CONTENTS

44th Annual Meeting of the European Thyroid Association ETA 2022

ORAL PRESENTATIONS

Saturday, 10th September 2022
Oral Session 1: Topic Highlights ............................................. OP-01-01–OP-01-06

Sunday, 11th September 2022
Oral Session 2: Pregnancy ................................................... OP-02-07–OP-02-11
Oral Session 3: Advanced Thyroid Cancer ............................... OP-03-12–OP-03-16
Oral Session 4: Basic 1 ......................................................... OP-04-17–OP-04-21

Monday, 12th September 2022
Oral Session 6: Hypothyroidism ........................................... OP-06-27–OP-06-31
Oral Session 7: Thyroid Cancer Basic ..................................... OP-07-32–OP-07-36
Oral Session 8: Basic 2 ......................................................... OP-08-37–OP-08-41
Oral Session 9: Thyroid Cancer Clinical ................................. OP-09-42–OP-09-46

Tuesday, 13th September 2022
Oral Session 11: Young Investigators / Basic ............................ OP-11-53–OP-11-58
Oral Session 12: Nodules and Diagnostic ............................... OP-12-59–OP-12-63

POSTER PRESENTATIONS

Poster Session 1 – Saturday, 10th September 2022
COVID & Thyroid Disease .................................................. PS1-01-01–PS1-01-09
Hypothyroidism .............................................................. PS1-02-10–PS1-02-18
Thyroid Cancer CLINICAL 1 ............................................. PS1-03-19–PS1-03-28
Thyroid Hormone transporters and development ................ PS1-04-29–PS1-04-36
Miscellaneous ............................................................... PS1-05-37–PS1-05-46

Poster Session 2 - Sunday, 11th September 2022
Hypothyroidism treatment .................................................. PS2-06-47–PS2-06-56
Graves’ Disease 1 ............................................................. PS2-07-57–PS2-07-66
Thyroid Cancer BASIC ..................................................... PS2-08-67–PS2-08-76
Thyroid Hormone ACTION ................................................ PS2-09-77–PS2-09-86
Nodules & cancer ............................................................ PS2-10-87–PS2-10-96

Poster Session 3 - Monday, 12th September 2022
Case Reports ................................................................. PS3-11-97–PS3-11-105
Graves’ disease 2 and Orbitopathy ..................................... PS3-12-106–PS3-12-113
Pregnancy & Iodine ........................................................ PS3-13-114–PS3-13-122
Thyroid Cancer CLINICAL 2 ............................................. PS3-14-123–PS3-14-132
Thyroid Cancer Diagnosis & Treatment .......................... PS3-15-133–PS3-15-141

AUTHOR INDEX
Oral Presentations
Cryo-electron microscopy structure of full length TSH receptor in complex with TSH receptor blocking human monoclonal autoantibody K1-70TM
Ricardo Núñez Miguel, Paul Sanders, Lloyd Allen, Michele Evans, Matthew Holly, William Johnson, Andrew Sullivan, Jennifer Miller-Gallacher, Jane Sanders, Jadwiga Furmaniak & Bernard Rees Smith

Methods
Recombinant human TSHR expressed in CHO cells was incubated with K1-70TM Fab, the complex solubilised in 10mM Tris pH7.5, 50 mM NaCl, 0.5% Na2O, 2% LMNG, 0.2% CHS and purified to homogeneity by affinity and size exclusion chromatography. Cryo-EM imaging was performed on a Titan Krios 300kV with a K3 Direct Electron Detector.

Results
The cryo-EM TSHR-K1-70TM structure was determined to a global resolution of 3.3Å. A model was built using the solved crystal structure of the TSHR LRD-K1-70TM complex and the AffaFold model of the TSHR. Model rebuilding and refinement were done in COOT v0.9 and Discovery Studio 2021 suite of programs. The cryo-EM structure shows full length TSHR in a monomeric state with all three domains; LRD, hinge region (HR) and transmembrane domain (TMD) visible. The binding arrangements of K1-70TM Fab with the LRD are similar to those observed in the crystal structure. The LRD and HR form the TSHR extracellular domain (ECD) in a similar arrangement to that seen in the crystal structure of the FSHR ECD and in the cryo-EM structure of the LH/CR. The structure shows the TSHR ECD positioned on top of the extracellular surface of the TMD. The HR helix and the HR C-terminus form interactions with the TMD N terminus, extracellular loops 1 and 2 and the extracellular part of helix 7. The relative positioning of the ECD and TMD in the TSHR is similar to that seen in the cryo-EM structure of the LH/CR inactive state. In particular the TSHR P10 region (amino acids 405-414), highly conserved in glycoprotein hormone receptors, is in a similar conformation to that seen in the LH/CR inactive state structure. The structure and spatial arrangements of the TMD helices in the two cryo-EM structures are similar except that the TSHR extracellular end of helix 6 is displaced by approximately 6.5Å compared to the LH/CR inactive state structure.

Conclusions
Our high resolution structure of full length TSHR in complex with K1-70TM provides an excellent basis for understanding the mechanism of TSHR activation.
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A randomized, double-blind, placebo-controlled trial of Vitamin D supplementation in patients newly diagnosed with Graves’ disease
Diana Grove-Laugesen, Eva Ebbehøj, Klavs Hansen, Torquil Watt & Rørsholm Danish

Objective
Vitamin D has potential immunomodulatory effects. We studied whether vitamin D3 supplementation affects the course of Graves’ disease (GD).

Methods
In a double-blind, placebo-controlled design, we randomized patients with a first time diagnosis of GD with hypothyroidism to daily supplementation with vitamin D3 70 mg (2800 IU) or placebo, as add-on to standard treatment with anti-thyroid drugs (ATD). The intervention was continued 12 months after cessation of ATD. Primary outcome was treatment failure (defined as either relapse of hyperthyroidism within 12 months after ATD cessation, failure to taper of ATD within 24 months of treatment, referral for radiodine treatment or thyroidectomy). Secondary outcomes included the risk of relapse of hyperthyroidism after achieving euthyroidism and the influence of age, sex, smoking status, and vitamin D status. Data was analyzed using an intention-to-treat approach.

Results
A total of 278 patients were randomized. At baseline, participants were 44 ± 1 years old, 79% were females, 35% had vitamin D insufficiency (<50 nmol/L), and 16% were smokers. The risk of treatment failure was 41% (95% CI, 33% to 50%) in the vitamin D group and 32% (95% CI, 24% to 40%) in the placebo group. This corresponded to a relative risk (RR) of 1.30 (95% CI: 0.95 to 1.78, P = 0.10) with vitamin D supplementation. The relapse rates were also similar in the two groups (RR of relapse with vitamin D: 1.50 (95% CI: 0.92 to 2.44), P = 0.01). Effects of the intervention showed a significant interaction with smoking status (P = 0.01). In non-smokers, vitamin D supplementation showed an unfavorable effect on risk of treatment failure (odds ratio (OR) 2.03; 95% CI, 1.15 to 3.59, P = 0.02) and relapse (OR 2.09; 95% CI: 1.04 to 4.18, P = 0.04); no effect was found among smokers. The effect of intervention was not affected by age, sex, or vitamin D status.

Conclusion
In GD, the course of the disease is not improved with vitamin D supplementation. On the contrary, we observed trends for increased risk of treatment failure and relapse of hyperthyroidism with vitamin D supplementation. Given the enormous interest in immune-modulating benefits of vitamin D mainly based on association studies, our findings are important and raise concern of uncritical use of high-dose vitamin D supplementation in Graves’ disease.
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The relationship between thyroid function and lipid metabolomics and response to combination thyroid hormone replacement
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Objective
Thyroid hormones are essential for maintaining metabolic balance and particularly influence lipid synthesis and degradation. Metabolomics and in-depth lipid profiling may enable us to assess for differential effects of thyroid hormones and provide insight into tissue thyroid status, that cannot be captured by levels of serum free thyroid hormones alone.

