptional coactivator Drosophila Eyes Absent Homologue Eya has a critical role in the development of a number of organs including the thyroid gland. Recent work has identified aberrant expression of Eya proteins in human breast carcinomas. We first examined which Eyas (Eya 1–4), if any, are expressed in normal thyroid cells. Using RT-PCR we identified Eya2 as the predominant Eya family member in PCCl3 cells. Moreover, Eya2 expression was further confirmed in human thyroid cancer cell lines: 90% (9 of 10) were found to express variable but significant levels by both RT-PCR and immunoblots. Immunohistochemistry analysis of human thyroid samples found that only weak Eya2 protein expression was detected both in the nucleous and the cytoplasm of follicular thyroid cells. By contrast, Eya2 is overexpressed in human thyroid cancer samples compared to normal thyroid and seems to be associated with aggressive clinicopathological features. Our results also suggest that Eya2 cooperates with Six1, a transcription factor that is part of the same conserved regulatory cascade involved in embryonic organ development. Six1 is not expressed in PCCl3 cells and is barely expressed in the normal thyroid gland. Interestingly, Six1 seems to correlate with Eya2 expression in human thyroid cancer. Preliminary results suggest that Eya2 and Six1 are both involved in migration and invasion of tumour cells as well as in metastasis formation in an orthotopic mouse model of thyroid cancer. Therefore, our results indicate an important role of the Eya-Six transcriptional signal pathway in thyroid cancer progression.

Supported by of Grants BFU-2010-16025, RETIC RD06/0020/0060 and S2011/BMD-2328 TIRONET.

PO31 Thyroid Hormone and Reproduction/Foeto-Maternal Unit

P281

THIOCYANATE FROM MATERNAL SMOKING INHIBITS NIS WITH INCREASED RISK OF IODINE DEFICIENCY IN MOTHER AND CHILD BUT PLACENTAL IODINE TRANSFER SEEMS TO BE UNAFFECTED

Andersen SL[1], *Nøhr SB*[2], *Wu CS*[3], *Olsen J*[3], *Pedersen KM*[4], *Laurberg P*[1]
[1]Department of Endocrinology, Aalborg Hospital, Aalborg, Denmark, [2]Postgraduate Education, Aalborg Hospital Science and Innovative Center, Aalborg, Denmark, [3]Section of Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark, [4]Department of Medicine, Vejle Hospital, Vejle, Denmark

Introduction: NIS (sodium iodide symporter) mediates iodine transport in the thyroid and the lactating mammary gland and NIS is identified in placental tissue, but the quantitative role of NIS in placental iodine transfer remains to be clarified. Thiocyanate which accumulates in smokers competitively inhibits NIS in the thyroid and the lactating mammary gland with increased risk of iodine deficiency as indicated by higher serum Thyroglobulin (s-Tg) among smoking mothers and their newborns.

Objectives: To test the impact of smoking induced NIS inhibition on placental iodine transfer. Our hypothesis was that smoking would lead to a higher degree of iodine deficiency in child than mother with a relatively higher increase in cord s-Tg.

Methods: 140 healthy, pregnant women admitted for delivery and their newborns were studied before the Danish iodine fortification of salt. Cotinine in urine and serum classified mothers as smokers (n=50) or non-smokers (n=90). One-third of the mothers (n= 47) had regular intake of iodine supplements. Maternal s-Tg at delivery and cord s-Tg were used as marker of iodine deficiency.

Results: In *the iodine supplement group* smoking and non-smoking mothers had similar s-Tg (mean 17.0 vs. 12.6 µg/l, p = 0.24) and cord s-Tg was similar (35.4 vs. 32.1 µg/l, p = 0.66). In *the no iodine supplement group* with iodine deficiency and high s-Tg, smoking mothers had higher s-Tg (40.2 vs. 24.4 µg/l, p = 0.004) and cord s-Tg was higher (smoking 80.2 vs. non-smoking 52.4 µg/l, p = 0.006). However, the ratio cord/maternal s-Tg was not higher in smokers (mean 2.06 vs. 2.22, p = 0.69).

Conclusions: Maternal smoking increased the risk of iodine deficiency among pregnant women and their newborns with higher s-Tg. However, s-Tg increased to a similar degree in mother and child with no evidence that NIS is important in placental iodine transfer.

P282

EVALUATION OF THE THYROID FUNCTION, IODINE URINARY EXCRETION AND THYROID VOLUME IN 300 WOMEN AT FIRST TRIMESTER OF PREGNANCY LIVING IN AN AREA OF MODERATE IODINE DEFICIENCY

Russo L[1], *Bottai S*[1], *Licari S*[1], *Frigeri M*[1], *Gambacciani M*[2], *Vitti P*[1], *Pinchera A*[1], *Tonacchera M*[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy, [2]University of Pisa, Department of Reproductive Medicine and Child Development, Pisa, Italy

Iodine deficiency during pregnancy causes maternal and fetal hypothyroidism and hypothyroxinemia.

Objective: Clinical and biochemical evaluation of thyroid function, thyroid autoantibodies, iodine urinary excretion and thyroid volume in pregnant women.

Methods and patients: 300 consecutive pregnant were analyzed by: clinical history, serum thyroid hormone (FT4 and FT3), TSH and thyroid antibodies measurements (TgAb and TPOAb), iodine urinary excretion, thyroid ultrasound.

Results: 121 (40,3%) were affected by thyroid disease (group I), 179 women (59,7%) didn't have any thyroid disease (group II).

Group I: 42 women (34,7%) used iodized salt, 17 (14,1%) used supplements with iodine, 45 pregnants (37,1%) didn't assume iodized salt or iodine supplements and 17 (14,1%) used both. 3 women (2,5%) were treated with MMI or PTU and 32 (26,4%) with L-T4.

Group II: 33 women (18,4%) used iodized salt, 42 women (23,5%) used supplements with iodine, 69 women (38,5%) didn't use either of them and 35 pregnants (19,6%) used both. Of 51 women, without thyroid disease, evaluated at first trimester: 41 women (80,4%) had TSH value between 0,4–2,5 mU/l, however 4 (7,8%) showed a condition of hypothyroxinemia (FT4< 8,6 pg/ml). 9 pregnants (17,6%) had TSH value < 0,4 mU/l and only one woman (2%) showed TSH >2,5 mU/ml.

In this group median of TSH was 0,848 mU/l, mean was 0,938 ± 0,573 mU/l. Median of FT4 was 10,3 pg/ml, mean was 10,445 ± 1,799 pg/ml. The mean thyroid volume was 10 ± 3,76 ml. The median of ioduria was 112 µg/l. 33 women (64,6%) had low level of urinary excretion of iodine (< 150 µg/l).

Conclusion: In 179 pregnant women not affected by thyroid diseases coming from an area of moderate iodine deficiency, 38% didn't use iodized salt or iodine supplements and about 65% had low level of ioduria. About 8% had isolated hypothyroxinemia.

P283

THYROID VOLUME AND THYROID HORMONE LEVELS IN PREGNANT WOMEN LIVING IN THE SOFIA AREA

Ivanova RB[1], *Kovatcheva R*[1], *Kirilov G*[1], *Ivanova RS*[1], *Dimitrova V*[2]
[1]University Hospital of Endocrinology, Thyroid and Metabolic Bone Diseases, Sofia, Bulgaria, [2]University Hospital of Obstetrics and Gynecology, Sofia, Bulgaria

Objectives: During pregnancy the markers of thyroid function - FT3, FT4 and TSH change according to the gestational period. The aim of our study was to assess thyroid function and thyroid volume in a population of healthy pregnant women living in the iodine sufficient area of Sofia.

Methods: 450 healthy pregnant women with no history of thyroid disease and 50 healthy age-matched women as controls were recruited. The pregnant women were divided in 3 groups according to the gestation week: I (1–12 g.w.) - 124; II (13–25 g.w.) - 177; III (26–37 g.w.) - 149. Thyroid palpation and ultrasound volume evaluation as well as TSH, FT4, FT3 were measured. A questionnaire including intake of iodated salt, supplements, smoking, miscarriages, weight and height was analyzed.

Results: Thyroid goiter grade 1a and 1b was found in 13% of all pregnant women and in 9% of controls. Ultrasound thyroid volume was significantly higher in subjects from group III (13.28 ml), compared to those from group I, group II and controls - 11.65 ml, 12.40 ml and 12.71 ml respectively. There was a positive correlation between thyroid volume and thyroid echogenicity, age, BMI, smoking, miscarriages or premature births. The median TSH was significantly higher in group II and III, compared to group I. The median FT4 (pmol/L) was 8.2, 9.1, 6.1 and 10.85 in the first, second, third trimesters and controls respectively.

Conclusions: In an iodine sufficient area, thyroid volume increases during pregnancy and is associated with changes in TSH. The decrease of free thyroxine in the third trimester of pregnancy is most likely not related to iodine supply.

P284

DETECTION OF THYROID DISFUNCTION IN EARLY PREGNANCY BY USING A UNIVERSAL SCREENING PROTOCOL

Diéguez M[1], *Aller J*[2], *Delgado E*[2], *Lavilla A*[2], *Pertierra J*[2], *Rabal A*[2], *Sánchez C*[2], *Herrero A*[3], *Menéndez E*[2]
[1]Hospital de Cabueñes, Endocrinology and Nutrition, Gijón, Spain, [2]Hospital Universitario Central de Asturias, Endocrinology and Nutrition, Oviedo, Spain, [3]Complejo Universitario de Salamanca, Endocrinology and Nutrition, Salamanca, Spain

Objective: To assess the efficacy of universal screening of thyroid dysfunction (TD) during early pregnancy.

Methods: We conducted this cohort study in a population in Northern Spain between February 2010 and February 2011. TSH and free T4 (FT4) were analyzed in 2517 consecutive pregnant women during the first trimester of pregnancy (median gestation 8 weeks). Trimester-specific population-based TSH and FT4 reference ranges were previously assessed. Thyroperoxidase antibodies (TPOAb) were checked in all patients with TD and TSH receptor antibodies (TRAb) in hyperthyroid patients. Patients with pregestational TD were excluded of the analysis.

Results: Universal screening identified 156 patients (6.2%) with TD, mean age 31.4±6 years. TD was classified as 23 clinical hypothyroidism (14.7%), 40 subclinical hypothyroidism (25.6%), 64 isolated hypothyroxinemia (41%), 12 clinical hyperthyroidism (7.7%) and 17 subclinical hyperthyroidism (10.9%). All hyperthyroid patients were TPOAb and TRAb negative. A high-risk case finding testing approach only identified 30 of the 156 patients with TD (19.2%). Older age (>35 years) was not associated with raised TSH, relative risk (RR) 0.9, 95% confidence interval (CI) 0.7–1.5.

TPOAb were detected in 42 patients (27%). Clinical hypothyroidism were diagnosed in 18 of TPOAb positive patients (42.9%) and in 5 of TPOAb negative patients (5%). We assessed a positive association between TPOAb positivity and risk of postpartum thyroiditis, RR 5, 95% CI 2–22 (p< 0,05) and persistent postpartum thyroid disease RR 4.7, 95% CI 2–11 (p< 0,01).

Conclusions: Compare to universal screening, a case-finding approach misses more than 80% of patients with TD in pregnancy. Age over 35 years does not identify patients at risk of TD. Pregnant women with positive TPOAb are at increased risk for postpartum thyroiditis and for postpartum persistent thyroid disease.

P285

SEVERE GESTATIONAL HYPOTHYROIDISM DUE TO ANTI-TSH RECEPTOR BLOCKING ANTIBODIES

Di Bella B[1], *Moleti M*[1], *Presti S*[1], *Di Mauro F*[1], *Sturniolo G*[1], *Violi MA*[1], *Agretti P*[2], *De Marco G*[2], *Tonacchera M*[2], *Trimarchi F*[1], *Vermiglio F*[1]
[1]Università degli Studi di Messina, Clinico-Sperimentale di Medicina e Farmacologia, Messina, Italy, [2]Università di Pisa, Endocrinologia e Metabolismo, Pisa, Italy

Autoimmune hypothyroidism due to TSH-receptor blocking antibodies (TBAb) is uncommon. When occurring in pregnancy, this condition may be responsible for feto-neonatal complications as a result of both maternal hypothyroidism and trans-placental TBAb transfer to the fetus.

Clinical case: September 2010: a 27 year-old woman was diagnosed with autoimmune severe hypothyroidism [TSH 325 mIU/L (n.v 0.4–4.0), FT4 1.54 pmol/L (n.v. 11.5–22.6), FT3 0.67 pmol/L (n.v. 3.7–8.3); TPOAb and TgAb positive]. Levo-thyroxine (LT4) treatment was started (100 µg/day) and euthyroidism achieved in November 2010 (TSH 0.34 mIU/L, FT4 18.6 pmol/L, FT3 7.0 pmol/L). In December 2010 pregnancy was ascertained (5 wks) and thyroid tests revealed L-T4 dose inadequacy [TSH 13.9 mIU/L (trimester-specific n.v.: 0.03–2.3); FT4 10.3 pmol/L (trimester-specific n.v.: 11.9–21)]. LT4

dose was increased (1300 µg/week) with prompt restoration of euthyroidism (January 2011, 8 wks: TSH 0.16 mIU/L). In the further follow-up LT4 dose was progressively adjusted to maintain TSH and FT4 within the normal range. TSH-receptor antibodies (TRAb) at 10, 20, 30 wks of gestation were positive with high titer (>40 UI/L). The assay for TBAb, performed by incubating CHO-TSHR cells, revealed an inhibition of cAMP production two, four and five-fold higher than that found with normal IgG at 10, 20 and 30 weeks, respectively.

Fetal/neonatal data: Morphological us, umbilical flowmetry and fetal echo-cardiography were normal for gestational age at 20 and 30 wks. Fetal thyroid volume and vascularization, bone maturation, and fetal mobility were normal as well. August 2011 (38 weeks): cesarean section delivery. Neonatal data: TSH 29.4, 25.9 e 4.4 µU/ml and FT4 22.0, 31.4 e 16.0 pm/L, at 12 and 36 hours and at 3 weeks of post-natal life, respectively. TRAb>40 UI/L at 36 hours. Thyroid us was normal.

Conclusion: Severe hypothyroidism in child-bearing age women should routinely advise TRAb assay.

P286

DOES THE PRESENCE OF THYROID ANTIBODIES AFFECT THE COURSE AND OUTCOME OF PREGNANCY IN TYPE1 DIABETIC WOMEN?