Methods
4,347 children from the Avon Longitudinal Study of Parents and Children who had thyroid function and plasma NMR metabolomics measured at age 7 were studied. Linear regression was performed to assess the association between thyrotropin (TSH), free tri-iodothyronine (FT3) or free thyroxine (FT4) and lipid metabolite levels. Analyses were adjusted for sex and BMI. We then studied 542 individuals from the WATTS trial where individuals were randomised to receive combination thyroid hormone replacement (liothyronine and levothyroxine(LT3 + LT4)) or standard levothyroxine(LT4) to compare selected metabolites and response to treatment as assessed by quality of life measures including general health questionnaire (GHQ).

Results
Multiple associations after correction for multiple testing were observed between TSH, FT3 and FT4 and lipid metabolites (P<0.001). The classic inverse association between TSH and free thyroid hormones was often not observed. Most robust and consistent associations were observed for FT3. The strongest lipid associations for FT3:FT4 ratio were taken forwards as markers of tissue T3 status and studied in the WATTS trial. After correction for multiple testing, 9 metabolomic markers of tissue T3 status were associated with improved GHQ in patients randomised to combination thyroid hormone replacement (LT3 + LT4) but not to standard treatment (LT4).

Conclusion
Our analysis has shown the broad and substantial impact of thyroid hormones, especially FT3, on lipid metabolomics and shown how each hormone has a different metabolic signature, with TSH alone being unable to capture this. Metabolomic markers may reflect individuals who might benefit from combination thyroid hormone replacement. This work has key implications for monitoring treatment response in hypothyroidism and thyroid hormone replacement.
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Sarcopenia as a prognostic factor in patients with advanced thyroid cancer treated with tyrosine kinase inhibitors
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Objective
Recent studies have shown that sarcopenia at cancer diagnosis is associated with a poor survival in patients with solid tumors. Up to now, few data are available among patients with advanced thyroid cancer, especially those treated with tyrosine kinase inhibitors (TKI). We retrospectively evaluated sarcopenia by Skeletal Muscle Index (SMI) in a cohort of advanced thyroid cancer patients before and during TKI treatment and investigated its association with treatment outcome.

Methods
Fifty-eight patients (28 females and 30 males age at the time of TKI treatment 67.5 ± 13.8 years) with advanced thyroid cancer were divided into Sarcopenia Group (SG) and Non-Sarcopenia Group (NSG) based on SMI values. SMI was measured by CT as the cross-sectional area of skeletal muscles at the third lumbar vertebra level, normalized by height squared (cm²/m²). Radiological evaluation was performed at baseline and on average every 3-6 months thereafter. Response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors v.1.1.

Results
The prevalence of pre-treatment sarcopenia was 20.7% and it was correlated with BMI categories (P = 0.04) and by presence of bone metastases (P = 0.02). The best basal SMI cut-off to predict sarcopenia occurrence were 37.6 cm²/m² from AUC = 0.88 95% CI: 0.8358-1; P < 0.0001) for females and 51.4 cm²/m² (AUC = 0.88 95% CI: 0.697-1; P < 0.0001) for males; the best BMI cut-off was 26.5 kg/m² (AUC = 0.920, 95% CI: 0.856-0.932, P < 0.003). The median progression-free survival (PFS) was 8.46 ± 6.87 months and 24.39 ± 18.96 months in SG and NSG (P = 0.008), respectively. At multivariate analysis, pre-treatment sarcopenia significantly affected treatment outcome, resulting the parameter that has the greatest impact on PFS (HR 4.29, 95% CI: 1.21–15.11, P = 0.02).

Conclusions
This is the first study that evaluated sarcopenia prevalence and its change over time in Caucasian patients with advanced thyroid cancer under TKI therapy. Sarcopenia seems to be a prognostic factor of TKI treatment outcome, suggesting the importance of the assessment of the nutritional status and body composition in advanced thyroid cancer patients.

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OP-01-06
Modeling braf-induced thyroid cancer development and cell redifferentiation using pluripotent stem cell-derived organoids
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Endocrine Abstracts (2022) Vol 84

OP-01-04
Selenoprotein deficiency disorder predisposes to aortic aneurysm formation
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Objectives
Mutations in SECISBP2 cause deficiency of selenoproteins, resulting in a multisystem disorder with abnormal circulating thyroid hormone and selenium levels and features due to lack of specific selenoproteins or loss of antioxidant selenoenzymes. Having observed early-onset, aneurysmal thoracic aortic dilation in four patients with this disorder, we studied zebrafish and murine Secisbp2 mutant models to determine whether the aortic phenotype and selenoprotein deficiency are causally related.

Methods
Analyses of histology, selenoprotein deficiencies, oxidative stress, DNA damage and apoptosis in intact and aortic vascular smooth muscle cells (VSMCs) from two patients following surgery, and in aortae from zebrafish Secisbp2 mutant and morpholino knockdown or VSMC-targeted, Secisbp2-deficient mouse models, were undertaken.

Results
Progressive, early-onset (age 10 to 41yrs) aneurysmal ascending aortic dilation occurred in four patients with biallelic mutations in SECISBP2, but without defects in known, thoracic aortopathy, genes. Histology of aneurysmal aorta showed cystic medial necrosis, with deficiency of antioxidant selenoenzymes, oxidative membrane lipid and DNA damage and apoptosis in both medial wall of aorta and cultured, medial VSMCs. Ventral aortic dilation increased tissue H2O2 formation with deficiency of antioxidant selenoenzymes, resulting in aortic degeneration.

Conclusions
We have documented thoracic aortic aneurysm formation in patients with SECISBP2 mutations and similar aortopathy in zebrafish or mice with global or VSMC-targeted inactivation of Secisbp2. We suggest that SECISBP2 is a novel genetic aetiology of TAA, with oxidative stress and cell death secondary to deficiency of antioxidant selenoenzymes mediating aortic degeneration.

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OP-01-05
Sarcopenia prevalence and its change over time in Caucasian patients with advanced thyroid cancer under TKI therapy

The prevalence of pre-treatment sarcopenia was 20.7% and it was correlated with BMI categories (P = 0.04) and by presence of bone metastases (P = 0.02). The best basal SMI cut-off to predict sarcopenia occurrence were 37.6 cm²/m² from AUC = 0.88 95% CI: 0.8358-1; P < 0.0001) for females and 51.4 cm²/m² (AUC = 0.88 95% CI: 0.697-1; P < 0.0001) for males; the best BMI cut-off was 26.5 kg/m² (AUC = 0.920, 95% CI: 0.856-0.932, P = 0.003). The median progression-free survival (PFS) was 8.46 ± 6.87 months and 24.39 ± 18.96 months in SG and NSG (P = 0.008), respectively. At multivariate analysis, pre-treatment sarcopenia significantly affected treatment outcome, resulting the parameter that has the greatest impact on PFS (HR 4.29, 95% CI: 1.21–15.11, P = 0.02).

Conclusions
This is the first study that evaluated sarcopenia prevalence and its change over time in Caucasian patients with advanced thyroid cancer under TKI therapy. Sarcopenia seems to be a prognostic factor of TKI treatment outcome, suggesting the importance of the assessment of the nutritional status and body composition in advanced thyroid cancer patients.

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Introduction

Due to their remarkable self-organizing structures and functional properties, organoids have become a powerful tool to model diseases ‘in a dish’. The use of organoids in cancer research emerged to better understand tumor behavior. Originally, adult stem cells (iASC)-derived organoids were derived from primary tumors while recent studies have reported the generation of cancer models arising from healthy cells by controlling oncogene expression. SC-derived cancer organoids can access the effects of oncogenes and early events driving tumorigenesis, role of cancer stem cells in tumor induction, genomic stability, effect of treatments and screening of new therapeutics.

Objectives

To generate a PTC organoid model by inducing the BrafV637E mutation in mouse ESC-derived functional thyroid follicles to better comprehend the oncogenic events driven by Braf-oncogene and develop a drug screening tool.

Methods

TRE-NKx2-1-Pax8, Btg-NES-BrafV637E-ERT2 mESCs were differentiated into thyroid follicles with doxycycline and hTSH/AMP. After follicle enrichment BrafV637E activation was induced with 4-Hydroxytamoxifen (4OHT). Organoids were then treated with agents previously described to inhibit Braf onco genesis (MEK, PI3K and histone deacetylase (VPA) inhibitors).

Results

TRE-NKx2-1-Pax8, Btg-NES-BrafV637E-ERT2 mESCs were able to differentiate into functional thyroid follicles with iodine-Tg (Tg-I) luminal accumulation. Starting six hours after 4OHT addition time-dependent dedifferentiation was observed; as evidenced by a decrease in mRNA expression of TSHR, Tg, Nis and Tpo. It was associated with an increase in ERK phosphorylation and proliferation. Activation of BrafV637E disrupted follicular organization and decreased Tg-I accumulation. 1,2I uptake and organification. Transcriptomic analysis revealed hyperactivation of PI3K, AKT, mTOR, TGF, cytokine signaling and promotion of Epithelial Mesenchymal Transition. Isolated inhibition of MEK and PI3K resulted in partial increase of Slc5a5/Nis levels, whereas treatment with VPA resulted in complete recovery. The combination of MEK and PI3K inhibitors resulted in complete re-expression of Nis, Tg, TSHR, Tpo and reorganization into functional follicles confirmed by the detection of Tg-I.

Conclusions

We demonstrate the generation of an mESC-derived organoid model that recapitulates the transcritptomic and 3D-histological features of PTC. The combination of MEK and PI3K inhibitors promoted Nis reexpression and thyrocy redifferentiation with recovery of follicular functionality. This mESC-derived PTC in vitro model opens new opportunities to study early mechanisms of carcinogenesis while providing a simple and efficient tool for screening new treatments for thyroid cancer.

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OP-02-08

Real world study on the impact of thyroid hormone treatment on pregnancy outcomes in women with subclinical hypothyroidism without TPOAb

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Context/Objective

Evidence on the impact of thyroid hormone treatment (LT4) on pregnancy outcomes in women with subclinical hypothyroidism (SCH) without TPOAb remains scarce. We assessed this relationship in a single centre in a real-world setting.

Design, Setting, Participants

Cross-sectional study in 1460 women screened for TSH, free T4 and thyroid peroxidase antibodies (TPOAb) at median 13 (11-17) weeks of gestation, during the period 2013-2014. Exclusion criteria were twin and assisted pregnancies, women treated with LT4 before screening, overt hypothyroidism, TPOAb positivity and hypothyroxaemia. The impact of LT4 on pregnancy outcomes was investigated in group of 53 women with SCH (TSH ≥ 3.46) LT4 was initiated at median 13 (10-22) weeks and at a mean dosage of 45.3 ± 16.3 µg/day. Women with SCH and not treated with LT4 served as controls (n = 18). The prevalence of pregnancy morbidities in these two groups was compared with that in a reference (REF) group of 1389 women (TSH < 3.74 mIU/L) using a χ2 test; results were adjusted for confounders and a p-value ≤ 0.025 was considered as significant.

Results

In the SCH control group, the prevalence of pre-eclampsia and gestational diabetes was (borderline and significantly) higher vs that in the REF group (16.7 vs 5.0%; P = 0.026 and 27.8% vs 18.9%; P = 0.014) but in the SCH treated group comparable vs the REF group (7.6% vs 5.0% and 22.6% vs 18.9%; P = 0.610 and 0.547, respectively). The prevalence of the other outcomes (preterm birth, blood loss at birth, emergency C-section and altered birth weight) were comparable between the intervention and REF group.
Conclusions
Women with SCH without TPOAb had a higher prevalence of pre-eclampsia and GDM compared with euthyroid women. However, in women with treated SCH, the prevalence of those outcomes was comparable with that in the euthyroid reference group, even when treatment was started late first / early second trimester. This is the first real-world study that shows a beneficial impact of LT4 on clinical pregnancy outcomes and therefore, adds some evidence to the current guidelines, proposing to treat women with SCH and no TPOAb.

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OP-02-09
Phytothyroidism and the risk of preeclampsia: A national and regional study of 1,014,775 pregnancies in Denmark
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Objectives
Maternal hypothyroidism in pregnancy has been proposed to increase the risk of preeclampsia, but uncertainties persist regarding the underlying causal mechanisms. Thus, it remains unclear if an increased risk of preeclampsia in hypothyroid pregnant women is caused by the lack of thyroid hormones or by the thyroid autoimmunity per se.

Methods
We performed a national and regional study in the Danish population. The national study was register-based, and the study population included all singleton pregnancies in Denmark from 1999-2015 (n=1,014,775). The regional study included the biochemical measurement of TSH, thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (Tg-Ab) (ADVIA Centaur XPT, Siemens). Inclusion criteria for the national study were gestational age 37 weeks or above at delivery, and delivery in a Danish hospital. Exclusion criteria were presence of any thyroid disease (e.g., hypothyroidism, hyperthyroidism, or thyroiditis) before or during pregnancy. The inclusion criteria for the regional study were gestational age 37 weeks or above at delivery, and delivery in a Danish hospital. Exclusion criteria were presence of any thyroid disease (e.g., hypothyroidism, hyperthyroidism, or thyroiditis) before or during pregnancy.

Results
In the nationwide study cohort, altogether 2.2% of pregnant women with no history of thyroid disease (reference group) were diagnosed with preeclampsia in the pregnancy. The prevalence of preeclampsia was 3.0% among pregnant women with hypothyroidism (aOR of 1.3 (95% CI: 1.2-1.4)) and 4.3% among women with newly diagnosed hypothyroidism in the pregnancy (aOR 1.7 (95% CI: 1.3-2.1)). In the regional cohort, altogether 2.4% of women with early pregnancy TSH in the range from 0.1-2.49 mIU/L (reference group) were diagnosed with preeclampsia in the pregnancy. The prevalence of preeclampsia was 3.2% among women with early pregnancy TSH in the range from 2.5 to 4.99 mIU/L (aOR 1.1 (95% CI: 0.8-1.5)) and 6.4% among women with TSH at or above 5.0 mIU/L (aOR 2.3 (95% CI: 1.2-4.4)). Considering thyroid autoimmunity, 2.2% of pregnant women with hypothyroidism was important. Furthermore, results did not support an association between thyroid autoimmunity and preeclampsia.

Conclusions
This study is the first to study the association of hypothyroidism and thyroid autoimmunity with the risk of preeclampsia in pregnant women. The results suggest that maternal hypothyroidism in pregnancy is associated with a higher risk of preeclampsia. Biochemical assessment of maternal thyroid function revealed that the severity of hypothyroidism was important. Furthermore, results did not support an association between thyroid autoimmunity and preeclampsia.

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OP-02-11
Association of thyroid function and tpoab positivity with the risk of postpartum depression: A population-based cohort study, systematic review, and meta-analysis
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Objective
We performed a national and regional study in the Danish population. The national study was register-based, and the study population included all singleton pregnancies in Denmark from 1999-2015 (n=1,014,775). The regional study included the biochemical measurement of TSH, thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (Tg-Ab) (ADVIA Centaur XPT, Siemens). Inclusion criteria for the national study were gestational age 37 weeks or above at delivery, and delivery in a Danish hospital. Exclusion criteria were presence of any thyroid disease (e.g., hypothyroidism, hyperthyroidism, or thyroiditis) before or during pregnancy. The inclusion criteria for the regional study were gestational age 37 weeks or above at delivery, and delivery in a Danish hospital. Exclusion criteria were presence of any thyroid disease (e.g., hypothyroidism, hyperthyroidism, or thyroiditis) before or during pregnancy.

Results
In total, 2004 women were included. Out of the 14 phthalate metabolites, higher MEP, MBP, MBzP and all metabolites of DEHP (MEHP, MEHBP, MEOPH, MECPP and MCMHP) were associated with lower hCG concentrations, with the largest effect estimate corresponding to a 0.15 IU/L decrease in hCG concentrations per 1 log-unit increase in urinary MBP concentrations (µg/g creatinine). We identified that of the 5 phthalate metabolites (MEP, MBP, MBzP and all metabolites of DEHP (MEHP, MEHBP, MEOPH, MECPP and MCMHP)) which were previously shown to be negatively associated with FT4 concentrations, hCG mediated 34% (MEOH, P = 0.004) to 60% (MBP, P = 0.03) of the association of all five phthalate metabolites with FT4.