Vasileiou V[1], *Sarantopoulou V*[1], *Philippou G*[1], *Lymberi P*[1], *Sarika L*[1], *Alevizaki M*[1], *Anastasiou E*[1]

[1]Alexandra Hospital, Diabetes Centre- First Endocrine Section, Athens, Greece

Introduction: In the literature there are only three papers so far, addressing the impact of thyroid antibodies (Anti-TPO) on pregnancy in Type1 Diabetic Women (DM1) and these present conflicting results. The aim of the study is to evaluate the presence of Anti-TPO in DM1 pregnant women and whether these are related with differences in thyroid function, metabolic control and pregnancy outcome.

Methods: In 78 DM1 women with singleton pregnancies Anti-TPO, Anti-Tg, TSH, FT4I (T4/TBC) were measured each trimester. At each visit (every 1–2 weeks) blood glucose, HbA1c, BMI, units of insulin/Kg were recorded, as were complications and pregnancy outcome.

Results: 27/78 women (34.6%) presented with positive Anti-TPO Abs and 51/78 (64.4%) with negative Anti-TPO Abs. Age, BMI and diabetes duration did not differ between the two groups.

Regarding thyroid function tests (TSH and FT4I during pregnancy) only first trimester TSH levels were statistically different between the two groups.

No differences were observed in glycaemic control (HbA1c), insulin requirements and birth weight.

There were no differences in the prevalence of diabetic complications, gestational hypertension-preclampsia, abortions or preterm deliveries.

Conclusion: One third of DM1 pregnant women presented with positive Anti-TPO Abs. However their presence was not related with worse metabolic control or adverse pregnancy outcome. It seems that early treatment of thyroid dysfunction and stricter metabolic control plays a more important role than the presence of thyroid antibodies with regard to the pregnancy outcome.

P287

IODINE STATUS OF PREGNANT WOMEN AND INFANTS IN EASTERN UKRAINE

Belykh N[1], *Mamenko M*[1]

[1]Luhansk State Medical University, Department of Postgraduated Education in Pediatrics, Luhansk, Ukraine

Iodine deficiency in the fetus is the result of iodine deficiency in the mother. The consequence of iodine deficiency during pregnancy is impaired synthesis of thyroid hormones by the mother and the fetus. Insufficient supply of thyroid hormones to the developing brain may result in mental retardation.

Our aim in this study was to evaluate the iodine status of pregnant women and their newborns.

Material and methods: A study was undertaken in 1052 healthy pregnant women in third trimester of gestation with normal thyroid function, without drugs known to influence thyroid function except iodine. Serum TSH, fT4, fT3, anti-peroxidase antibodies (n=252) and urinary iodine concentration (UIC) were determined, thyroid volume were evaluated by ultrasonography (n=1052).

Results: Ten percent of studied pregnant women had a diet rich with iodine carriers, 37.5% household had a diet iodine salt and 25.6% obtained iodine supplements. Thirty six percent appeared to have a goiter; median goiter volume was 16.7 mL (range 7.2–33.5mL). Median UIC was 78.2µg/L (range 17.0–510.7µg/L), only 14.2% of women had UIC ≥150 µg/L. Median UIC was significantly higher in the group receiving iodine supplements than in the group without iodine supplements: 146.9 µg/L *v.* 67.3 µg/L respectively, p< 0.001. Median serum TSH was normal: 1.9 mIU/L (range 0.6 до 7.8 mIU/L). Thirty one percent women have gestational hypothyroxinemia, 22.4% pregnant have low fT3/fT4. Neonatal TSH performed on the third day of life as a neonatal screening test for hypothyroidism: median value was 3.2 mIU/L (range 0.01–17.1 mIU/L). The results >5 mIU/L have 20.6% newborns.

Conclusion: Insufficient iodine supplementation leads to the gestational hypothyroxinemia, maternal and infant's hypothalamic-thyroid dysfunction, perinatal abnormalities and high rate of transient neonatal hyperthyrotropinemia.

P288

THYROID FUNCTION IN WOMEN UNDERGOING TO CONTROLLED OVARIAN HYPERSTIMULATION

Del Ghianda S[1], *Benelli E*[2], *Ruggiero M*[3], *Artini P*[3], *Simoncini T*[3], *Loconte E*[1], *Vitti P*[4], *Tonacchera M*[5]

[1]University of Pisa, Dep of Endocrinology, Pisa, Italy, [2]University of Pisa, School of Medicine, Dep of Endocrinology, Pisa, Italy, [3]University of Pisa, Dep Reproductive Medicine, Pisa, Italy, [4]University of Pisa, Pisa, Italy, [5]University of Pisa, School of Medicine, Pisa, Italy

Objective: Thyroid gland and gonadal axes are closely related before and during pregnancy. The optimal setting to investigate the effects of gonadal axes on thyroid function is the controlled ovarian hyperstimulation (COH) that leads to elevated serum oestrogens and TBG levels. Previous data indicated an increased serum TSH levels twenty days after COH. Besides COH has a greater impact on thyroid function in women with autoimmune thyroiditis. The aim of our study was to investigate the early changes in TSH, FT3 and FT4 in women undergoing to COH.

Patients and methods: 34 women undergoing to COH for different causes (polycystic ovary syndrome, tubal diseases, male infertility) were evaluated. TSH, FT4, FT3, tireoglobuline (Tg), TBG, thyroglobulin and thyroperoxidase antibodies were measured in all subjects at the start of COH, after six days, during follicular transvaginal aspiration and after two weeks. Controlled ovarian stimulation was carried out with recombinant FSH and hpHMG within a long protocol with GnRh agonist or a flexible GnRh antagonist protocol. Recombinant HCG was administered when at least two follicles reached a mean diameter of 18 mm. After approximately 36 hr, transvaginal follicular aspiration was performed for oocyte retrieval. IVF or intracytoplasmic sperm injection and embryo transfer were performed as appropriate.

Results: Serum TSH values decreased after six days (from 2.15±1.35 to 1.52±0.89 µU/ml, p< 0.05) compared with baseline values; after two weeks from the start serum TSH levels increased (from 2.15±1.35 to 2.29±1.80 µU/ml, p>0.05). We also observed a rise of FT3 and FT4 during the two weeks that was not statistically significant.

Conclusion: This study showed a precocious decrease on serum TSH values after COH. We speculate a possible direct effect on hypothalamic-pituitary-thyroid axes due to the acute high serum FSH levels.

PO32 Environmental Factors and Drugs Affecting Thyroid Function 2

P289

THYROID FUNCTIONAL STATUS IN CHRONIC KIDNEY DISEASE (CKD)

Hossain M[1], Hasan M[1], Ahmed P[1], Monoarul Islam AKM[1], Islam Chowdhury N[1], Shah K[1], Begum N[1]
[1]Rajshahi Medical College Hospital, Nuclear Medicine, Rajshahi, Bangladesh

Background: The kidney normally plays an important role in the metabolism, degradation and excretion of thyroid hormones. Therefore, impairment in kidney function leads to disturbed thyroid physiology. All levels of the hypothalamic-pituitary-thyroid axis may be involved, including alterations in hormone production, distribution, and excretion. As a result, abnormalities in thyroid function tests are common in chronic kidney disease.

Objectives: This study was done to find out the effect of chronic kidney disease on thyroid functional status.

Methods: A total of 100 patients suffering from different stages of chronic kidney disease were included for this study during the period of January 2010 to December 2010 at the Centre for Nuclear Medicine & Ultrasound, Rajshahi, Bangladesh.

Results: This study showed high prevalence of primary hypothyroidism (11%), low T3 syndrome (45%) and subclinical hypothyroidism (5%) in chronic kidney disease patients. Furthermore, there is an increasing trend of decreased thyroid functional status along with decrease of estimated GFR (eGFR).

Conclusions: Chronic kidney disease impairs thyroid functional status in different ways. So thyroid functional status should be evaluated in each and every patient of CKD. That can reduce the morbidity and mortality rate of CKD patients as well as reduce the social burden and health expenditure.

Key words: Chronic kidney disease (CKD), estimated GFR (eGFR), Primary hypothyroidism, Subclnical hypothyroidism, Low T3 syndrome.

P290

AMIODARONE INDUCED SUBCLINICAL THYROID DYSFUNCTION – WHAT TO EXPECT DURING FOLLOW UP? IS THERE REASON FOR AMIODARONE WITHDRAWAL?

Aleksić ŽP[1], Aleksić AZ[2], Mitov VM[2], Jolić AD[2], Vešović DM[3]
[1]Health Center Zaječar, Neclear Medicine, Zaječar, Serbia, [2]Health Center Zaječar, Internal Medicine, Zaječar, Serbia, [3]American School of Medicine, Belgrade, Serbia

Amiodarone (AMD), iodine rich antiarrhytmic, can induce thyroid dysfunctions.

Aim: Was to asses clinical characteristics of patient (pts) with AMD induced subclinical thyroid dysfunctions (SCTD) and thyroid status outcome during follow up.

Method: 248 pts on AMD treatment, avarage age 63.5 yeras, 144 males and 104 females, AMD treatment duration 24 months (mediana), have been followed up, avarage duration 16 months, clinicaly and biochemicaly, using commercial ACCESS chemi-lummino-immunoassay kits for TSH, FT4 and FT3. Pts were from the region of sufficient iodine supply. Diagnostic criterion for subclinical thyrotoxicosis (SCT) was TSH < 0.1 m IU/L, normal or slightly elevated FT4, up to 10 measuring units above the upper refference range value and normal FT3; for subclinical hypothyroidism (SCH), TSH in the range of 4–15 m IU/L and normal FT4.

Results: 63% of pts remained euthyroid, 16% developed clinical thyroid dysfunction (CTD), 21% developed SCTD - 15% SCH and 6% SCT. Avarage age and AMD treatment duration didn't differ among pts, but there were statisticaly signifficant more women and more with goiter pts with SCTD. All SCTD pts were asymptomatic. In SCH pts 45% became euthyroid with or without AMD withdrawal (18% and 27%), 49% remain subclinicaly hypothyroid with or without AMD withdrawal (15% and 34%), one pt became hypothyroid one year after AMD withdrawal, one pt developed AMD induced thyrotoxicosis (AIT) during follow up and AMD treatment. During follow up 92% of SCT pts became euthyroid with or without AMD withdrawal (31% and 61%), 8% remined subclinicaly thyrotoxic despite AMD withdrawal.

Conclusion: Most AMD induced SCTD do not progress to CTD, even during continuation of AMD treatment. AMD withdrawal is not necessary, but carefull monitoring of thyroid status is obligatory. There is possibility for SCH to progress to AIT.

Key words: Amiodarone, subclinical thyroid dysfunction, subclinical hypothyroidism, subclinical thyrotoxicosis

P291

THE EFFECT OF POTASSIUM IODIDE ON RADIOACTIVE IODINE UPTAKE OF THE HEALTHY JAPANESE

Kunii Y[1], Noh J[1], Mukasa K[1], Sekiya K[1], Iwaku K[1], Matsumoto M[1], Yoshihara A[1], Ohe H[1], Suzuki A[2], Uruno T[2], Ito K[2]
[1]Ito Hopsital, Internal Medicine, Tokyo, Japan, [2]Ito Hopsital, Surgery, Tokyo, Japan

Background: It is reported that taking stabilization iodine (SI) is effective for the prevention of thyroid nodules and cancers increased by radioactive iodine exposure. The Japanese, who even live in iodine sufficient area, follows the guidelines of the amount of SI which based on the data of iodine deficient area.

Objective: To evaluate the effect of 10 mg potassium iodide (KI) on thyroid 24 hours radioactive iodine uptake (24RAIU) and thyroid functions in Japanese healthy volunteers under everyday meal intake.

Method: Twenty-one (17 men, 4 women) adults were participated in this study. The average age was 35.3±10.0 years old. Thyroid autoantibodies were negative in all subjects.

Thyroid functions, urinary iodine concentration (U-I), and 24RAIU were measured in the state of the everyday meal intake. Then, thyroid functions, U-I and 24RAIU after taking 10 mg KI were measured at least 7 days interval from post examination. We also evaluated 24RAIU after continues doses of 10mg KI for 14 days in three subjects.

Results: The average of 24RAIU without KI is 14.3±5.0%. The average of 24RAIU (3% (range 1–7)) with 10 mg KI is significantly lower compared to that of without KI value (paired t, $p < 0.0001$). The inhibition rate was 83.3% (range 40–92.3%). U-I (μg/24h) were changed from 271.7 (54.5–1512.2) to 2769.5 (1147.7–8059.6) ($p < 0.0001$) by taking 10mg KI. There were no significant differences in FT3, FT4 and TSH between without and with KI intake.

24RAIU after two weeks of 10 mg KI use were 5%, 2% and 4%, respectively. The thyroid functions were maintained in almost normal range.

Conclusion: In the healthy adult Japanese, a single dose of 10mg KI might be enough dosage to inhibit 24RAIU. In addition, the escape from the Wolff-Chaikoff effect did not happen even if we had taken10 mg KI for two weeks.

P292

THE PITUITARY-THYROID AXIS IN ADULTHOOD IS UNINFLUENCED BY BIRTH WEIGHT. EVIDENCE FROM A STUDY OF EXTREMELY BIRTH WEIGHT DISCORDANT MONOZYGOTIC TWIN PAIRS

Brix TH[1], Frost M[2], Petersen I[2], Christiansen L[2], Hegedüs L[1], Christensen K[2]
[1]Odense University Hospital, Endocrinology and Metabolism, Odense, Denmark, [2]University of Southern Denmark, The Danish Twin Registry, Odense, Denmark

Background: Low birth weight has been associated with changes in thyroid function in adulthood. However, it is unknown whether the association is explained by foetal programming or underlining genetics and environmental factors.

Objective: To assess whether birth weight influence the set point of the pituitary-thyroid axis in adults.

Design and setting: Discordant-twin study.

Participants: 153 birth weight discordant monozygotic twin-pairs with a median age of 58 years [min: 30. Max: 75 years] were ascertained from the Danish Twin Registry in 2010

TSH, T3, and T4 were measured. Birth weights were retrieved from midwife records (individuals born before 1973) and the Danish Birth Record Registry (all other participants)

Results: When the twins were investigated as singletons birth weight were inversely associated with TSH, T3, and T4 after adjustment for age, sex, BMI and use of tobacco products. In contrast, TSH and T3 were similar in the within twin-pair analyses, while T4 tended to be higher in twins with lowest birth weight (median difference 0.3 mIU/L). When analyses were repeated in twin-pairs (n=46 pairs) characterized by extreme difference in birth weight (>0.5kg), TSH, T3 and T4 were similar in twins with high and low birth weight. The proportion of individuals with TSH above 4 mIU/L or below 0.3 mIU/L was identical in both groups.

Conclusions: This study shows no evidence of an association between birth weight and adult pituitary-thyroid axis set point after control for genetics and environmental factors.