Conclusions
This is the first study to suggest phthalates act as a hCG disruptor. We also show that higher phthalate exposure during early pregnancy is associated with lower hCG concentrations, resulting in lower FT4 concentrations which is likely mediated through reduced stimulation of the thyroid gland.

DOI: 10.1530/endoabs.84.OP-02-11
literature assessing the association of thyroid function and/or TPOAb positivity with risk of PPD and an aggregate data meta-analysis on included studies to generate a pooled risk estimate.

Results
There was no association of TSH or FT4 levels with the risk of postpartum depression (log_TSH OR:0.79, 95%CI 0.56-1.13, P = 0.20; FT4 OR:1.02, 95%CI 0.96-1.08, P =0.57) in Generation R study. There was also no association of TPOAb positivity with PPD (OR:0.79, 95%CI 0.45-1.31, P = 0.39). Additional analyses assessed an impaired thyroidal response to hCG stimulation and defined the combined effects of a high hCG with either a high TSH or low FT4 as an alternative marker of TPOAb positivity. We identified that an impaired thyroidal response to hCG stimulation was associated with a lower risk of PPD (P for interaction TSH=0.04 and FT4=0.06). In our systematic review, two out of 1219 identified articles were included and they were both eligible for a meta-analysis. The risk of PPD (pooled OR) for TPOAb positivity was 1.20 (95%CI 0.46-3.16).

Conclusions
Our original study is by far the largest study on this topic showing that neither TPOAb positivity nor TSH or FT4 were associated with PPD. Our systematic review revealed high heterogeneity and suboptimal methodological quality in the current literature, but overall does not support a link with PPD. Although TPOAb-positive women should be monitored for postpartum thyroiditis, there does not seem to be an indication to screen for postpartum depression. Further research should focus on other factors potentially involved in the etiology of PPD.

Open Session 3: Advanced Thyroid Cancer

OP-03-12
Clinicopathological and epidemiological features of thyroid cancer patients intended to initiate systemic therapy
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Objectives
The majority of patients with differentiated thyroid carcinoma (TC) have an excellent prognosis, with a 5-year survival rate of 98.3%, and only rarely reaches an advanced stage of disease. The present study aims to identify the clinicopathological and epidemiological features at the time of diagnosis of a group of patients who required to be treated with systemic therapy with tyrosine-kinase inhibitors (TKI).

Methods
We retrospectively evaluated 136 patients with thyroid carcinoma who were addressed to TKI between 2012 and 2022 and followed at the Endocrine Unit of the University Hospital of Pisa. Demographic, clinical and pathological data were collected at the moment of the initial diagnosis and at the moment the systemic therapy was started.

Results
Sex distribution was equal: 69 females (50.7%) and 67 males (49.3%). The mean age was advanced both at diagnosis (59.01 ± 10.44 years) and when systemic therapy was started (68.85 ± 8.52 years). The histotypes (available in 135 cases) were distributed as follows: 72 papillary thyroid carcinomas (PTC) (53.8%), 27 follicular TC (20.1%), 14/51 minimally invasive (25%), 6/16 oxyphil (37.5%). Regarding TNM classification, primary tumors were frequently classified as T3 in 44% (39.8%) with distant metastasis (DM). At the moment of starting systemic therapy was started (68.85 ± 8.52 years). All the relapses were preoperatively marked by ultrasound-guided administration of technetium Tc-99m albumin colloid (0.1 ml).

Results
The main localization of relapse was the thyroid bed – central neck compartment (178; 70.1%). Recurrence diameters ranged from 2 to 17 mm. In 71% of cases intraoperative localization and removal of TC recurrence. Intraoperative localization and removal of TC recurrence was performed. There were 180 (70.9 %) women and 74 (29.1%) men, mean age 47 years (median 50.7 years) with 7.82 years of the mean follow-up (median 5.81 years). All the relapses were preoperatively marked by ultrasound-guided administration of technetium Tc-99m albumin colloid (0.1 ml).

Results
The main localization of relapse was the thyroid bed – central neck compartment (178; 70.1%). Recurrence diameters ranged from 2 to 17 mm. In 71% of cases intralesional administration of the radiotracer was used and in 29% the radiotracer was applied in the lesion area. There was no difference in the efficacy of the relapse removal between these groups (P=0.926). In 55 patients (21.7%) multifocal recurrence was found and removed. No differences in the efficacy of relapse removal were observed depending on the histological type and multifocal nature of recurrence (P=0.08). In 19 patients (7.5%) relapse was not found in ROLL procedure (necessity of reoperation). No differences were found between the recurrent laryngeal nerve paresis after the primary and secondary operation (P=0.7) as in the case of postoperative hypoparathyroidism (P=0.4). More than 1 reoperation was performed in 42 patients. In this subgroup, 1 death (2%) was observed. Disease progression was noted in 12 patients (25%) and complete remission was found in 28 (56%). In the whole group, complete remission was observed in 198 patients (78%) during the follow-up.

Conclusions
The ROLL technique in TC is a safe and effective procedure that facilitates intraoperative localization and removal of TC recurrence.

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OP-03-13
Thyroid cancer relapse as a challenge to a surgeon: The efficacy of radioguided occult lesion localization (ROLL) technique
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Introduction
Reoperation due to recurrent or persistent thyroid cancer (TC) poses a real challenge to a surgeon who must properly estimate the benefit risk ratio.

Material and methods
A retrospective study of 254 TC patients (186 papillary TC, 24 follicular TC, 34 medullary TC, 10 poorly differentiated TC) reoperated on from 2002 and 2018 was performed. There were 180 (70.9 %) women and 74 (29.1%) men, mean age 47 years (median 50.7 years) with 7.82 years of the mean follow-up (median 5.81 years). All the relapses were preoperatively marked by ultrasound-guided administration of technetium Tc-99m albumin colloid (0.1 ml).

Results
The main localization of relapse was the thyroid bed – central neck compartment (178; 70.1%). Recurrence diameters ranged from 2 to 17 mm. In 71% of cases intralesional administration of the radiotracer was used and in 29% the radiotracer was applied in the lesion area. There was no difference in the efficacy of the relapse removal between these groups (P=0.926). In 55 patients (21.7%) multifocal recurrence was found and removed. No differences in the efficacy of relapse removal were observed depending on the histological type and multifocal nature of recurrence (P=0.08). In 19 patients (7.5%) relapse was not found in ROLL procedure (necessity of reoperation). No differences were found between the recurrent laryngeal nerve paresis after the primary and secondary operation (P=0.7) as in the case of postoperative hypoparathyroidism (P=0.4). More than 1 reoperation was performed in 42 patients. In this subgroup, 1 death (2%) was observed. Disease progression was noted in 12 patients (25%) and complete remission was found in 28 (56%). In the whole group, complete remission was observed in 198 patients (78%) during the follow-up.

Conclusions
The ROLL technique in TC is a safe and effective procedure that facilitates intraoperative localization and removal of TC recurrence.

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Entrectinib in patients with ntrk fusion-positive (ntrk-fp) thyroid cancer: Updated data from startrk-2

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Objectives
NTRK gene fusions are oncogenic drivers in many solid tumours, including thyroid cancers. In the phase 2 study STARTRK-2 (NCT02568267), entrectinib (a CNS-active tropomyosin receptor kinase [TRK] inhibitor) demonstrated efficacy in patients with NTRK-fp thyroid cancer (objective response rate [ORR]; 49%; clinical cut-off: 31 Oct 2018; n = 5). We report updated data from a larger cohort with longer follow-up.

Methods
Adult patients with TRK-inhibitor naïve, locally advanced/metastatic NTRK-fp thyroid cancer, with or without baseline CNS metastases, were enrolled. Tumour responses were assessed by blinded independent central review (BICR) per RECIST v1.1 at Week 4 and every 8 weeks thereafter. Primary endpoints: ORR and duration of response (DoR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), intracranial (IC) efficacy and safety. Enrolment cut-off: 31 July 2019; clinical cut-off: 31 August 2020.