P293

PREVALENCE OF IODINE INTAKE INADEQUACY IN A GROUP OF ELDERLY BRAZILIAN WOMEN

Destefani SA[1], Corrente JE[2], Paiva SAR[1], Mazeto GMFS[1]
[1]Botucatu Medical School - Sao Paulo State University - Unesp, Internal Medicine, Botucatu, Brazil, [2]Institute of Biosciences - Sao Paulo State University - Unesp, Biostatistics, Botucatu, Brazil

Objectives: To evaluate the prevalence of inadequacy in the iodine intake (PIII) in a group of elderly women in the city of Bauru, Brazil, through a 24-hour recordatory.

Casuistic and methods: We have evaluated 135 elderly patients [average age of 68.23 (±7.86) years; 79.3% white; median income of 1.5 minimum wage /month; average body mass index-BMI of 27.8 (±5.6) kg/m^2], assisted by the City Program of Assistance to the Elderly (PROMAI) of Bauru city, Brazil, as to the iodine intake, through two 24-hour recordatory, with a gap of 30 days between them. The food amount was transformed into grams and inserted into the program DiedPro 5i®, which provided the nutrient's intake amount, to calculate the PIII. They were also evaluated as to the serum levels of free-thyroxin (FT4) and thyrotropin (TSH) (reference values of 0.8–1.9 ng/dL and 0.4–4.0 mUI/mL, respectively), being classified as euthyroid or as possible hypo or hyperthyroid.

Results: The average iodine intake of the group was of 100.7±39.2mg. The average serum levels of FT4 was of 1.1±0.2ng/dL and the median of TSH was of 2.2mIU/mL. Twenty-nine patients (21.5%) presented thyroid dysfunction: 27 (20%) with hypothyroidism (3 with overt hypo) and two (1.5%) with hyperthyroidism (1 with overt hyper). The average iodine intake of patients with hypothyroidism was of 92.7mg and with hyperthyroidism was of 154.0mg, while the average of those without any dysfunction was of 101.7mg. The PIII was of 44%, 42% and 57% in general patients, euthyroid and hypothyroid, respectively. Considering the co-variables age, race, income, BMI, TSH, FT4 and arterial hypertension, these prevalences were of 51%, 48% and 66%.

Conclusions: In this study, it has been observed that there is an increased PIII, particularly in hypothyroid patients.

P294

INNOVATIVE METHODS OF IODINE PROPHYLAXIS: FROM IODINE-FORTIFIED VEGETABLES TO HUMANS

Dimida A[1], Frigeri M[1], De Servi M[1], Agretti P[1], De Marco G[1], Ferrarini E[1], Piaggi P[1], Grasso L[1], Aghini-Lombardi F[1], Vitti P[1], Pinchera A[1], Tonacchera M[1]
[1]Department of Endocrinology, Pisa, Italy

Iodine deficiency (ID) is the result of insufficient dietary iodine intake and has multiple adverse effects due to inadequate thyroid hormones production. The most effective way to control iodine deficiency is through the universal salt iodisation (USI). USI alone may not be sufficient to assure adequate iodine nutrition.

Objectives: Biofortification of vegetables with iodine offers an excellent opportunity to increase iodine intake. In this study we tested the intake of vegetables (potatoes, tomatoes, carrots and green salad) fortified with iodine in 50 healthy volunteers to assess the efficiency of this model of iodine prophylaxis.

Methods: Each portion of vegetables (200 g of potatoes, 100 g of carrots 100 g of tomatoes and 70 g of salad) contains about 45 ug of iodine (30% of RDA). The volunteers consumed a portion of vegetables, 5 times/week for 1 week. To assess the iodine intake we measured iodine excretion in urine. The first urine samples were obtained before starting the study, successively, we measured the urinary iodine 7 days following the intake of the vegetables in the diet and then 7 days after the end of vegetables intake.

Results: The median urinary iodine before the treatment was 98,3 mcg/L, during the treatment was 117,5 mcg/L and after the treatment was 85 mcg/L. Our results indicate that the median urinary iodine has increased by 19% and return to the basal values after the discontinuation of the intake.

Conclusions: Biofortification of vegetables with iodine provide a mild increase in UI concentration that, together with the abitual use of iodised salt, contributes to improve the iodine nutritional status of the population without risk of iodine excess.

P295

CHARACTERISTICS OF THYROID AUTONOMY BEFORE AND TEN YEARS AFTER INCREASE IN MANDATORY SALT IODIZATION

Gaberscek S[1], Bajuk V[2], Zaletel K[1], Pirnat E[1], Hojker S[1]
[1]University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Medical Faculty in Ljubljana, Ljubljana, Slovenia

Objectives: Reports on thyroid autonomy (TA) after a change in iodine supply usually include TA presented with overt or subclinical hyperthyroidism and no data on the radioiodine treatment. Therefore, our aim was to establish the frequency of TA presented with euthyroidism, subclinical or overt hyperthyroidism and the required dose of radioiodine before and ten years after increase in mandatory salt iodization. At the beginning of 1999, Slovenia increased iodization of salt from previous 10 mg of potassium iodide to 25 mg per kg.

Methods: We reviewed records of all patients referred for the first time in 1998 and 2009 to the Thyroid Department at the University Medical Centre Ljubljana which has a stable catchment area of 1 million inhabitants for more than 20 years. TA was diagnosed by thyroid scintigraphy with the Technetium-99m pertechnetate. Patients were negative for TSH receptor antibodies. Euthyroid, subclinically or overtly hyperthyroid patients with TA were included. The applied dose of radioiodine was evaluated.

Results: In 1998, significantly more patients presented with TA than in 2009 (383 out of 3243, 11.8% and 333 out of 4546, 7.3%, respectively, $p< 0.001$). In 1998, the ratio between hyperthyroid and euthyroid patients was higher than in 2009 (6:1 and 2.1:1, respectively, $p< 0.001$). In 1998, patients were younger than in 2009 (mean 63.8±13.9 and 66.8±14.9 years, respectively, $p=0.006$). Hyperthyroid patients were older than euthyroid both in 1998 (mean 64.8±13.8 and 57.8±12.9 years, respectively, $p< 0.001$) as well as in 2009 (mean 68.9±14.1 and 62.3±15.8 years, respectively, $p< 0.001$). In 1998, mean applied dose of radioiodine was lower than in 2009 (667±156 and 777±155 MBq, respectively, $p< 0.001$).

Conclusions: Ten years after increased salt iodization TA is less frequent, patients are not so often hyperthyroid, they are older and cured with higher doses of radioiodine than before the increase.

P296

CHANGES IN THE THYROID GLAND UNDER THE INFLUENCE OF BISPHOSPHONATES

Luzin V[1], Fomina K[1], Yeryomin A[2], Zakharov A[1], Fastova O[1]
[1]Lugansk State Medical University, Lugansk, Ukraine, [2]Lugansk State Medical University, Human Anatomy, Lugansk, Ukraine

Objectives: Now bisphosphonates are widely used to treat bone diseases. This drugs provides effects not only on the bones, but their effects on other organ systems are not well understood. Therefore, the aim of our work is to study in experiments on white laboratory rats of different ages structural features of the thyroid gland with increased exposure of the body content of hydrocortisone, dexamethasone, a bisphosphonate "Zometa".

Methods: To identify the morphofunctional features of the thyroid gland of control and experimental animals, the organ was studied on the cellular level: larger and smaller diameters of the follicles.

Results: The height of the follicular epithelium is reduced by 12.79% - 21.83% among all age series of animals after the injections of of hydrocortisone and to 10.00% - 13.06% in mature rats after the injections of dexamethasone. After the injections of "Zometa" the most significant deviations from control values in upwards were obtained from immature animals (at 18.76% - 22.45%), due to the rapid growth of the thyroid gland and formation of its function in this age. In rats after the injections of hydrocortisone and "Zometa" area and height of the thyrocytes were not significantly different from control (up 0.60% - 4.83%).

Discussion: Our results show that bisphosphonates compensate the negative effect of glucocorticoids on thyroid function.

PO33 Hypothyroidism Clinical 2

P297

DIFFERENT REQUIREMENT OF LEVOTHYROXINE (LT4) REPLACEMENT THERAPY IN CONGENITAL HYPOTHYROIDISM WITH RESPECT TO ADULT IATROGENIC HYPOTHYROIDISM

Bagattini B[1], Montanelli L[1], Di Cosmo C[1], Ciampi M[1], Pinchera A[1], Vitti P[1], Tonacchera M[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

Objective: To compare the daily weightbased dosage of the replacement therapy with LT4 in athyreotic adult patients affected by congenital hypothyroidism (CH) and adult hypothyroid patients treated with total thyroidectomy (TT).

Patients and results: 35 patients (24 females and 9 males) aged 17 to 26 years were included. Group CH: 12 adult patients (mean age 19.9 yr) with athyreotic CH treated with LT4 since the first days of life; Group TT: 23 adult patients (mean age 23.3 yr) with hypothyroidism for TT. At the time of the observation all patients presented free thyroid hormones within the normal range and serum TSH between 0,3 and 3 µUI/ml, undetectable serum TG and antithyroid antibodies.

CH patients showed serum TSH values significantly higher with respect to TT patients (p=0.02), in particular CH subjects showed median serum TSH values higher than TT patients (CH: median=1.53 µUI/ml; TT: median=0.53 µUI/ml). The daily weightbased dosage of the replacement therapy with LT4 in CH was significantly higher with respect to TT ($p< 0.05$), in particular subjects with CH showed mean LT4 dosage higher than TT patients (CH: mean=2.03 µg/Kg, SD=0.29; TT: mean=1.76 µg/Kg, SD=0.26).

FT4 and FT3 were significantly higher in CH with respect to TT patients ($p< 0.01$), (FT4: CH: mean=14.58 pg/dl, SD=1.03; TT: mean=12.07 pg/dl, SD=2.24. FT3: CH: mean=3.95 pg/dl, SD=0.45; TT: mean=3.56 pg/dl, SD=0.43), with no significant difference in FT3/FT4 ratio (p=0,38; CH: 0,284; TT: 0,304).

Conclusions: CH patients required a daily LT4 dose/Kg higher than TT patients, when measured in the adult age even presenting higher serum TSH, FT4 and FT3 values, with a comparable FT3/FT4 ratio. The higher requirement of replacement therapy in adult patients with congenital hypothyroidism could be explained by a lack of thyroid hormones since fetal life in CH, which could determine a different setpoint of the hypothalamus-pituitary-thyroid axis.

P298

LACTOSE INTOLERANCE: A NOVEL OCCULT CAUSE OF THYROXINE MALABSORPTION

Virili C[1], Cellini M[2], Santaguida MG[1], Del Duca SC[2], Brusca N[2], Gargano L[3], Centanni M[2,3]
[1]'Sapienza' University of Rome, Experimental Medicine, Rome, Italy, [2]'Sapienza' University of Rome, Dept of Medico-Surgical Sciences and Biotechnologies, Latina, Italy, [3]AUSL Latina, UOC Endocrinologia, Latina, Italy

Objectives: Increased need for thyroxine may occur in patients with gastrointestinal diseases (Helicobacter pylori infection, chronic gastritis and celiac disease) and this may be the case also for lactose intolerance but there is a lack of methodical studies. This study was aimed at investigating the therapeutic dose of T4 required in hypothyroid patients with definite diagnosis of lactose intolerance.

Methods: In a large population of consecutively examined outpatients we have identified 39 hypothyroid patients, in need for T4 treatment, with clinical symptoms suggestive for lactose intolerance. This diagnosis was confirmed in 25 patients, based on the results of lactose breath test. Following the exclusion of patients non compliant and/or with other confounding factors (interfering drugs and/or other gastrointestinal diseases etc), 16 patients (all women; median age=37 years) met the criteria and represented the study group. These were spontaneously in a lactose-reduced diet. The dose of T4 required in these patients to attain serum TSH levels to within 0.5–2.5 mU/l was compared with that observed in 68 age-matched hypothyroid patients with no evidence of malabsorption.

Results: The serum TSH target was obtained in three months in 56/68 controls and in only 4/16 patients with lactose intolerance (Fisher´s exact test; $p< 0.0001$; OR= 14.0). In patients without malabsorption, the therapeutic target has been reached in 5±2 months (median TSH=1.02 mU/L; FT4=1.29 ng/dl), at a median dose of T4 of 1.31 µg/Kg/day. To reach a similar therapeutic goal (median TSH=1.28 mU/L; FT4=1.29 ng/dl) in patients with lactose intolerance, a longer period of time (10±3 months) and an higher median dose of T4 (1.72 µg/Kg/day; +31%; p=0.0008) were needed, as compared with patients without malabsorption.

Conclusions:

a) increased T4 need is a novel characteristic of lactose intolerance, despite dietary lactose reduction;
b) Lactose intolerance is a putative condition, often occult, of T4 malabsorption.

P299

FT4 LEVELS DO NOT REFLECT EUTHYROIDISM IN CENTRAL HYPOTHYROID L-T4 TREATED PATIENTS. A THERAPEUTIC TARGET TO BE RECONSIDERED AND IMPLICATIONS FOR TREATMENT

Gullo D[1], Ielo C[1], Latina A[1], Tita P[1], Marturano I[1], Vigneri R[1]
[1]Garibaldi-Nesima Hospital, University of Catania Medical School, Endocrinology, Catania, Italy

Objectives: In central hypothyroidism (CH) the treatment of choice, as in primary hypothyroidism, is levothyroxine (L-T4). TSH values are not reliable as an accurate reflection of thyroid status and FT4 is currently used to adjust the replacement dose. We evaluated in a large series of CH patients whether L-T4 monotherapy can normalize serum thyroid hormones and if FT4 levels may reflect adequate treatment.

Methods: In a cross-sectional retrospective study of 77 central hypothyroid patients, median age 55 (IQR 36–68) yrs, M=37 F =40, with normal FT4 levels under levothyroxine monotherapy (reference range 9.01–20.59 pmol/L), patients' FT3 and FT4 values where compared to a cohort of euthyroid controls (n=3,875).

Results: In L-T4-treated CH patients median FT4 levels were not different from euthyroid controls (14.0 pmol/L vs 13.8 pmol/L, P=0.112), whereas median FT3 values were significantly lower (3.23 vs 4.47, $P< 0.001$). FT3/FT4 ratio, an index of peripheral deiodination, was 0.23 vs 0.32 ($p< 0.001$). Among the L-T4-treated CH patients FT3 leves were all below median FT3 normal values; moreover, 32.5% of them had lower serum FT3 than the refer-

ence range (2.93–6.01 pmol/L). FT3 and FT4 levels were influenced by both gender and age.

Conclusions: CH patients on L-T4 therapy despite normalization of serum FT4 concentrations have FT3 levels lower than euthyroid controls and in one third of cases lower than the reference range, indicating that their ability to convert T4 to T3 is insufficient. These results cast doubts on the validity of FT4 measurement to assess thyroid status in CH patients. Moreover, L-T4 monotherapy may not be adequate to ensure euthyroidism in a subgroup of CH patients who may require a more physiological treatment with combined therapy administration of L-T4 and liothyronine preparations.

P300

CONGENITAL HYPOTHYROIDISM CAUSED BY A NOVEL HOMOZYGOUS MUTATION IN THE THYROGLOBULIN GENE

De Marco G[1], *Agretti P*[1], *Bagattini B*[1], *Ferrarini E*[1], *Dimida A*[1], *Molinaro A*[1], *Vitti P*[1], *Pinchera A*[1], *Tonacchera M*[1]
[1]Università di Pisa, Pisa, Italy

Objective: Congenital hypothyroidism (CH) due to thyroglobulin deficit is an autosomal recessive disease characterized by goiter, lower serum TG, elevated serum TSH levels with low levels of thyroid hormones and a negative perchlorate discharge test. The aim of this study was to perform the genetic analysis of the TG gene in two sisters born from consanguineus parents and affected by CH.

Patients and methods: The proband and her sister were identified at neonatal screening and treated with L-Thyroxine (L-T4) after hypothyroidism confirmation. After discontinuation of therapy, no organification defect was shown after ^{123}I scintigraphy and perchlorate test, serum TG was undetectable and thyroid ultrasound showed an eutopic thyroid gland. DNA was extracted from peripheral white blood cells of the two sisters and the father. All 48 exons of TG gene were amplified by polymerase chain reaction (PCR) and subjected to direct sequencing.

Results: In the blood of the patient and her sister a new homozygous point mutation in exon 10 of TG gene was identified. The mutation determined a stop codon at position 768 (R768X) resulting in a early truncated protein. The father was heterozygous carrier of the mutation.

Conclusions: Genetic analysis of TG gene was performed in two sisters affected by CH. A new point mutation of the TG gene determining a stop codon at position 768 of the protein was identified. The early truncated protein resulted not functioning and was responsible of the observed phenotype.

P301

FREQUENCY OF PDE8B GENE POLYMORPHISMS IN PATIENTS AFFECTED BY SPORADIC AND FAMILIAR NONAUTOIMMUNE SUBCLINICAL HYPOTHYROIDISM

Agretti P[1], *Ferrarini E*[1], *De Marco G*[1], *Dimida A*[1], *Niccolai F*[1], *Molinaro A*[1], *Pinchera A*[1], *Vitti P*[1], *Tonacchera M*[1]
[1]Università di Pisa, Pisa, Italy

Objectives: Nonautoimmune subclinical hypothyroidism is characterized by elevated serum levels of TSH in the presence of normal thyroid hormone levels and absence of anti-thyroid antibodies. As a result of a genomic-wide study, a strong association between three polymorphic variants in exon 1 of human phosphodiesterase 8B (PDE8B) gene (rs4704397, rs6885099 e rs2046045) and serum levels of TSH has been recently reported. In this study was evaluated the frequency of PDE8B gene polymorphisms in a group of patients affected by sporadic or familial nonautoimmune subclinical hypothyroidism.

Patients and methods: The study group comprised 113 patients affected by sporadic (101) or familial (12) nonautoimmune subclinical hypothyroidism with elevated serum TSH levels (medium serum TSH 8.997±12.48 mU/ml) and normal FT3 and FT4 levels. Genomic DNA was obtained from whole blood of patients using standard procedures to genotype patients for specific single nucleotide polymorphism (SNP) of PDE8B gene by TaqMan SNP genotyping assay, and to sequence the entire coding region of the TSHr gene.

Results: The ancestral allele associated with increased TSH level was present in 82/113 patients (73%) for rs4704397, in 79/113 patients (70%) for rs6885099 and in 84/113 patients (74%) for rs2046045. However, similar values of serum TSH were detected in patients with minor or major allele for each polymorphism. Genetic analysis revealed the presence of TSHr gene mutations at the heterozygous state (D36H, P52T polymorphic variants; P68S, R109Q and P162A mild inactivating mutations) in 17/113 patients.

Conclusion: A prevalence of the minor allele of PDE8B gene associated with elevated serum levels of TSH was demonstrated in patients affected by sporadic or familial nonautoimmune subclinical hypothyroidism, however significant differences in circulating TSH in patients with minor or major alleles for each polymorphism were not identified, demonstrating the lack of association between the polymorphisms and circulating TSH levels.

P302

TREATMENT OF HYPOTHYROIDISM IN ELDERLY PATIENTS

Gasparyan E[1], *Ostashko G*[2], *Dimnova S*[2], *Gasparyan A*[3]
[1]I. Mechnikov North-Western State Medical University, Endocrinology, Saint Petersburg, Russian Federation, [2]St. Eugene Hospital № 46, Endocrinology, Saint Petersburg, Russian Federation, [3]Medical Centre 'Professor', Endocrinology, Saint Petersburg, Russian Federation

Aim: Evaluating the results and adequacy of the treatment of elderly patients suffering from primary overt hypothyroidism in order to optimize substitutive therapy and improve the quality of life.

Material and methods: Efficiency of therapy of primary overt hypothyroidism has been estimated in 656 patients, aged 60–87. All the patients got substitutive therapy with euthyrox or thyroxine once a day. The levels of cholesterol, FT4 and TSH were checked during the first visit of the doctor and three, six months later.

Results: Clinical and laboratory methods confirmed euthyroidism in 436 (66%) patients. 105 (16%) patients showed medicamental thyrotoxicosis, which is why the thyroid hormone dose was decreased, resulting in significant improvement of the patients health and normalization of the TSH and FT4 levels 3 and 6 months later. 115 (18%) patients showed decompensation of hypothyroidism. The correction of the therapy by increasing a thyroid hormone brought a considerable improvement of the patients' condition and caused the decrease of the average TSH level to normal. However, in 44 patients the attempt to increase a thyroid hormone dose failed. Even at a slight increase of the dose, we observed worsening of the patients' condition in the absence of significant dynamics in ECG. The average TSH level in the group was 12.1±0.8 mME/l. In this connection the correction of cardiac therapy was held and thyroid hormones were administered twice a day in order to improve their tolerance. A good therapeutic effect was attained: the average TSH level in this group of patients became 4.4±0.6 mME/l 3–6 months later.

Conclusions:

- In elderly patients hypothyroidism was compensated only in 66% of cases. 16% of patients showed overdosage of thyroid hormones and 18% of patients were decompensated.
- Thyroid hormones are much better tolerated by elderly patients and are more effective when taken twice a day.

P303

THE LINK BETWEEN HYPOTHYROIDISM AND MORTALITY IS EXPLAINED BY COMORBIDITY RATHER THAN HYPOTHYROIDISM PER SE. EVIDENCE FROM A DANISH NATIONWIDE REGISTER-BASED STUDY OF TWINS AND SINGLETONS

Thvilum M[1], *Brandt F*[1], *Almind D*[2], *Christensen K*[2,3,4], *Brix TH*[1], *Hegedüs L*[1]

[1]Odense University Hospital, Department of Endocrinology and Metabolism, Odense C, Denmark, [2]University of Southern Denmark, The Danish Aging Research Center and The Danish Twin Registry, Odense C, Denmark, [3]Odense University Hospital, Department of Clinical Genetics, Odense C, Denmark, [4]Odense University Hospital, Department of Clinical Biochemistry and Pharmacology, Odense C, Denmark

Background: Hypothyroidism is associated with increased morbidity including a number of potentially lethal conditions, such as hypertension and cardiovascular disease. However, it is still debated whether hypothyroidism is associated with increased mortality. Our objective was to investigate, at a nationwide level, whether hypothyroidism influences mortality and, if so, the impact of co-morbidity and genetic confounding.

Subjects and Methods: Observational cohort study using record-linkage data from nationwide Danish health registers; 4851 singletons and 928 twins from same sex pairs diagnosed with a first episode of hypothyroidism were identified. Cases were matched 1:4 with non-hypothyroid controls according to age and sex. In addition same sex twin pairs discordant for hypothyroidism were identified. Cases and controls were followed over a mean period of 8.4 years (range 0–32 years) and the hazard ratio (HR) for mortality was calculated using Cox regression analyses.

Results: In singletons, mortality was increased by 22% in subjects with hypothyroidism (HR 1.22; 95% CI: 1.15–1.30). The impact of hypothyroidism on mortality attenuated after stratification for degree of preexisting co-morbidity, using the validated Charlson score (Charlson score accounts for multiple comorbidities by creating a weighted sum score) (HR 1.09; 95% CI: 0.99–1.21). Hypothyroidism was not associated with an increased mortality in the analyses of the disease discordant twin pairs (HR 1.03; 95% CI: 0.74–1.42). Stratifying for zygosity yielded essentially similar results in monozygotic (HR 1.00; 95% CI: 0.54–1.83) and dizygotic same sex pairs (HR 1.04; 95% CI: 0.71–1.52).

Conclusion: The lack of an association between hypothyroidism and mortality among individuals without preexisting co-morbidity and within twin pairs discordant for hypothyroidism, suggests that the increased mortality in hypothyroidism is due to confounding rather than hypothyroidism *per se*.

P304

TRENDS IN THYROID HORMONE PRESCRIBING IN THE UK 2000–2009

Taylor P[1], *Iqbal A*[2], *Sayers A*[3], *Greenwood R*[4], *Dayan C*[1]

[1]Cardiff University, CEDS, Cardiff, United Kingdom, [2]University of Sheffield, Department of Endocrinology, Sheffield, United Kingdom, [3]University of Bristol, Bristol, United Kingdom, [4]UHBT, Bristol, United Kingdom

Objective: Hypothyroidism is common and predominantly managed in primary care. Symptoms are non-specific, with thyroid function tests required for diagnosis. We sought to investigate current practice in levothyroxine prescribing in primary care.

Methods: Data was collected from the GPRD on the median TSH at index levothyroxine prescription. Individuals on levothyroxine prior to 2000, or on thyroid altering medication or with a history of prior thyroid or pituitary disease were excluded.

Results: Data was available on a total of 59,316 patients who commenced levothyroxine between 2000 - 2009. During this period the number of patients commencing on levothyroxine (as indicated by new prescriptions) rose threefold from 2022 *to* 6223 peaking in 2006 at 7792. Overall 62.2% of individuals were prescribed levothyroxine with an initial TSH less than 10mU/l. The odds of having a prescription adherent to guidelines fell steadily over this time, p for trend < 0.001. The increase in prescribing appeared to be most marked in subjects with TSH levels between 5–10 mU/l at first prescription; the proportion in this category increased from 41% in 2000 to 45% in 2009 peaking at 51% in 2008.

Conclusion: There has been a very marked increased in the number of people being started on levothyroxine in the period 2000–2009. This was associated with a relative increase in prescribing for patients with subclinical hypothyroidism such that currently more than 60% of prescribing is outside current guidelines. Randomised controlled trials with sufficient power to assess the health consequences of borderline and subclinical hypothyroidism and its treatment are therefore urgently needed to address the risks and benefits of current practice.

P305

EXPERIENCE OF THE FIRST YEAR OF NEWBORN SCREENING FOR CONGENITALHYPOTHYROIDISM (CH) IN GEORGIA

Beridze N[1], *Takaishvili R*[1], *Azikuri T*[1], *Takaishvili B*[1], *Mumladze M*[1], *Iashvili M*[2]

[1]Express diagnostics, Tbilisi, Georgia, [2]Georgian Patriarkhat St. Joakim and St. Ann Maternity Home, Tbilisi, Georgia

Background and aim: Revelation of the incidence of CH is of great value at the background of iodine deficiency (ID) existing in Georgia. Screening on CH in our company with consequent monitoring of the newborns with neonatal hyperthyreotropinemia (NHT) started in September 2010.

Materials and methods: During first year period 70731 newborns from all over Georgia underwent TSH (mU/L) determination from blood spots, taken at 24–72 hours after birth and venous blood FT4(ng/dl) and TSH at two weeks after birth using DELFIA kits were measured. Infants with NHT(cut off level 20mU/L) were consulted by pediatrician, endocrinologist and their blood thyreoglobulin (TG) level(ng/dl) and thyroid volume (cm3), using ultrasound investigation were examined.

Results: Transitory NHT had 280 infants (1:253 live births), mediana 46,5(range28,7–210), boys151, girls 129.23 infants had CH (1:3075 live births), girls -boys ratio-2,8/; ten with subclinical CH (Gr.1) and 13 -overt CH(Gr.2). Most of the babies were clinically euthyroid except 8,3%, having prolonged jaundice,5%-constipation,3,3%-sleepiness and 0,33% macroglossia. Most of the mothers with high NHT did not receive iodide supplementation during pregnancy. No one received high doses of iodine or anti-thyroid drugs. Heredity for thyroid pathology ranged 34–41%. No case of goiter and thyroid agenesis was detected. Gr.1 thyroid volume median- 1,3 was 2,6 times greater than of Gr.2- 0,5(P< 0,001) and their neonatal and two- weeks TSH levels were lower compared to GR.2 p< O. O5. Two infants of Gr.2 with pronounced thyroid hypoplasia (volume 0,2cm3) had low TG level-2,5–3,6. The rest had moderately elevated TG levels with median of Gr.2- 168,5, that was significantly higher compared to Gr.1- 72,1, P< 0,01.

Conclusion: Thus, CH in Georgia develops without goiter and with marked hypoplasia in severe cases that is possibly conditioned by ID and hereditary predisposition to the thyroid pathology.

PO34 Hyperthyroidism Clinical

P306

AN AUDIT OF PATIENTS (N=322) UNDERGOING DEFINITIVE TREATMENT OF HYPERTHYROIDISM AT A UK DISTRICT GENERAL HOSPITAL BETWEEN 2002 AND 2010

Taylor M[1], *Skene A*[1]
[1]Royal Bournemouth Hospital, Bournemouth, United Kingdom

The Royal Bournemouth Hospital is a District General Hospital in the South of England serving a population of 300,000. We have audited the treatment and outcomes of patients proceeding to definitive treatment for hyperthyroidism.

In the period 2002–2010, 278 patients underwent radio-iodine treatment for treatment of hyperthyroidism. During the same period 44 patients underwent surgery for treatment of hyperthyroidism.

The demographics of the population treated with radio-iodine were as expected, woman n=219, men n=59, with a mean age of 60.2 (youngest 15.6 yrs, oldest 95.1 years). Paediatric patients are managed at a neighbouring Hospital.