Results
The efficacy-evaluable population included 13 patients with ≥1 year of follow-up: 10 (77%) had papillary and three (23%) had other types of thyroid cancers. Median age was 55.0 years (range: 26–78); 7 patients (54%) had received ≥2 prior lines of therapy; and 7 patients (54%) had investigator-assessed baseline CNS metastases. Median survival follow-up was 36.1 months. Responses for all patients and patients with papillary NTRK-fp thyroid cancer are shown in the Table. Median DoR, PFS and OS for all patients were 13.2 months (95% CI 7.9–19.9 months), 19.9 months (95% CI: 6.5–33.8) and 19.9 months (95% CI: 14.5–NE), respectively. In patients with BICR-assessed baseline CNS metastases (n = 6), IC-ORR was 50% (3/6; 95% CI: 11.8–88.2) and median IC-PFS was 15.0 months (95% CI: 6.3–NE). In the safety-evaluable population (n = 16; all treated patients), 10 patients (63%) had a Grade ≥3 treatment-related adverse event (TRAE). There were two deaths (15%) due to TRAEs. TRAEs leading to dose reduction, interruption and discontinuation occurred in 31%, 38% and 19% of patients, respectively. Conclusions

In this updated analysis with more than twice the number of patients previously reported, ORR was numerically higher compared with the prior analysis and entrectinib demonstrated durable systemic and IC responses. No new safety signals were identified.

NTRK-fp thyroid cancer

<table>
<thead>
<tr>
<th>ORR, n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N = 13)</td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>7 (54) 25.1–80.8</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (23) 11.8–88.2</td>
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<tr>
<td>Stable disease</td>
<td>2 (15)</td>
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<tr>
<td>Progressive disease (PD)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>1 (8)</td>
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</table>

Papillary thyroid cancer (n = 10)

<table>
<thead>
<tr>
<th>ORR, n (%)</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>5 (50) 18.7–81.8</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>1 (10)</td>
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<tr>
<td>Non-CR/non-PD</td>
<td>0</td>
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<td>Missing/unevaluable</td>
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</table>

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Assessment of adrenal function in a large series of patients confirms that adrenal insufficiency is a common cause of fatigue during treatment with multikinase inhibitors (MKIs)

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Background
Fatigue is one of the most frequently reported adverse events in patients treated with multikinase inhibitors (MKIs). It is present in about 59% and 24% of patients treated with lenvatinib and vandetanib, respectively, associates with a decreased quality of life and often leads to treatment discontinuation. In 2018, for the first time, a correlation between fatigue and primary adrenal insufficiency (PAI) was demonstrated in 12 patients treated with lenvatinib and vandetanib (Colombo et al., JCEM 2018). These data were confirmed more recently by the evaluation of adrenal function in 13 patients treated with lenvatinib (Monti et al., Thyroid 2022).

Aim
To assess adrenal function in a larger series of patients who developed MKIs treatment.

Methods
Adrenal function has been monthly evaluated, for an average follow-up of 38 months (6-161 months), in 32 patients receiving MKIs and developing fatigue during treatment (23 on Lenvatinib, 7 on Vandetanib and 2 on Selpercatinib). In particular, cortisol and ACTH levels were evaluated together with 250-μg ACTH stimulation test (performed at the time of ACTH elevation above the normal limits).

Results
A high percentage of patients with fatigue, 23/31 (74%), had a significant elevation of basal ACTH with normal cortisol levels during MKIs treatment (18/23 on lenvatinib, 4/7 on vandetanib and 1/2 on selpercatinib). Moreover, 8/23 patients (6 on lenvatinib and 2 on vandetanib) showed an impaired response to the ACTH test, thus confirming PAI diagnosis. The onset of PAI occurred after an average period of 14 months (range 3-61) from the start of MKIs treatment. Cortisone acetate (CA) replacement therapy was recommended in 9 patients (all the patients with an impaired cortisol response to ACTH stimulation and in 1 patient with only ACTH elevation and fatigue degree 2 according to the CTCAE version 4.03), and improved fatigue in 6 of them (67%).

Conclusions
Data on a large series confirm that a high percentage of patients on MKIs show ACTH levels above the normal levels, and fatigue can be totally or partially related to the development of PAI in these patients. The first evidence of reduced adrenal function is the progressive rise of basal ACTH levels with cortisol values within normal limits. Moreover, a reduced cortisol response to the 250-μg ACTH stimulation test is observed in some of these patients. Replacement therapy with CA improves fatigue and, therefore, adherence to therapeutic regimens, avoiding dose reductions or discontinuation.

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A clinical and molecular study of a real-world cohort of braf v600e anaplastic thyroid carcinoma treated with dabrafenib and trametinib

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OP-03-14

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Introduction and objectives
Anaplastic thyroid cancer (ATC) has a very low overall survival (OS) and progression free survival (PFS) due to fast growth and resistance to non-target therapies. A recent phase II study showed a dramatic increase in OS and PFS of BRAF V600E mutated ATC patients treated with Dabrafenib and Trametinib (DT). However, as commonly reported in melanoma durable responses in ATC may be compromised by resistance mechanisms. Until now only a few case reports and a small case series has been published. We present our experience with DT in BRAF-positive ATC patients and compare the outcomes with usual therapy. In addition, we studied the molecular alterations at baseline and during progression in DT group.

Materials and methods
ATC patients treated between May 2018 and October 2021 were included. BRAF positive patients underwent next generation sequencing (NGS) at baseline and at progression. Bioinformatic analyses filtered and selected relevant somatic genomic variants. Patients were classified in the following groups: BRAF WT under compassionate care (CC); BRAF wild type (WT) under multimodal therapy (MT) with surgery, radiotherapy ± chemotherapy or Ivenatib and BRAF V600E treated with DT. Response was assessed monthly in the first 6 months and then every 3 months by RECIST 1.1: OS, PFS, duration of response (DOR) was estimated with Kaplan-Meier method and compared with log-rank test.

Results
27 ATC patients were included (CC = 10, MT = 8 and DT = 9). Median follow-up was 24, 96 and 410 days for CC, MT and DT respectively due to differences in survival time. Median OS was 39, 156 and 475 days for CC, MT and DT respectively ($P<0.001$). At 12 months only patients in the DT group were alive (71%). Median PFS and DOR were 270 and 215 days, respectively (MT group < 32 days) ($P<0.001$). In the DT group only 1 patient needed trametinib dose reduction to 225 mg/d and no G3 adverse events were reported. Molecular profiling by NGS showed that the nine patients in the DT group had a BRAF V600E and a 1ER3p mutation at baseline. In one of the four clinical disease progressions during DT treatment a pathogenic NRAS mutation was found.

Conclusions
Our results show a significant real-world efficacy of DT in both OS and PFS compared with contemporary standard treatment with a good safety profile. Molecular profiling allowed the patient with RAS mutations to change treatment compared with contemporary standard treatment with a good safety profile.

Conclusions
Age and WDF are both factors that decrease intrahepatic TH levels. The decrease in intrahepatic $T_3$ concentration in old mice WDF could explain why TH supplementation was more effective in reducing hepatosteatosis in older patients.

OP-04-18
Differential impact of intrathyroidal IL-4 expression on thyroiditis development in C57BL/6J and NOD.H2H4 THYR-IL4 mice
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Introduction
Interleukine-4 (IL-4) a T-helper type 2 cytokine (Th2), has been implicated in the pathogenesis of autoimmune thyroid diseases (AITD). However, the role of IL-4 in Hashimoto’s thyroiditis (HT) pathogenesis remains controversial. In this study, we investigated whether a constitutive IL-4 overexpression in the thyroid tissue (Thyr-IL4) could influence the development of thyroiditis in resistant (C57BL/6) or susceptible (NOD.H2H4) mouse strains.

Methods
Thyr-IL4 C57BL/6 parental strain and NOD.H2H4 mice were exposed to 0.05% of NaI supplemented water during 8 and 16 weeks. Disease development was evaluated by measuring serum TgAbs, as well as quantifying the immune cell infiltration by immunostaining. Bow cryostomy and cytokine mRNA expression. Thyroid function was also evaluated through serum TSH levels as well as mRNA expression of thyroid differentiation markers.