In terms of activity of Iodine^{131} adminstered, the mean activity was 520 MBq (range 300–800). During the period of Hospital follow-up, 61% of patients had developed post I^{131} hypothyrodism (170/278), 28% remained euthyroid (78/278), 18% developed transient biochemical hyperthyroidism and 4% developed recurrent hyperthyroidism (10). During the period 2002–2010 16 patients received a second treatment with Iodine^{131}.

In the same period 44 patients underwent Thyroidectomy for treatment of hyperthyroidism, women n=41, men n=3. Mean age 41 years. The reasons for proceeding to surgery were patient-choice, concerns about worsening of eye disease, and issues concerning young children at home and family planning considerations.

This audit has summarised the definitive treatment of hyperthyroidism at a District General Hospital. The results have shown that for the vast majority of patients that radio-iodine treatment is effective and associated with a low level of recurrent hyperthyroidism and low morbidity.

P307

LATE MANIFESTATION OF SUBCLINICAL HYPERTHYROIDISM AFTER GOITROGENESIS IN AN INDEX PATIENT WITH A N670S TSH RECEPTOR GERMLINE MUTATION CAUSING FAMILIAL NON-AUTOIMMUNE AUTOSOMAL DOMINANT HYPERTHYROIDISM (FNAH)

Schaarschmidt J[1], *Özerden M*[2], *Paschke S*[1], *Jaeschke H*[1], *Huth S*[1], *Eszlinger M*[1], *Meller J*[2], *Paschke R*[1]
[1]University of Leipzig, Department of Internal Medicine, Neurology and Dermatology, Leipzig, Germany, [2]University of Göttingen, Department of Nuclear Medicine, Göttingen, Germany

In 27 families with FNAH reported up to date, the onset of hyperthyroidism varies from 18 months to 60 years. Also the manifestation of goiters is variable in these families.

A 74 year old women was first presented at the age of 69 years in 9/2006 with tachyarrythmia and hypertension. After initial treatment of her hypertension and oral anticoagulation for her intermittant atrial fibrillation 3/2007, a thyroid workup revealed a suppressed TSH of 0,029 (normal >0,4 mIU/L) and normal fT3 and fT4. TPO, TSH receptor (TSHR) and thyreoglobulin antibodies were negative. Thyroid ultrasound revealed a thyroid volume of 102 ml with several nodules with diameters of up to 2,6 cm right and up to 1,8 cm left. Szintigraphy showed a homogeneous Tc uptake of 1,95%. She was treated with 1 GBq I131 in 6/2007. Until 9/2011 her thyroid function was normal (TSH 1.99 mIU/L) and her thyroid volume decreased to 90 ml. Her brother and sister do not suffer from thyroid diseases. Her 45 year old daughter and her 16, 12 and 11 year old grandsons do not have symptoms of hyperthyroidism and displayed normal TSH, fT3 and fT4 in 2010.

Because of the diffuse Tc uptake and the negative TPO, TSHR and thyreoglobulin antibodies, genetic analysis of her TSHR genes were performed. In spite of her negative family history for hyperthyroidism. Sequencing revealed a N670S TSHR germline mutation. This TSHR germline mutation's constitutive activity could previously only be demonstrated in HEK but not in COS cells.

This case illustrates the necessity to analyse patients with hyperthyroidism accompanied by diffuse Tc uptake and negative TPO, TSHR and thyreoglobulin antibodies for TSHR germline mutations. Moreover, it demonstrates that TSHR germline mutations may first lead to long standing nodular goitrogenesis before the late manifestation of subclinical hyperthyroidism.

P308

THE UTILITY OF RADIOIODINE UPTAKE AND THYROID SCINTIGRAPHY IN THE MANAGEMENT OF HYPERTHYROIDISM

Hong SI[1]
[1]Kwangju Veterance Hospital, Kwangju, Korea, Republic of

The only direct test of thyroid function employs a radioactive isotope of iodine as a tag for the body´s stable form of iodine. However, this test less frequently used than in the past. The value of RAIU in the diagnosis and management of hyperthyroidism is unsettled. And there is no report concerning with them in Asian population. Our objectives were to determine the influence of thyroid uptake and scintigraphy on the diagnosis of hyperthyroidm and the prediction of outcome following therapy. Study subjects were 46 patients who visited The Thyroid Clinic in Kwangju Veterance Hospital for the treatment of thyrotoxicosis from Jan. 2006 to Dec. 2010. We determined the relationship between 6-h 123I uptake and the thyroid function test. The mean age of the patients was 62±21,(M:F 8:38). There was good agreement between clinical and scintigraph diagnosis(Cl 0.55–0.67, p< 0.003). Treatment outcome was not associated with scintigraph diagnosis (P = 0·98) or radioiodine uptake at 6 h (P = 0·2). Thyroid scintigraphy and uptake studies did not influence diagnosis or treatment outcomes in most cases of hyperthyroidism. Our findings do not justify their routine use. Selective scanning will reduce cost without compromising diagnostic accuracy or treatment outcomes.

P309

GESTATIONAL HYPERTHYROIDISM IN WOMEN FROM MILD TO MODERATE IODINE DEFICIENCY (ID) AREAS

Presti S[1], *Moleti M*[1], *Di Bella B*[1], *Sturniolo G*[1], *Di Mauro F*[1], *Violi MA*[1], *Trimarchi F*[1], *Vermiglio F*[1]
[1]Università degli Studi di Messina, Clinico-Sperimentale di Medicina e Farmacologia, Messina, Italy

Graves' disease (GD) and gestational transient thyrotoxicosis (GTT) are the main causes of hyperthyroidism in pregnancy, their prevalence ranging between 0.1–0.4% and 0.3–11%, respectively.

Aim of the study: To evaluate both prevalence and outcome of gestational hyperthyroidism in mild to moderate ID areas.

Subjects and methods: 482 consecutive pregnant women who had never undergone thyroid function evaluation before and enrolled within 13 wks of gestation. Serum FT3, FT4, TSH levels were measured every 6 wks up to pregnancy term, while anti-TPO antibodies at enrollment only. Anti-TSH receptor antibodies (TRAb) were tested when TSH was below the lower limit of the trimester-specific reference range (1st 0.03 mU/L; 2nd and 3rd 0.3 mU/L).

Results: Thirty-two/482 (6.6%) pregnant women had serum TSH values < 0.03 mU/L at first sampling. Of these, 17/32 (53.1%) were overtly hyperthyroid, and 15/32 (46.9%) had subclinical hyperthyroidism. TRAb assay revealed the autoimmune origin of hyperthyroidism in 6/32 (18.7%) women. Of the remaining 26/32 (81.2%) TRAb-negative women, 12/26 (46.1%) were diagnosed with GTT and 14/26 (53.8%) showed isolated hypothyrotropinemia. Of the 6 GD women, 1/6 spontaneously recovered from hyperthyroidism at early 2nd trimester, whereas 2/6 were given anti-thyroid drugs, and 3/6 showed FT4 levels that were consistently at the upper normal limit for general population. TRAb titer decreased of 33–82% over gestation in 4/6, and became undetectable in the remaining 2/6 GD women. Of the 12 GTT women, 1/12 miscarried at early gestation. In the remaining 11/12, spontaneous remission of hyperthyroidism occurred, mostly within the 20th week.

Conclusion: The high prevalence of autoimmune hyperthyroidism (6/482, 1.2%), occasionally found in pregnancy, represents a further reason for recommending systematic and early thyroid function testing in pregnant women.

P310

EFFICENCY OF RADIOIODINE THERAPY WITH A FIX DOSE OF J-131 IN TOXIC THYROID ADENOMA

Petrovski Z[1], *Trajkovska K*[1]
[1]Clinical Hospital, Department of Nuclear Medicine, Bitola, Macedonia, the Former Yugoslav Republic of

Purpose: The aim of this study was to estimate the results obtained using a fix dose of J-131 in the treatment of the solitary toxic thyroid adenoma.

Material and method: We have performed radioiodine therapy in 81 patients (pts), 62 female and 19 male (average age 47 years) with solitary toxic thyroid adenoma. 59 pts received fix dose J-131 of 925 MBq, while 22 pts were treated with calculated (MBq/gr) dose 555–1100 MBq. Previosly 54(66%) pts were clinically hyperthyreotic and received thyreostatic medicamentation which were interrupted one week before the administration of J-131. Those patients who were in euthyreotic state, value of TSH was suppressed and have hot nodule in thyroid scan.77(93,8%) pts received a single dose, while 5(6,2%) pts needed two and more doses. Results of thyroid metabolism and volume of nodules were evaluated 6monts to 10 years after treatment.

Results: From 62 radioiodine treated pts with fix dose 7(11,2%) became hypothyroid pts,53(86,1%) euthyroid pts and 3(3,7%) recurrent hyperthyroid pts, in comparison with 22 treated pts with calculated J-131 dose: 3(13,6) hypothyroid pts, 16(82,9%) euthyroid pts and 1(4,5%) recurrent hyperthyroid. The size of the nodules became unpalpable in 23(28,2%) pts, decreased evidently in 42(51,8%) pts and remained unchanged in 17(20,0%) of the treated pts.

Conclusion: A fix dose of J-131 is simple, safe and efficient in the treatment of solitary toxic thyroid adenoma. There was not significant different in incidence of late follow-up results of hypothyroidism and recurrent hyperthyroidism between fix dose and calculated MBq/gr dose.

P311

DIAGNOSIS AND TREATMENT OF HYPERTHYROIDISM : RESULTS OF THE FRENCH SURVEY THYRDEL

Goichot B[1], *Caron P*[2], *Bouée S*[3], *N'daye N*[1], *Landron F*[4]
[1]Hôpitaux Universitaires de Strasbourg, Internal Medicine, Endocrinology and Nutrition, Strasbourg, France, [2]CHU Toulouse, Endocrinology, Toulouse, France, [3]Cemka-Eval, Epidemiology & Statistics, Bourg la Reine, France, [4]Merck Serono, General Medecine and Specialties, Lyon, France

Objectives: Modalities of diagnosis and treatment of hyperthyroid patients are variable among endocrinologists.

Methods: In the Thyrdel survey, 263 French endocrinologists reported data on 1144 consecutive patients seen for hyperthyroidism (mean age 48.7 ± 16.5 years, female 76%).

Results: 82% of the patients had clinical symptoms of thyrotoxicosis (thermophobia, tachycardia, weight loss, gastrointestinal symptoms) and patients older than 65 years had less symptoms but more cardiac arythmia than younger patients. Palpitations, thermophobia, sweating, polydipsia and weight loss were more frequent among patients whose TSH was below 0.1 mU/L compared to patients with 0.1< TSH< 0.4 mU/L (p< 0.05). Subclinical hyperthyroidism (decreased TSH with normal FT4 concentrations) was present in 18.3% (Graves' disease 11.0%, multinodular goiter 49.5%, iatrogenic 7.9%, toxic adenoma 61.4%, thyroiditis 35.3%). Anti-TPO and anti-TSH receptor antibodies were measured in 48.2% and 56.3% of the patients, respectively. Ultrasonography was performed in 94% of patients whereas thyroid scan was done in 40% of them. Thyrotoxicosis was related to Graves' disease (70%), multinodular goiter (10%), iatrogenic (10%), toxic adenoma (6%) and thyroiditis (3%). Therapeutic management depends on the etiology of hyperthyroidism : for the first episode of Graves' disease, antithyroid drugs were the first line in 91%, and « block and replace » (BR) protocol was used in 54% of the patients. Surgery was prefered to ^{131}I therapy in multinodular goiter and toxic adenoma. Euthyroidism was obtained after 3 months in 65% of Graves' disease (more frequently with the BR treatment than with the "dose-adjusted"), in 75% of patients with multinodular goiter, toxic adenoma, thyroiditis and in 59% of iatrogenic thyrotoxicosis.

Conclusion: the French Thyrdel survey describes the clinical signs or symptoms of hyperthyroidism in a large cohort of patients, and the treatment modalities used by the endocrinologists to control hyperthyroidism.

P312

THE USEFULNESS OF 99MTC-SESTAMIBI THYROID SCAN IN THE DIFFERENTIAL DIAGNOSIS OF ELEVEN CASES OF AMIODARONE-INDUCED THYROTOXICOSIS

Souto SB[1], *Vieira T*[2], *Nogueira C*[1], *Carvalho-Braga D*[1], *Pereira J*[2], *Carvalho D*[1]
[1]Centro Hospitalar São João, Endocrinology, Porto, Portugal, [2]Centro Hospitalar São João, Nuclear Medicine, Porto, Portugal

Introduction: Amiodarone-induced thyrotoxicosis(AIT) is a multifaceted condition with difficulties in differential diagnostic with therapeutic implications. It may be classified as:(i)type 1, caused by excessive thyroidal hormone synthesis and release induced by iodine load in patients with underlying thyroid autonomy; (ii)type 2, a destructive process in patients with normal thyroid gland and (iii)type 3, indefinite forms. This differentiation has important therapeutic implications.

Purpose: To evaluate 99mTc-sestaMIBI(MIBI) thyroid scintigraphy in addition to other diagnostic tools in diagnosis of AIT.

Methods: Eleven AIT patients (4-women, 7-men), long-term treated with amiodarone(AM), aging 65±11.99 years old in average, were evaluated. At the time of diagnosis, 10 patients were drug treated, which was withdrawn, and one patient stopped therapy 9 months before diagnosis. One patient had previous history of thyroid disease and another had familial history. MIBI thyroid scintigraphy was performed in all patients, along with biochemical analysis of serum-free thyroxine, free tri-iodothyronine, thyroid stimulating hormone, anti-thyroglobulin, anti-thyroid peroxidase and anti-TSH receptor autoantibodies and thyroid colour-flow Doppler sonography(CFDS).

Results: On the basis of clinical, instrumental and laboratory data (excluding MIBI scintigraphy) and follow-up, nine of AIT patients could be subdivided into two with AIT 2, five with AIT 1 and two with indefinite forms. Two patients did not have enough follow-up to conclude AIT type, but were initially classified as type 2. In six patients, final diagnosis was similar to MIBI scintigraphy. MIBI scintigraphy was superior to all other diagnostic tools, namely CFDS.

Discussion: Twenty-four hours radioiodine uptake was not performed, because high levels of ingested iodine with AM usually result in 24-hr uptakes less than 1% in most patients with AIT. Thyroid MIBI scintigraphy may be proposed as an easy and highly effective tool for differential diagnosis of different forms of AIT. Nevertheless, real usefulness of this expensive procedure in cases of AIT should to be confirmed by larger studies.

P313

MOST ASPECTS OF THYROID-SPECIFIC QUALITY OF LIFE WAS MARKEDLY IMPROVED 6 MONTHS AFTER TREATMENT OF GRAVES´ DISEASE

Cramon P[1], *Bjorner JB*[2], *Hegedüs L*[3], *Bonnema SJ*[3], *Groenvold M*[4], *Rasmussen AK*[1], *Feldt-Rasmussen U*[1], *Watt T*[1]
[1]Rigshospitalet - Copenhagen University Hospital, Dept. of Endocrinology, Copenhagen, Denmark, [2]National Research Centre for the Working Environment, Copenhagen, Denmark, [3]Odense University Hospital, Dept. of Endocrinology, Odense, Denmark, [4]University of Copenhagen, Institute of Public Health Science, Copenhagen, Denmark

Objectives: Effect of treatment of Graves' disease (GD) on thyroid-specific quality of life (QoL) has never previously been evaluated using validated tools. The aim was to examine thyroid-specific QoL before and 6 months after treatment of GD, using the validated ThyPRO questionnaire.

Methods: The study included 59 newly referred patients (86% females, median (interquartile range) age 47(38–56)) with active GD (suppressed TSH

and positive TRAb, without orbitopathy), treated with antithyroid drugs, surgery or radioiodine. Baseline ThyPRO scores were compared with 751 respondents from the general population. Changes in patient scores 6 months after treatment were tested with paired t-tests and evaluated by effect sizes.

Results: At baseline, patients had significantly poorer scores than the general population on all scales (norm data available for 9 scales). QoL improved significantly after treatment on 9 of 13 scales (table 1). Large effects were found for the Hyperthyroid- and Tiredness scales. However, patients still had worse scores on all 9 available norm reference scales.

Conclusions: Patients with GD had impaired thyroid-specific QoL before treatment. Treatment improved QoL markedly, particularly hyperthyroid symptoms, tiredness and anxiety, but patients still had poorer QoL than the general population 6 months after treatment. Future analyses should identify risk factors for persistent QoL impairment.

P314

MODERATE ALCOHOL CONSUMPTION MAY PROTECT FROM GRAVES´ HYPERTHYROIDISM – A POPULATION-BASED CASE-CONTROL STUDY

Carlé A[1], *Pedersen IB*[1], *Knudsen N*[2], *Perrild H*[2], *Ovesen L*[3], *Rasmussen LB*[4], *Jørgensen T*[5], *Laurberg P*[1], *DanThyr, The Danish Investigation of Iodine Intake and Thyroid Diseases*
[1]Department of Endocrinology & Medicine, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark, [2]Endocrine Unit, Medical Clinic I, Bispebjerg Hospital, Copenhagen, Denmark, [3]Department of Internal Medicine, Slagelse Hospital, Slagelse, Denmark, [4]Ministry of Food, Agriculture and Fisheries, National Food Institute, Technical University of Denmark, Copenhagen, Denmark, [5]Research Centre for Disease Prevention and Health, Copenhagen County, Copenhagen, Denmark

Objectives: We have recently demonstrated that alcohol consumption may be an important protective risk factor for development of autoimmune hypothyroidism. A similar protective role of alcohol has been shown in several autoimmune diseases such as SLE and RA. Now, we wish to study the association between alcohol consumption and Graves´ hyperthyroidism.

Methods: We prospectively identified patients with incident Graves´ hyperthyroidism (n=272) in a Danish population, and recruited age-sex-region-matched controls with normal thyroid function (n=1,088) from the same population. Participants gave information on alcohol intake, smoking, previous diseases, education, and family history of hyperthyroidism for the case-control-study. The association between alcohol intake and development of Graves´ hyperthyroidism was analyzed in conditional Cox regression models.

Results: Graves´ patients had a lower reported alcohol consumption than controls (median units of alcohol (12g) per week: 2 vs. 4, p< 0.001). In a multivariate regression model, higher alcohol consumption was associated with a low risk for development of Graves´ hyperthyroidism (Table 1)

Similar results were found for maximum previous alcohol consumption during a calender year. No interaction was found with type of alcohol consumed (wine vs. beer), age, sex, or region of inhabitancy.

Conclusions: Graves´ disease may be more dependent on environmental factors such as alcohol intake than hitherto anticipated.

PO35 Graves' Disease and Orbitopathy Basic/Translational

P315

BIMATOPROST ($PGF_{2\alpha}$) EFFECTS ON ADIPOCYTE BIOLOGY? RELEVANT TO GRAVES' ORBITOPATHY

Draman MS[1], *Grennan-Jones F*[1], *Zhang L*[1], *Kyaw Tun T*[2], *McDermott J*[2], *Moriarty P*[3], *Morris D*[4], *Lane C*[4], *Sreenan S*[2], *Dayan C*[1], *Ludgate M*[1]
[1]Institute of Molecular & Experimental Medicine, School of Medicine, Cardiff University, Cardiff, United Kingdom, [2]Department of Diabetes and Endocrinology, Connolly Hospital, Blanchardstown, Ireland, [3]Royal Victoria Eye & Ear Hospital, Dublin, Ireland, [4]Department of Ophthalmology, Cardiff and Vale University Health Board, Cardiff, United Kingdom

Background: Graves' Orbitopathy (GO) is the commonest extrathyroidal manifestation of Graves' hyperthyroidism. GO tissue remodelling, by increased proliferation, excess adipogenesis and hyaluronan overproduction, produces exophthalmos. Enophthalmos occurs in some glaucoma patients treated with Bimatoprost (prostaglandin F2α, PGF2α) eye drops.

Hypothesis: We hypothesise that the enophthalmos is secondary to reductions in orbital tissue proliferation, adipogenesis or hyaluronan production and/or increased lipolysis.

Table 1. Mean ThyPRO scale scores (0–100, increasing scores with worsening QoL) (for Abstract P313).

	Goitre	Hyperthyroid	Hypothyroid	Tiredness	Cognition	Anxiety	Depressivity	Emotional susceptibility	Impaired daily life
Norm reference	5	12	14	35	14	13	22	23	-
GD: Baseline	17	50	33	68	33	41	39	50	38
GD: 6 months	13	23**	24**	45**	24*	21**	31	35**	22**
GD: Effect size	0.21+	1.13+++	0.37+	0.83+++	0.35+	0.77++	0.33+	0.56++	0.53++

*p< 0.01, **p< 0.001. Scores did not improve significantly on 4 scales: Eye Symptoms, Impaired Social Life, Impaired Sexlife and Cosmetic Complaints. + Small effect (0.2–0.5), ++ Moderate effect (0.5–0.8), +++ Large Effect (>0.8).

Table for Abstract P314.

Alcohol consumption$	Cases	Controls	Univariate OR (95% CI)	Multivariate OR# (95% CI)
0 units/wk.	75 (27.6%)	133 (12.2%)	1.74 (1.18–2.56)**	1.70 (1.14–2.54)*
1–2 units/wk.	79 (29.0%)	246 (22.6%)	1 (reference)	1 (reference)
3–10 units/wk.	93 (34.2%)	503 (46.2%)	0.55 (0.39–0.77)***	0.54 (0.38–0.77)***
11–20 units/wk.	20 (7.4%)	147 (13.5%)	0.38 (0.22–0.66)***	0.38 (0.21–0.66)***
≥ 21 units/wk.	5 (1.8%)	59 (5.4%)	0.21 (0.08–0.57)**	0.21 (0.08–0.56)**

$ alcohol consumption in the year preceding diagnosis
# adjusted for smoking, family history of thyrotoxicosis, education, co-morbidity
* < 0.05, ** < 0.01, *** < 0.001

Aims: To apply in vitro models to determine which of these is affected by PGF2α using the 3T3-L1 murine preadipocyte cell line and primary human orbital fibroblasts from GO patients (n=3) and people free of GO (n=3).

Methods: 3T3L1 cells were cultured in complete medium with (10^{-8}M) PGF2α added on day 0. Direct cell counting was performed on days 1/2/3. For adipogenesis, differentiation medium (DM) containing insulin, pioglitazone and hydrocortisone was added to confluent cells and PGF2α (10^{-8}M and 10^{-7}M) was added on alternate days. Adipogenesis was evaluated morphologically and RNA was extracted (day 10) for QPCR measurement ($2^{-\Delta\Delta C}$T method) of adipogenesis markers, PPARγ (early) and GPDH (late). One way ANOVA was used in the analysis. Data presented as mean±SD.

Results: PGF2α reduced 3T3L1 proliferation at day 1 (47.0±6.0%), 2 (67.2±20.5%) and 3 (76.7±14.1%) versus untreated, $p < 0.001$. Similar effects were observed in human orbit. This is not due to toxicity (trypan blue exclusion on PGF2α (10^{-8}M to 10^{-6} M) treated cells revealed >90% survival). In DM, the presence of PGF2α did not modify differentiation assessed morphologically but measures of GPDH at 10^{-8}M showed an increase in the adipogenesis by 1.73 fold whilst at 10^{-7}M the opposite effect was observed (0.27 fold). Similar effects were observed using PPARγ as differentiation marker.

Conclusions: We show that PGF2α reduces preadipocyte proliferation but has biphasic effects on adipogenesis. Further experiments will determine whether Bimatoprost might be useful in GO treatment.

P316

DOES COMBINED ACTIVATION OF THE TSHR AND THE IGF1-R CONTRIBUTE TO THE PATHOGENESIS OF GRAVES´ ORBITOPATHY?

Grennan-Jones FA[1], *Zhang L*[1], *Draman MS*[1], *Lane C*[2], *Dayan CM*[1], *Ludgate M*[1]
[1]Cardiff University, Institute of Molecular and Experimental Medicine, Cardiff, United Kingdom, [2]Cardiff and Vale University Health Board, Department of Opthalmology, Cardiff, United Kingdom

Background: Graves' orbitopathy (GO) is an autoimmune condition, its close association with Graves´ disease suggests that the TSHR may be a shared auto-antigen. More recently, the IGF1-R has been identified as a putative second major auto-antigen which may interact with the TSHR and contribute to the tissue remodelling observed in GO.

Objectives: To examine the effect of combined TSHR and IGF1-R activation on proliferation, adipogenesis and HA production in primary orbital fibroblasts and to investigate mechanism(s) which may drive observed changes.

Methods: We applied in-vitro models using primary orbital fibroblasts experiencing activation of the TSHR (activating mutation, TSH or M22 - monoclonal thyroid stimulating antibody) or the IGF1-R (1–100ng/ml IGF1) or both in combination and compared the findings with controls.

Results: Activation of IGF1-R alone, but not the TSHR alone, significantly increased orbital fibroblast proliferation, but when combined, the effects of IGF1-R activation (IGF1-R*) were abrogated by TSHR activation (TSHR*). There was no spontaneous adipogenesis with IGF1-R* or TSHR*, alone or combined. In the case of Hyaluronan (HA, measured in culture medium) production, we found a clear synergistic effect with IGF1R* and TSHR* combined, but did not see any change in HA production for either receptor alone. Further experiments were conducted to elucidate possible mechanisms. TSHR transcript levels were not altered by IGF1 or by M22, similarly neither agent modulated IGF1-R transcript expression. Finally we used CHO and orbital cells transfected with wtTSHR to study effects of IGF1, M22 and TSH treatment on cell signalling. Using Western Blot analysis we found pAKT was up-regulated by IGF1 (24 hours), M22 and TSH did not modify this response. Similarly IGF1 did not modulate the p-CREB response of TSH in preliminary studies.

Conclusion: Further experiments should elucidate the mechanisms leading to the observed synergistic effects of TSHR* and IGF1-R* on orbital HA production.

P317

HIF-1 DEPENDENT GENE EXPRESSION IS INVOLVED IN PATHOGENESIS OF GRAVES´ ORBITOPATHY

Berchner-Pfannschmidt U[1], *Müller M*[1], *Fandrey J*[2], *Steuhl K-P*[1], *Eckstein AK*[1]
[1]Klinik für Augenheilkunde/Vorderer Augenabschnitt, Universität Duisburg-Essen, Essen, Germany, [2]Institut für Physiologie, Universität Duisburg-Essen, Essen, Germany

Excessive orbital fibroblast (OF) proliferation and extracellular matrix production, adipogenesis as well as inflammation resulting in the expansion and remodeling of orbital tissue, are characteristic of Graves´ orbitopathy (GO). The expansion of the orbital tissue may leads to ischemic hypoxia in the orbita. It is well known that hypoxia induces HIF-1 (Hypoxia-inducible factor-1) dependent gene expression. Many HIF-1 target genes are involved in the induction of inflammatory cell recruitment, cell matrix formation, proliferation, differentiation and adipogenesis.

Our aim was to analyse the hypoxia-dependent gene expression in resident OFs that are involved in GO. Therefore primary human OFs were obtained from 16 patients with active, severe GO and from 8 healthy control subjects. By western-blot analysis and immunofluorescence microscopy we found that HIF-1α was enhanced stabilized in OFs from GO patients under normoxia as well as under hypoxic conditions. Real time PCR revealed that HIF-1α mRNA level was induced in GO patients independently of the oxygen concentration. Furthermore we analysed HIF-1 target gene expression by real time PCR. In OFs from GO patients the mRNA expression of prolyl-hydroxylase 2 (oxygen sensing), glucose transporter 1 (energy metabolism) and vascular endothelial growth factor (angiogenesis, inflammation) was induced compared to control OFs from healthy persons.

We report distinct, constitutive changes in HIF-1α expression followed by hypoxia-inducible gene expression in OFs from GO patients. Our findings strongly suggest that HIF-1 dependent gene expression is induced in OFs from GO patients. With HIF-1 we report a new potential targeting molecule for specific pharmacological inhibition of the local inflammatory response characteristic of GO.

P318

INHIBITION OF THE ACID SPHINGOMYELINASE/ CERAMIDE SYSTEM PREVENTS HALLMARKS OF GRAVES OPHTHALMOPATHY (GO)

Meyer zu Hörste M[1,2], *Ströher E*[1], *Zhang Y*[2], *Röck K*[3], *Fischer JW*[3], *Berchner-Pfannschmidt U*[1], *Gulbins E*[2], *Eckstein A*[1]
[1]University of Duisburg-Essen, Ophthalmology, Essen, Germany, [2]University of Duisburg-Essen, Molecular Biology, Essen, Germany, [3]University of Duesseldorf, Pharmacology and Clinical Pharmacology, Duesseldorf, Germany

Pathologic proliferation of orbital fibroblasts and the transformation of these cells to adipocytes, excessive production of extracellular matrix, and inflammation are hallmarks of the pathogenesis of Graves ophthalmopathy (GO). These processes result in remodeling of the orbital tissue with the typical symptoms of lid retraction, periorbital swelling, disfiguring proptosis, optic nerve compression, and impaired ocular motility caused by fibrotic changes in the extraocular muscles. We demonstrate that a stable change in the phenotype of orbital fibroblasts from GO patients results in a constitutive overactivity of acid sphingomyelinase and a high release of ceramide in these cells. High activity of the acid sphingomyelinase/ceramide system in orbital fibroblasts results in a constitutive increase of proliferation of GO orbital fibroblasts, release of reactive oxygen species, and formation of hyaluronan. These hallmarks of GO are corrected upon pharmacologic or siRNA-mediated inhibition of acid sphingomyelinase. Our findings identify the acid sphingomyelinase/ ceramide system as a key mechanism in the pathophysiological changes affecting orbital fibroblasts during GO and provide a rationale for inhibiting acid sphingomyelinase activity as a novel treatment for GO.