Results
After 16 weeks of NaI treatment circulating TgAbs were significantly higher in transgenic susceptible NOD.H2H4 animals. NOD.H2H4 Thy-IL4 mice developed also intense lymphocytic infiltration. Moreover the relative mRNA expression of TNFα, IL-10, TGFβ, TNFα, IL-17 and IL-13 was also significantly increased in treated transgenic animals compared to WT mice. Chronic administration of iodide induced an important increase in serum TSH levels in transgenic NOD.H2H4 animals with the development of large colloid goiter. In addition, as expected in the escape from the Wolff-Chaikoff block, mRNA expression of the iodide symporter Nis was reduced in both WT and Thy-IL4 animals. In contrast, for the thyroiditis resistant parental strain, no circulating TgAbs could be detected in the serum of WT and transgenic C57BL/6 mice. As previously reported, WT C57BL/6 animals did not show thyroidal leukocyte infiltrates 16 weeks after NaI treatment. Surprisingly, the transgenic parental strain show intense leukocyte infiltration scattered throughout the thyroid tissue associated with enhanced expression of TGFβ, TNFα, IL-10, TNFα, IL-5 and IL-13. Thy-IL4 C57BL/6 animals developed also thyroid goiter with increased TSH levels. However, instead of a correct Wolff-Chaikoff escape present in WT animals, the Nis mRNA expression remained elevated in transgenic mice.

Conclusions
We have shown that prolonged expression of IL-4 in the thyroid associated to a chronic administration of iodide exacerbate thyroiditis disease in spontaneous NOD.H2H4 mice and can induce auto-immune thyroid infiltrate in C57BL/6 resistant genetic background.

OP-04-19
A thyroid hormone-independent role for transthyretin in neural stem cells of the postnatal mouse subventricular zone?
Pieter Vancamp1, Karine Le Blay2, Barbara Demeneix1 & Sylvie Remaud4
Rewiring of liver diurnal transcriptome rhythms by triiodothyronine (T3) supplementation

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Cellular 24-hour rhythms depend on transcriptional programs controlled by a set of circadian clock genes/proteins. Systemic factors like humoral and neuronal signals, oscillations in body temperature, and food intake align physiological circadian rhythms with external time. Thyroid hormones (THs) are major regulators of circadian clock target processes such as energy metabolism, but little is known about how fluctuations in TH levels affect the circadian coordination of tissue physiology. In this study, a high triiodothyronine (T3) state was induced in mice by supplementing T3 in the drinking water, which affected body temperature, and oxygen consumption in a time-of-day dependent manner.

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CryO-electron microscopy structures of human thyroid peroxidase (TPO) in complex with tpo antibodies

Stuart Baker, Ricardo Núñez Miguel, Daniel Thomas, Michael Powell, Jadwiga Furniak & Bernard Rees Smith Rsr Limited

Objectives
Thyroid peroxidase (TPO) is a key enzyme in the synthesis of thyroid hormones and is a target for autoimmune responses in autoimmune thyroid disease. TPO autoantibody (TPOAb) binding epitopes have been mapped on the peroxidase domain (POD) and the complement control protein like domain (CCP). This study aimed to solve the molecular structures of TPO bound to TPO antibodies.

Methods
An extracellular domain (ECD) of human TPO (amino acids; aa 1-839) was expressed in insect cells. Fab's were prepared from two TPO antibodies; a human monoclonal autoantibody 2G4 and a mouse monoclonal antibody 4FS. The structures of TPO-2G4 and TPO-4FS complexes were determined by cryo-electron microscopy using a Titan Krios 300KV with a Falcon 5 Direct Detector.

Results
The structure of TPO-2G4 was solved at 3.92Å and TPO-4FS at 3.44Å resolutions. The solved ECD structure comprises the POD, the CCP and an incomplete epidermal growth factor like domain (EGF). The POD Arg396 and Arg491 hold the haem group and form salt bridges with the two carboxylic groups of the haem. His494 acts as the proximal histidine interacting with the iron ion of the haem. The enzyme active site is located at the distal side of the haem and is lined by Glu235, Asp238, His239 and Glu299. A calcium ion is coordinated by Asp240, Thr231, Phe323, Asp325 and Ser327. 2G4 and 4FS bind to TPO in different orientations. For both antibodies the binding epitopes are located exclusively on the POD. The binding interface for 2G4 is larger (214Å²) than for 4FS (195Å²). 2G4 interacts with aa 194-277 and 604-628 whereas 4FS with aa 461-659 with three common residues Glu604, Ala607 and Asp608 for both epitopes. In both complexes the antibody heavy chains make greater contributions to the interface than the light chains. 2G4 and 4FS binding sites on the POD are distinct from the CCP and EGF with no contacts between antibodies and the CCP or EGF. Any conformational movement of the CCP towards antibody epitopes on the POD would be prevented by a disulphide bond between POD Cys768 and CCP Cys794.

Conclusions
Human TPO molecular structure has now been solved. This should be helpful in assessing the autoimmune responses to TPO in more detail and developing TPO enzyme inhibitors for therapeutic applications.

DOI: 10.1530/endoabs.84.OP-04-21

Update on the role of carboleuco-1 in cell homeostasis and oxidative stress in hashimoto’s thyroiditis and graves’ autoimmune thyroid disease. Marie-Christine Man1, Chantal Daumerie2, Antonella Boschi3, baleschki leito4, Mouad Michel5, Benoît Lengeli6, Behets Catherine6, Lancelot Marique7, Victoria Van Regemorter8, Weronica Alexis9, Van Regemorter Elliot8, Herrn Michael1, de Bourvonville Marc3, de Ville de Goyet Christine10 & Julie Craps10

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Caveolin-1 (cav1) is a member of the thyroxisome multiprotein complex required for thyroid hormones synthesis which is decreased in Hashimoto’s thyroiditis (HT) and excessive in Graves’ disease (GD). Both pathologies are characterized by oxidative stress (OS), the production of reactive oxygen species (ROS) exceeding the antioxidant defenses. The aim of this study is to correlate cav1 expression and OS in HT and GD. Primary cultures of human thyrocytes were treated or not with Th1 (Interleukin-1α and Interferon) or Th2 (Interleukin-4) cytokines. Thyroid samples from HT and GD patients were compared to paranozoidal tissues of patients with multinodular goiter (controls). Orbital fats were obtained from controls or patients with Graves’ orbitopathy (GO). Samples were processed for RT-PCR, Western blots or immunohistochemistry to analyze the expression of T4, cav1, 4-hydroxynonenal (HNE), caspase-6, catalase, peroxiredoxin 1 (PRDX1), sirtuin-1 (sirt1), NADPH oxidase (NOX4 and NOX2).

In HT, the glands comprised a mix of normal and altered follicles. The altered follicles, located within inflammatory areas, did not express cav1 and were unable to form and store T4 in the follicular lumen. T4 being detected inside the cytoplasm. They also highly expressed HNE, an OS marker, and presented numerous dead cells labelled with caspase-6. In primary cultures, Th1 cytokines decreased cav1 but also catalase and PRDX1 which detoxify H2O2 and sirt1 known to positively regulate antioxidants expression. At the opposite, in GD, thyroids, all the follicles were able to form and store T4. Cav1 protein was increased as compared to controls and properly located at the apical pole. The high HNE expression indicative of OS correlated with an increase of NOX4 continually generating H2O2. However, antioxidants like catalase were upregulated to cope with ROS production so that there were few dead thyrocytes.

Interleukin-4 which could mimic GD did not influence cav1 expression. Of interest, in GO orbital adipocytes, NOX4 was also increased, as well as NOX2, inducing OS further aggravated in these cells by a reduction of catalase. In conclusion, cav1 expression is diagnostically opposed in HT and GD. In HT, the downregulation of cav1 by Th1 cytokines induces thyroxisome disruption, hypothyroidism and intracellular H2O2 production responsible for OS still aggravated by a Th1-induced decrease of sirt1 and antioxidant defenses. In GD, cav1 overexpression could be correlated with hyperthyroidism and NOX4 could be the prime target to prevent OS.

**OP-05-23**

**Cut-offs for thyroid peroxidase and thyroglobulin antibodies in early pregnancy are not similar and may differ from non-pregnant individuals: evidence from 10,905 Danish pregnant women**

Stine Linding Andersen, Niels Henrik Bruun, Peter Astrup Christensen, Simon Lykkeboe, Anne Handberg, Annette Bohl Hansen, Maja Berg Hjelm, Louise Knøsgaard, Nanna Maria Uldall Torp, Allan Carle, Jesper Scott Karmisholt, Peter Vestergaard & Stig Andersen

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**Objectives**

Thyroid disease in women of reproductive age is predominantly of autoimmune origin, and thyroid peroxidase antibodies (TPO-Ab) as well as thyroglobulin antibodies (Tg-Ab) are key markers of autoimmune hypothyroidism. Adding to this, much focus in pregnancy is on euthyroid women who are positive for thyroid autoantibodies. The observational findings are diverse, and evidence to substantiate the applied cut-offs for definition of thyroid autoantibody-positivity in early pregnant women is warranted.

**Methods**

The North Denmark Region Pregnancy Cohort, 2011-2015, includes biochemical assessment of thyroid function, TPO-Ab, and Tg-Ab (ADVIA Centaur XPT, Siemens Healthineers) in stored blood samples from 14,030 early pregnancy women. Antibody cut-offs recommended by the manufacturer (non-pregnant) were 60 U/ml for both TPO-Ab and Tg-Ab. Within the cohort, euthyroid singleton pregnant women with no history of thyroid disease were identified for establishment of antibody cut-offs (reference cohort). TPO-Ab and Tg-Ab showed skewed distributions with 50.7% and 66.4% of the values below the detection limits of 28 U/ml and 15 U/ml, respectively. Thus, antibody cut-offs (95% percentiles) were established by Regression on Order Statistics.

**Results**

Altogether 10,905 pregnant women were included in the reference cohort, and the established cut-offs for thyroid autoantibodies within the cohort were 59 U/ml (TPO-Ab) and 33 U/ml (Tg-Ab). The cut-offs were then applied in the full cohort of 14,030 pregnant women showing that 1,545 women (11.0%) were TPO-Ab positive, 1,870 (13.3%) were Tg-Ab positive, and 1,079 (7.7%) were TPO-Ab and Tg-Ab positive. Considering maternal thyroid function by antibody-status (Table), TSH was higher and free T4 lower among antibody-positive as compared to antibody-negative women with each of the applied cut-offs.

**Conclusions**

In a large cohort of Danish pregnant women, cut-offs for TPO-Ab and Tg-Ab in early pregnancy were established while considering the skewed distributions. The established cut-offs were not similar for TPO-Ab and Tg-Ab, and the cut-off for Tg-Ab was lower than recommended in non-pregnant individuals. The findings are important regarding classification of exposure in pregnancy outcome studies and specifically regarding the assessment of thyroid autoimmunity per se.

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**OP-05-24**

**Sirolimus for Graves’ orbitopathy: A novel drug for the management of patients with moderate-to-severe Graves’ orbitopathy**

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**Background**

Sirolimus is an immunosuppressive drug with anti-fibrotic and anti-proliferative activities. In vitro, sirolimus inhibits differentiation of orbital fibroblasts from patients with Graves’ orbitopathy (GO), suggesting a possible use in clinical practice.

**Methods**

We performed a retrospective investigation aimed at evaluating the effects of sirolimus as a second-line treatment for moderate-to-severe, active GO, compared with methylprednisolone. The investigation entailed data analysis of unselected, consecutive patients with moderate-to-severe, active GO, treated off-label with sirolimus (2 mg orally on first day, followed by 0.5 mg/day for 12 weeks) or methylprednisolone [500 mg iv/weekly (6 weeks), 250 mg/weekly (6 weeks)], as a second-line treatment, over a period of 18 consecutive months. The primary objective was the overall GO outcome at 24 weeks based on a composite evaluation. Secondary objectives at 24 weeks were: 1) improvement in quality of life, evaluated using a specific questionnaire (GO-QoL); 2) reduction of proptosis; 3) reduction of the clinical activity score (CAS); 4) improvement of eye ductions; and 5) reduction of eyelid aperture.

**Antibody-positive TPO-Ab > 59 U/ml**

<table>
<thead>
<tr>
<th>Antibody-positive TPO-Ab (U/ml)</th>
<th>Median (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (&gt; 59 U/ml)</td>
<td>1.545 (1.73)</td>
<td>1.67-1.79</td>
</tr>
<tr>
<td>Free T4 (&gt; 33 U/ml)</td>
<td>1.545 (15.61)</td>
<td>15.46-15.71</td>
</tr>
</tbody>
</table>

**Antibody-negative TPO-Ab ≤ 59 U/ml**

<table>
<thead>
<tr>
<th>Antibody-negative TPO-Ab (U/ml)</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (&gt; 59 U/ml)</td>
<td>12.485 (1.07)</td>
</tr>
<tr>
<td>Free T4 (&gt; 33 U/ml)</td>
<td>12.485 (15.99-16.07)</td>
</tr>
</tbody>
</table>

**Conclusions**

Sirolimus for Graves’ orbitopathy: A novel drug for the management of patients with moderate-to-severe Graves’ orbitopathy

**DOI:** 10.1530/endoabs.84.OP-05-23
The association of HT with further autoimmune disorders is characterized by a...
The optimal ranges of thyroid function based on the risk of cardiovascular disease and mortality: an individual participant data meta-analysis

FT4 concentrations >85th percentile while 5% and 10% for men with FT4 concentrations >75th and >90th percentiles respectively.

Conclusion
Overall TSH was not associated with CVD events. FT4 between the 20th and 40th percentiles represented the optimal health ranges based on the risk of cardiovascular disease and mortality, which has potential implications for treatment targets when managing clinical and subclinical thyroid disease.

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**OP-06-29**

Central hypothyroidism ensuing endonasal transsphenoidal pituitary surgery: the role of a post operative TRH stimulation test
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Objectives
The goal of this study was to evaluate the value of a TRH stimulation test to assess the risk of permanent central hypothyroidism after transsphenoidal pituitary surgery.

Methods
A retrospective cohort study was performed, evaluating the results of a routinely performed TRH stimulation test executed in the first 2 weeks after transsphenoidal pituitary surgery in patients admitted to the Ghent University Hospital between 1/1/2010 and 31/12/2019. The presence of central hypothyroidism was evaluated 6-18 months post-surgery by extracting the diagnosis from the patient file, combined with double checking based on the presence of T4 substitution therapy and corresponding thyroid function tests within this timeframe.

Results
After exclusion of patients with central hyperthyroidism and patients who received additional radiotherapy within the first 18 months after the surgery, 116 patients were included, 18 of whom developed permanent central hypothyroidism. Postoperative central hypothyroidism was significantly associated with a low TSH at the start of the TRH stimulation test, as well as with a low maximum TSH and a low maximum TSH increase from baseline after TRH administration. A peak TSH of <2.0 mU/l during the test had a sensitivity of 100% and a specificity of 87.2% to identify patients at risk for permanent central hypothyroidism.

Conclusions
Our data support the use of a postoperative TRH stimulation test with a cut-off value of 2.0 mU/l as maximum reached TSH value during the test as a screening tool to identify patients at risk of permanent central hypothyroidism after transsphenoidal pituitary surgery.

DOI: 10.1530/endoabs.84.OP-06-29

**OP-06-30**

Levothyroxine replacement therapy overuse and factors guiding successful treatment discontinuation: short and long-term observation data of a large cohort
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Background
Levothyroxine (LT4Rx) is one of the most prescribed drugs worldwide the vast majority of patients receive long-term treatment. However, in a recent study of 291 subjects, it was found that 60% were euthyroid 2 months after LT4-Rx discontinuation1. Aims of the study
A prospective clinical cohort follow-up study was carried out. In 688 subjects (82% females) aged 48.01±15.96 (range 17-84years) with 8.59±6.98 years on LT4Rx without a solid diagnosis of hypothyroidism, treatment was abruptly interrupted. The indications for treatment were nodeole(s) (33%), undefined (27%), post-partum (7%) and Hashimoto’s thyroiditis (33%). A short period of follow-up was initiated in 54% of subjects (≤ 4 months, Group A) and long-term follow-up in the rest (up to 60 months, Group B). The subjects were evaluated when LT4Rx was discontinued, 2-4 months later, and at the end of follow-up. At each time point, estimation of TSH, FT4 levels, and thyroid ultrasound was performed. A TSH value of ≥4.5IU/ml was considered as underlying hypothyroidism.