P319

BIOCHEMICAL CHARACTERIZATION OF AUTOANTIBODIES TO THE IGF1-RECEPTOR

Minich W[1], *Welsink T*[1], *Schwiebert C*[1], *Koehrle J*[1], *Eckstein A*[2], *Schomburg L*[1]
[1]Charité Universitätsmedizin Berlin, CVK, Institute for Experimental Endocrinology, Berlin, Germany, [2]University Hospital Essen, Department of Ophthalmology, Essen, Germany

Introduction: Stimulating autoantibodies against the TSH receptor are associated with Graves´ Disease. Indirect evidence suggested that autoimmunity against the IGF1 receptor (IGF1R) contributes to Graves´ Orbitopathy (GO). We have recently reported a similar prevalence of IGF1R autoantibodies in GO patients and healthy controls.

Objective: We aimed to characterize the biological activities of IGF1R autoantibodies with respect to the signalling of IGF1.

Methods: In vitro binding studies with autoantibody-positive sera in comparison to control were conducted on recombinant IGF1R and IGF1R fragments. Cell culture studies were performed analysing whether IGF1R autoantibodies exert IGF1-like activities or inhibit IGF1-signalling. Effects of crude serum samples were compared with purified IgG preparations.

Results: IGF1R autoantibody-positive sera efficiently precipitated recombinant IGF1R in vitro, but control samples did not. Isolated IgG from positive sera but not from control sera inhibited IGF1-induced autophosphorylation of IGF1R in hepatocarcinoma HepG2 cells. There were no effects by IgG on IGF1R autophosphorylation without IGF1 co-stimulation. Growth of MCF7 breast cancer cells was inhibited by incubation with IGF1R-autoantibodies supporting their classification as IGF1 antagonists. The autoantibodies failed to efficiently precipitate shorter fragments of the IGF1R implying that conformational epitopes of IGF1R are bound.

Conclusions: Our studies verify the existence of autoantibodies to IGF1R in humans. However, the biological characterization indicates that these antibodies are of antagonistic activity as compared to the natural ligand IGF1 and inhibit IGF1-dependent signalling by binding conformational epitopes of IGF1R. These observations support the notion that IGF1R autoantibodies are not involved in GO pathogenesis.

Supported by German Federal Ministry of Economics and Technology (BMWi), project KF2257304AJ0 within the ZIM program, and GraKo 1208/2 program of DFG.

PO36 Thyroid Gland Development/ Thyroid Hormone Synthesis

P320

REGULATION OF THE SODIUM IODIDE SYMPORTER GENE EXPRESSION BY RESVERATROL

Giuliani C[1], *Di Santo S*[1], *Bucci I*[1], *Monaco F*[1], *Napolitano G*[1]
[1]University 'G. D'Annunzio' Chieti-Pescara, Dept. of Medicine and Sciences of Aging, Chieti, Italy

Resveratrol is a flavonoid which has anti-inflammatory, antioxidant, hypolipemic and anti-proliferative properties. For these reasons it is under investigation in several clinical trials. Previous experimental studies showed that Resveratrol can inhibit the growth of follicular and papillary thyroid cancer, and a recent study, conducted on the rat thyroid cell line FRTL-5, has demonstrated that this compound increased iodide influx between 6 and 12 hours of treatment (Thyroid, 2010, 20: 195).

Objective: To further evaluate the effect of Resveratrol in the regulation of the sodium-iodide symporter gene, we performed experiments using the FRTL-5 cells treated with Resveratrol for longer time, assessing the expression of the NIS gene.

Methods: Resveratrol effect was studied using Northern blotting and iodide uptake assays.

Results: Northern blotting assays showed that the treatment of FRTL-5 cells with Resveratrol 10 µM significantly decreased NIS RNA after 12 hours (43±5% of control values), with a maximum effect after 24 hours (5±2% of control values), this effect persisted after 48 hours. The treatment of the cells with Resveratrol for 48 hours was able to decrease iodide uptake, confirming a functional effect of this compound.

Conclusions: These results show that Resveratrol has a complex effect on thyroid cells, since after a transient increase of iodide uptake (between 6 and 12 hours), it causes a strong and transcriptional downregulation of NIS gene and function. The data are important to understand the effect of Resveratrol on thyroid cells and to evaluate its potential clinical use in thyroid diseases. Further experiments are needed to confirm these effects in vivo.

P321

IDENTIFICATION OF MUTATIONS OF GENES INVOLVED IN THYROID HORMONE SYNTHESIS IN PATIENTS WITH CONGENITAL HYPOTHYROIDISM

Kumorowicz-Czoch M[1], *Hermanns P*[2], *Madetko-Talowska A*[3], *Tylek-Lemanska D*[4], *Pohlenz J*[2], *Starzyk J*[1]
[1]Department of Pediatric and Adolescent Endocrinology, Chair of Pediatrics, Polish-American Institute of Pediatrics, Jagiellonian University Medical College, Cracow, Poland, [2]Childrens Hospital of the University of Mainz, Molecular Endocrinology, Mainz, Germany, [3]Division of Medical Genetics, Chair of Pediatrics, Polish-American Institute of Pediatrics, Jagiellonian University Medical College, Cracow, Poland, [4]Division of Mass Screening and Metabolic Diseases, University Children's Hospital, Cracow, Poland

Introduction: Thyroid dyshormonogenesis (TDH) is a genetically heterogenous group of hereditary defects in the enzymatic cascade of thyroid hormone synthesis that result in congenital hypothyroidism (CH).

Objectives: The aim of the study was to identify and estimate the prevalence of mutations in selected genes in patients with CH and morphological characteristics of TDH (CH-TDH).

Patients: In 8 patients with CH-TDH: age, gender, TSH, free T4 and thyroglobulin level, thyroid ultrasonographic findings were recorded.

Methods: DNA isolation was performed with MasterPure™ DNA Purification Kit for Blood Version II (Epicentre Biotechnologies). Samples of genomic DNA were used in screening for the mutations of Pendrin, TPO, TG, NIS, THOX2, DUOXA2, DEHAL1 genes. Each exon of selected genes was amplified via PCR reaction with the use of primers located in the flanking intron sequences. PCR products were sequenced directly with the use of big dye terminator sequencing reactions. Analysis were performed on a 3100 Avant Genetic Analyzer (Applied Biosystems). In the case of genetic changes detected in the patients, parents blood samples were drawn for DNA analysis.

Results: Three different heterozygous mutations in gene encoding TPO (exon 8, 11 and 14) were revealed. All the mutations detected in the patients were also present in their mother or father. One patient was diagnosed as compound heterozygote; two patients showed heterozygous mutation. In the sequence of TG and THOX2 genes four different SNPs were detected.

Conclusions: The results revealed mutations of TPO gene and SNP variations of TG or THOX2 genes in the CH-TDH patients. Higher amount of heterozygous vs. compound heterozygous mutations may imply intronic TPO gene mutations, monoallelic expression or regulatory changes. All detected genetic changes were known and described in literature.

P322

SCREENING OF MUTATION IN HOMEOBOX GENES HOXA3, HOXB3, HOXD3 AND PITX2, WHICH ARE POTENTIALLY RELATED TO THYROID DEVELOPMENT, IN FOUR PATIENTS WITH FAMILIAL AND SPORADIC THYROID HEMIAGENESIS

Kizys MML[1], *Nesi-França S*[2], *Cardoso MG*[3], *Harada MY*[1], *Soares F*[1], *Chiamolera MI*[1], *Dias da Silva MR*[1], *Maciel RMB*[1]
[1]Universidade Federal de Sao Paulo, Medicine, Sao Paulo, Brazil,
[2]Universidade Federal do Parana, Pediatrics, Curitiba, Brazil,
[3]Universidade Federal de Sao Paulo, Biochemistry, Sao Paulo, Brazil

Introduction: Congenital hypothyroidism (CH) is the most frequent endocrine disorder in newborns. In 85% of cases, CH is due to disturbances in the gland's organogenesis, which result in thyroid hypoplasia, agenesis, ectopy or hemiagenesis. The molecular mechanisms leading to the formation of the two thyroid symmetrical lobes, which are impaired in hemiagenesis, are little known.

Objective: The aim of this work was to search for mutations in thyroid developmental candidate-genes, many of them either related to or responsible for hemiagenesis (other organs) in human and animal models: HOXA3, HOXB3, HOXD3 and PITX2. We first focused on these homeobox family members because they are involved in other organ development and left-right asymmetry and due to familial cases.

Methods: Total DNA from peripheral blood was extracted from four patients with thyroid hemiagenesis, and then the entire coding region of all these genes was amplified by PCR reaction containing specific primers of each exon, followed by PCR product purification and direct sequencing by Sanger method.

Results: Herein we describe familial cases of thyroid hemiagenesis in two generations, including the proband and his father, in addition to other two sporadic cases. We have not found any mutations in all above-mentioned genes, but polymorphisms on *HOXD3* gene (rs34729309, rs1051929 and a new synonymous variant NP_008829.3:p.314; C>G).

Conclusion: These results may suggest the existence of other left-right thyroid asymmetry candidate-genes in humans as classical mendelian mutation-causing disease, as well as other etiopathogenic mechanism such as epigenetic modifications in one of these thyroid gland developmental genes, especially for sporadic hemiagenesis patients.

P323

THYBE1 IS A LONG NON-CODING RNA TIGHTLY REGULATED IN THYROID FOLLICULAR CELLS

D'Onofrio B[1], *D'Andrea B*[1], *De Menna M*[1], *De Vita G*[1], *Di Lauro R*[1]
[1]Università di Napoli Federico II, Biologia e Patiologia Cellulare e Molecolare, Napoli, Italy

Molecular mechanisms regulating early thyroid morphogenesis are largely unknown. To identify genes involved in thyroid morphogenesis we performed an unbiased search for transcripts enriched in the early thyroid primordium. Candidate genes showing high and specific expression in the thyroid bud have been identified by comparing the transcriptome profile of E10.5 thyroid progenitor cells with that of the whole embryo. We obtained a list of genes prioritized for prevalent expression in the thyroid bud. The gene that best fits such criterion is a novel gene for a long non-coding RNA that we named Thybe1 for Thyroid bud-enriched 1. Thybe1 shows strong and highly specific expression in mouse thyroid both during development and in the adult. Its genomic locus shows a partially overlapping head-to-head arrangement with that of the protein encoding gene Klhl14. Interestingly, we observed that Thybe1 and Klhl14 are both expressed in FRTL-5 rat follicular cells and strongly repressed by Ras-driven transformation. With the aim of understanding the transcriptional regulation of Thybe1 and to define a possible mechanism of co-regulation with Klhl14, we mapped the 5' and 3' ends of Thybe1. We found that a previously uncharacterized transcript is expressed in thyroid cells. We are currently performing Thybe1 gain- and loss-of-function experiments to define its possible role in thyroid cell physiology. Furthermore, we generated a Thybe1 floxed allele in order to obtain both constitutive and conditional KO mouse lines. Phenotypes of both mouse lines will be analyzed and will provide definitive results on the role of such gene in the whole organism and more specifically in the thyroid gland.

P324

MORPHOMETRIC CHANGES OF THE THYROID GLAND AGAINST INFLUENCE OF GLUCOCORTICOIDS AND ZOLEDRONIC ACID "ZOMETA"

Luzin V[1], *Fomina K*[1], *Yeryomin A*[1], *Zakharov A*[1], *Fastova O*[1]
[1]Lugansk State Medical University, Human Anatomy, Lugansk, Ukraine

Objectives: Diseases of the bones are widespread now. Doctors are actively using zoledronic acid products for treatment of them, but often do not take into account their impact on other organ systems of human body. Unfortunately, this effects on other organ systems are not well understood. Therefore, our purpose is to examine histomorphometric features of the thyroid gland structure in an experiment on white laboratory rats of different ages with increased influence of glucocorticoids and zoledronic acid ("Zometa"). This work was carried out in accordance with the plan of research of SI "Lugansk State Medical University".

Method: To identify the morphofunctional features of the thyroid gland of control and experimental animals, the organ was studied on the cellular level: larger and smaller diameters of the follicles.

Results: The larger and smaller diameters of the follicles of the immature and mature rats after injection of hydrocortisone are higher than control values at 6.70% - 13.92%, in old animals - at 16.77% - 23.22%. After exposure of dexamethasone deviations are less marked, above the 0.71% - 11.84%. In animals treated with "Zometa", maximum and minimum diameters of the follicle are lower than the control values at 6.50% - 18.18% among all series.

Discussion: It was revealed that application of glucocorticoids leads to the changes in thyroid gland structure in rats of various age and these changes are noted at cellular level of its structural organization. Introducing of zoledronate into the rat organism decreases negative effect of glucocorticoids.

P325

THE COMBINED EFFECT OF GLUCOCORTICOIDS AND ZOLEDRONIC ACID ON THE THYROID GLAND

Luzin V[1], *Fomina K*[1], *Yeryomin A*[1], *Zakharov A*[1], *Fastova O*[1]
[1]Lugansk State Medical University, Human Anatomy, Lugansk, Ukraine

Objectives: Unfortunately, any of the medicines is the main action, and undesirable effects. Zoledronic acid products are not an exception. Therefore, our purpose is to examine morphofunctional features of the structure of the thyroid gland in an experiment on white laboratory rats of different ages with increased influence on an organism content of hydrocortisone, dexamethasone, a bisphosphonate "Zometa" separately, as well as their combined effect.

Methods: An experimental study was performed on 372 male rats. Depending on their age, we divided them into three series (immature rats - 5 weeks from birth; mature - 2.5 months., senile changes of rat period - 11 months).

Results: During the light-optical study of histological sections of organs from rats with elevated levels of hydrocortisone we found, that thyroid gland parenchyma is later differentiated into lobules that are separated by proliferation of connective tissue layers. There is a shift of the secretory cycle with a lag phase of elimination. After the introduction of "Zometa" border segments more clearly defined already by day 7 of observation in immature rats, in contrast to intact animals.

Discussion: As a result of microscopic studies, we found that the application of "Zometa" on the background of high concentration of hydrocortisone in the organism leads to slight changes in the structural and functional aspects of thyroid gland in rats of all age periods.

PO37 Clinical Thyroidology

P326

PREVALENCE OF VITAMIN D DEFICIENCY IN SUBJECTS WITH THYROID DYSFUNCTION

Borissova A-MI[1], Shinkow A[2], Vlahov J[2], Dakovska L[2], Metalova T[2], Svinarov D[3], Kasabova I[3]
[1]Medical University Sofia, Clinic of Thyroid and Metabolic Bone Disorders, Clinical Center of Endocrinology, Laboratory of Clinical Pharmacology, University Hospital "Alexandrovska", Sofia, Bulgaria, [2]Medical University Sofia, Department of Thyroid and Metabolic Bone Diseases, Sofia, Bulgaria, [3]Medical University Sofia, Laboratory of Clinical Pharmacology, University Hospital "Alexandrovska", Sofia, Bulgaria

The issue of vitamin D deficiency has been drawing much interest recently. Up to the moment no systematic study of the problem has been done in Bulgaria. The data on the relationship of vitamin D deficiency and thyroid dysfunction is also scarce. The aim of the current work is to investigate the prevalence of vitamin D deficiency in sibjects with hypothyroidism and hyperthyroidism

Material and methods: A random sample of 2032 subjects - 1076 (53%) female and 956 (47%) male, aged 49.30±14.75 (20–80 y) were studied. The serum levels of TSH, FT4, 25(OH) D were measured. Thyroid dysfunction was defined as hypothyroidism (TSH >5.6 mU/l) and hyperthyroidism (TSH< 0.34 mU/l). Vitamin D deficiency was defined as 25(OH) D levels < 25 nmol/l.

Results: The mean 25(OH)D level was 38.75±17.09 nmol/l. Hypothyroidism was found in125 (6,15%) of the studied subjects, hyperthyroidism - in 91 (4.47%). 25(OH)D levels were lower in the hypothyroid group (35.67±17.13 nmol/l), but the difference was significant only to the euthyroid subjects (38.90±17.05 nmol/l, p< 0.04), but not to the hyperthyroid (40.19±17.41 nmol/l, p=NS). Vitamin D deficiency was found in 18.7% of the subjects with hyperthyroidism and in 32% of those with hypothyroidism (p=0.030). The prevalence in the euthyroid subjects was 20.7% (NS).

Conclusions: We have found lower vitamin D levels in the hypothyroid subjects with a higher prevalence of the vitamin D-deficient subjects. Additional factors that may influence the synthesis and metabolism of vitamin D should be analyzed for firmer conclusions.

P327

THYROID AND THYMIC EXERESIS IN SURGERY OF HYPERPARATHYROIDISM

Diaconescu MR[1], Glod M[1], Costea I[1], Grigorovici M[2], Diaconescu S[3]
[1']Gr T Popa' University of Medicine and Pharmacy, Surgery, Iasi, Romania, [2]CF Universitary Hospital, Pathology, Iasi, Romania, [3']Gr T Popa' University of Medicine and Pharmacy, Pediatrics, Iasi, Romania

Background: Owing to close anatomical and embriological connexions between thyroid, parathyroids and the thymus, manifold coexisting pathology can be identified during the surgery of hyperparathyroidism (Hp).

Material and methods: In this retrospective study we investigated the incidence, his-tology, and management of thyroid and thymic synchronous lesions in a series of 82 patients with Hp operated on in the last three decades. Demography, clinical records, biochemical dates, imaging procedures, pathology diagnosis results and surgical protocols were revised.

Results: Between 1983–2012, 82 cases of Hp {54 females and 25 males; R 2,3/1 of 15–72 (mean 46,5) years} underwent surgery in our clinic for primary (20 cases) or renal (62 cases: 27 secondary and 35 tertiary) Hp. Concomitant thyroid exeresis we-re done in 21 patients (2 subtotal thyroidectomies, 4 lobectomies, 6 atypical resecti-ons and 9 diagnosis biopsies) with associated uni or bilateral (multi)nodular or dif-fuse goitres. Histology showed 8 colloid goitres, 3 follicular adenomas, 2 nodular hy-perplasias,4 thyroiditis,2 papillary microcarcinomas and 2 with normal thyroid tissue. Excision of the fibrofatty tissue in total parathyroidectomies for renal Hp (19 cases), revealed 1 thymoma, 1 thymic cyst and thymic rests in 6 patents.

Morbidity in these combined operations was no significantly increased compared to the parathyroid explorations alone.

Discussions and conclusions: Meticulous pre and intraoperative evaluation in all the cases of hyperparathyroidism enables the actually shift from bilaterally neck explora-tion to the miniinvasive surgery rising however the potential risk of missing thyroid or thymic significant lesions. Anyway the surgeon dedicated to this pathology must be aware of the possibility of encountering such synchronous associations and make generous indications of their complete cure in a single operation.

P328

ASSOCIATION OF NEONATAL THYROID-STIMULATING HORMONE (TSH) CONCENTRATIONS WITH PSYCHOSOCIAL, INTELLECTUAL AND PSYCHOMOTOR DEVELOPMENT OF PRESCHOOL CHILDREN

Trumpff C[1,2], Vanderfaeillie J[1], Vandevijvere S[2,3]
[1]Vrije Universiteit Brussel, Brussels, Belgium, [2]Scientific Institute of Public Health, Brussels, Belgium, [3]Université Libre de Bruxelles, Brussels, Belgium

Objectives: Some European countries still suffer from Mild Iodine Deficiency (MID). MID during pregnancy may impair intellectual, psychosocial and psychomotor development of children and may lead to Attention deficit and hyperactivity disorder (ADHD). Neonatal TSH concentration is a good indicator of iodine deficiency in late pregnancy. This study aims to investigate the association between neonatal TSH level and intellectual, psychomotor and psychosocial development of 4–5 year old children. It is hypothesized that elevation of TSH at birth is associated with impaired intellectual and psychomotor development and with behavioural problems at 4–5 years.

Methods: The study will include 380 Belgian preschool children with a TSH concentration between 0 and 15 mU/L at screening. For each sex and TSH-interval (0–1 mU/L, 1–2 mU/L, 2–3 mU/L, 3–4 mU/L, 4–5 mU/L, 5–6 mU/L, 6–7 mU/L, 7–8 mU/L, 8–9 mU/L, 9–15 mU/L) 19 newborns will be randomly selected after excluding infants with congenital hypothyroidism, low birth weight and premature infants. Neonatal TSH was measured in dried blood spots collected by heel stick 3 to 5 days after birth using the Autodelphia method. Cognitive abilities and psychomotor development will be assessed using respectively the Wechsler Preschool and Primary Scale of Intelligence-III and the motor scale of the McCarthy Scales of Children's Abilities. Psychosocial development will be measured using the Child Behaviour Check List for ages 1½-5 years. In addition the parents will complete a general questionnaire in order to account for confounding factors.

Results: The results of the study will be available by September 2013.

Conclusions: The study might have implications on the use of neonatal TSH screening results for monitoring iodine intake among the population and might require definition of new TSH cut-offs to be used by neonatal screening centres in order to recall certain neonates.

P329

PATHOLOGY OF THYROID GLAND IN PATIENTS WITH ACROMEGALY

Khyzhnyak O[1], Mykytyuk M[2], Karachentsev I[3], Sulima T[3], Alekseeva I[3]
[1]Institute for Endocrine Pathology Problems, Clinical Endocrinology, Kharkiv, Ukraine, [2]Institute for Endocrine Pathology Problems, Kharkiv, Ukraine, [3]Institute for Endocrine Pathology Problems, Clinical, Kharkiv, Ukraine

Aims: to investigate GH effects on thyroid gland structure and function in patients with active acromegaly.

Subjects and methods: 97 patients (37 men and 60 women; aged (48.71±12.18) years were under investigation. Among them 21 patients (22.1%) were newly diagnosed, the others have had acromegaly in progress which was diagnosed as not suppressible by oral glucose tolerance test (OGTT). Macroadenoma of hypophysis were revealed in all patients (67 - somatotropinoma, 30 - somatomammotropinoma). Blood samples for TSH, T4, T3, T4f, T3f, and GH measurements were taken in fasting state and after OGTT. USD was done by Aloka SSD-1100 (Japan). Data are given as M±SD.

Results: Structural abnormality of TG such as goiter, mono- and multiple-nodules were found out in 85.6% of patients. GH level was 19.5±18.0 ng/ml, with somatomamotropinoma - 33.7±32.7 ng/ml. Thyroid hormonal spectrum in both groups was in the normal range (TSH - 0.91±0.1mU/ml; T4 - 113.8±5.7 nmol/L; T3 - 2.39±0.45 nmol/L; T4f - 12.5±0.6 pmol/L; T3f - 2.23±0.15 pg/

ml). Hyperplastic effect of GH on TG was approximated by equation TGvol ≈ 1/ (0.05 + 0.08/GH) (R^2=24%; P=0.0004). The main increase in TG-volume was investigated in patients with GH level from 0.4 to 20 ng/ml. The associations were found out between GH and thyroid hormones. Best fitting models of approximation are presented by the following equations: T4f ≈ 6.48*GH0,21 (R^2=19%; P=0.002); T3f ≈ 1/ (0.53 + 0.95/GH) (R^2=17%; P=0.04).

Conclusion: High level of GH in patients with acromegaly may lead to major structural and minor functional changes of TG. Predominantly the TG structure and T4 production were affected by GH. In fact TSH, T3 and T3f were kept in the normal range due to mechanism of self-regulation. In patients with acromegaly several regulatory pathways may protect TG against excessive anabolic action of GH.

P330

MATERNAL AND FOETAL RAT´S HYPOTHYROIDISM DURING GESTATION AND LACTATION UNBALANCES CORTICAL VGLUT1-VGAT IMMUNOREACTIVITY AND ALTERS ATTENTION DEFICIT AND ANXIETY

Navarro D[1], *Mayvi A*[1], *Navarrete F*[1], *Giner M*[1], *Pacheco P*[1], *Morreale de Escobar G*[2], *Manzanares J*[1], *Berbel P*[1]
[1]Inst. de Neurociencias, Sant Joan D´Alacant, Spain, [2]Inst. Investigaciones Biomedicas de Madrid, Madrid, Spain

Our goal was to study the radial distribution of glutamatergic (VGlut1) and GABAergic (VGAT) immunoreactive (ir) buttons in the cerebral cortex and the analysis of behavioural alterations affecting attention deficit and anxiety of rats in early and late developmental hypothyroidism.

Hypothyroidism was induced by adding 0.02% methimazole (MMI) and 1% KClO4 to the drinking water from E10 (group MMI-10) or E21 (group MMI-21) until day of sacrifice (P40–50). Acoustic prepulse inhibition and elevated plus-maze tests were used to evaluate attention deficit and anxiety, respectively. The results were compared to control rats.

The number of VGlut1-ir mossy buttons (from de-convoluted confocal images) in the strata oriens and radiatum of CA3 decreased in MMI-10 and MMI-21 rats. The percentage of VGlut1-ir buttons in the radiatum proximal of CA1 and granular and moleculare medial of DG (likely affecting the afferents from layer 2 of the medial entorhinal cortex) significantly decreased both in MMI-10 and MMI-21. In contrast, this percentage increased in the lacunosum-moleculare of CA1 and in the moleculare distal and proximal of DG. The percentage of VGAT-ir buttons in the radiatum of CA1 and CA3 and moleculare medial of DG decreased in MMI10 compared to MMI21 and C rats. In the somatosensory cortex, both the percentage of VGlut1-ir and VGAT-ir buttons decreased in layers II-III and increased in layers V-VI in MMI-10 and MMI-21. The percentage of prepulse inhibition at 74, 82 and 90 dB prepulses and the acoustic startle amplitude decreased in MMI-10 and MMI-21 rats. In addition, the percentage of time in the open arms of the elevated plus-maze increased both in MMI-10 and MMI-21 rats.

In conclusion, pre and postnatal hypothyroidism significantly affect the ratio of VGlut1/VGAT ir buttons, induce attention deficit and reduce anxiety-like behaviour, as might occur in children with ADHD born to hypothyroxinemic women.

Supported SAF2009-10689.

P331

SHORT-TERM EFFECTS OF BISPHOSPHONATES ON BONE TURN-OVER MARKERS IN GLUCORTICOID PULSE-THERAPY FOR GRAVES'OPHTHALMOPATHY

Borzì G[1], *Muscia V*[1], *Le Moli R*[1], *Furneri MT*[1], *Padova G*[1]
[1]University of Catania, Biomedicine, Clinical and Molecular, Catania, Italy

Introduction: Glucocorticoids (GCs) represent an effective treatment for Graves'ophthalmopathy (GO). Long-term use of GCs can lead to osteoporosis. Studies on the effect of i.v. GCs on bone are scanty.

Aim: We evaluated biochemical markers of bone metabolism variations during the above described therapy.

Methods: In this preliminary study 5 patients (females) with GO treated with i.v. methylprednisolone (MPDS) 500 mg once weekly for 6 weeks and 250 mg once weekly for 6 weeks were observed. Calcium and calcitriolo supplements and alendronate 70 mg once weekly were prescribed at the start of treatment. We evaluated serum calcium, phosphate, PTH, amino-propeptides of type 1 collagene (P1NP) and carboxyterminal-propeptides of type 1 collagene (beta-CTX) concentrations and urinary 24-hours calcium and phosphate levels baseline and weekly for six weeks.

Results: Thyroid function was not significantly different between the patients. In all of them beta-CTX in second week was higher (0.52 ± 0.29 ng/ml) than baseline (0.41 ± 0.18ng/ml), but not in a significative way; it could express that there is not a significative increase of bone resorption after the first MPDS infusion; moreover, beta-CTX progressively decreased in subsequent weeks, reaching a statistical significance in sixth week, when it was significantly lower than in second week and even versus baseline value (0.34 ± 0.23 ng/ml, $P < 0.05$). There were not significative difference in other bone biochemical parameters between baseline and during the six weeks observations.

Conclusions: The absence of bone markers variations and the beta-CTX decrease during the treatment could express a reduction of bone resorption and therefore the protective effect of therapy with alendronate and calcium and calcitriolo supplements yet in the first weeks of treatment.

European
Thyroid Journal

Author Index

Numbers refer to abstract numbers

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Published by S. Karger AG, Basel

Accessible online at:
www.karger.com/etj