Results
Among the entire cohort, 158 subjects became hypothyroid, while the remaining 530 remained euthyroid off LT4-Rx (23 vs. 77%, P<0.001). On subgroup analysis, 40% of subjects comprising Group A became hypothyroid, whereas the corresponding value for Group B was 5%. In Group A, the rationale for LT4Rx, LT4 dose, LT4 dose/BMI, TSH levels, and the existence of thyroid autoantibodies (ATA) were significantly different in those who became hypothyroid. No difference among any parameters evaluated was observed in Group B. Subjects with a diagnosis of Hashimoto’s thyroiditis, positive ATA, higher TSH values, and higher LT4 dose were significantly more likely to become hypothyroid. Furthermore, in Group A, 15.4% became hypothyroid with baseline TSH>3IU/ml vs. 5.4% with baseline TSH<3IU/ml (P<0.001); the corresponding values for Group B were 44.4% vs. 10.0% (P<0.001), respectively.

Conclusions
These findings suggest considerable overuse of thyroxine administration. In cases of uncertainty, the existence of nodules, low-normal TSH level a relatively small T4 dose, and absence of ATA are strong indicators of euthyroid patients’ overuse of the LT4Rx and, accordingly, treatment discontinuation is strongly advised. Furthermore, in the case that a subject does not become hypothyroid 2-4 months post treatment discontinuation, the likelihood of developing hypothyroidism long-term is insignificant.

Reference

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**OP-06-31**

Does subclinical hypothyroidism add on any symptoms? evidence from a danish population-based study
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Background
Few studies have scrutinized the spectrum of symptoms in subclinical hypothyroidism.

Methods
From three DanThyr cross-sectional surveys performed in the period 1997 to 2005, a total of 8,903 volunteers participated in a comprehensive investigation including blood samples and questionnaires on previous diseases, smoking habits, alcohol intake, and education. From the three surveys we included patients with unknown subclinical hypothyroidism (n=376) and euthyroid controls (n=7,619). For further comparison we also added patients newly diagnosed with autoimmune overt hypothyroidism (n=140) recruited from a previous study. We explored to which extent patients with subclinical hypothyroidism reported 13 previously identified hypothyroidism-associated symptoms (tiredness, dry skin, mood lability, constipation, palpitations, restlessness, shortness of breath, wheezing, globus sensation, difficulty swallowing, hair loss, dizziness/vertigo, and anterior neck pain). In various uni- and multivariate regression models we searched for circumstances predicting why some patients have more complaints than others.

Results
Subclinically hypothyroid patients did not report higher hypothyroidism score (median, IQR), 2 (0-4) vs. 2 (0-4), P=0.25 compared to euthyroid controls. Within the group of subclinically hypothyroid patients co-morbidity had the highest impact on symptoms (tiredness, shortness of breath, wheezing; all P<0.001); TSH level had no impact on symptom score; low age was accompanied

Endocrine Abstracts (2022) Vol 84
with higher mental burden (tiredness, $P<0.001$; mood lability, $P<0.001$; restlessness, $P=0.012$), whereas shortness of breath was associated with high BMI ($P<0.001$) and smoking ($P=0.007$).

Conclusion
Patients with a thyroid function test suggesting subclinical hypothyroidism do not express thyroid disease related symptoms more often than euthyroid subjects. In subclinical hypothyroidism, clinicians should focus on undiagnosed co-morbidity and should optimize treatment of known concomitant diseases rather than expecting symptomatic relief following levo-thyroxine substitution.

DO: 10.1530/endoabs.84.OP-06-31

Oral Session 7: Thyroid Cancer Basic

OP-07-32
The micro-rna content of extracellular vesicles in papillary thyroid cancer: from identification in mouse thyroid tumour to detection in patient plasma
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Background
Papillary thyroid carcinoma (PTC) is the most frequent subtype of thyroid cancers. Despite good prognosis in most cases, post-surgery recurrences and metastases can occur. Moreover, differential diagnosis between benign and malignant nodules is still challenging. Gaining knowledge about extracellular vesicles (EVs) in PTC could have a double benefit: a better understanding of PTC clinical behaviour, and the discovery of accessible (and accurate) diagnostic tools.

Aims
The goals of this project are to (i) identify miRNAs actors and markers, released via EVs by the tumor, (ii) decipher the mechanisms by which they impact thyroid cancer and its microenvironment, and (iii) evaluate the diagnostic value of circulating miRNAs.

Methods and results
Using a mouse model mimicking human PTC, we isolated EVs from dissociated control- and early and late PTC-tissue by differential ultracentrifugations. Vesicles in the high-speed pellet were characterized in-depth and sequencing was performed to identify tumor-derived EV-miRNAs. We focused on 4 miRNAs differentially more abundant in EVs from PTC tissues. In silico analysis revealed their enrichment in immune-related pathways, consistently with the massive recruitment of macrophages observed in our model. We investigated the distribution of EV-miRNAs according to their cellular source. Using the Nanoview technique, we showed that the number of EVs bearing epithelial and immune markers was increased in PTC tissues. The 4 miRNAs were mostly expressed, and deregulated, in epithelial cells. We thus propose that their increased abundance in epithelial-EVs could affect the immune microenvironment of PTC. In parallel, the miRNAs candidates were quantified in tissues, in plasma and in plasma-EVs from patients treated for thyroid diseases. Two miRNAs, miR-146b-5p and miR-21a-5p were more abundant in tissue and plasma-EVs isolated from patients with PTC, as compared to benign diseases.

Conclusions
We provided a gradual tissue- and EV-miRNAs profiling during PTC development which allowed the identification of EV-miRNAs that could (i) support the establishment of a permissive microenvironment for tumor development and (ii) contribute to thyroid cancer diagnosis.

DO: 10.1530/endoabs.84.OP-07-32

OP-07-33
Hürthle cell tumors vs oncogenic variants of the follicular cell derived thyroid tumours: a comprehensive analysis based in transcriptome, proteome and cvn profiling
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Objectives
Hürthle cell (oncocytic) lesions can be metaplastic or neoplastic events. The neoplastic entities -formerly, oncogenic variant of follicular tumours; Hürthle cell neoplasm (HCN) - include HC adenomas and HC carcinomas and have been recognized as a separate class of tumours by the WHO. The remaining of the thyroid tumours demonstrating “mitochondrion-rich cells” and oncogenic morphology are referred under the umbrella term of “oncocytic variant”. However, this rigid separation between the two groups of tumors, characterized by the presence of a mitochondrial-rich cytoplasm, is not clarified, and is not universally accepted. This brings the question if the “oncocytic cells” are different from “mitochondron-rich cells”, or if they represent a sort of continuum? Thus, we conducted a comparative transcriptomics, proteomic and CNV analysis in the group of HCNs vs mitochondrial-rich non-Hürthle thyroid tumours (other thyroid tumours demonstrating oncogenic morphology).

Methods
Eighteen thyroid tissue samples obtained from the biobank of the pathology department. The cohort of 12 HCN (7 HCC, 5 HCA) and 6 non-HCNs (2 PV-PTC, 3 WT-UMP, 1 NIFTP with oncogenic morphology). We have compared the groups HCNs vs non-HCNs. RNA was sequenced using Ion AmpliSeq Transcriptome Human Gene Expression Kit and analysed using Transcriptome Analysis Console Software. For proteomic analysis, liquid Chromatography Analysis/Mass Spectrometry were done using the software Proteome Discoverer 2.4.0.305. Shallow whole-genome sequencing of DNA samples was performed using Illumina platform. BWA was used to map sequencing reads to human reference. Then QDNNaseq was used to access the CNV among the genome regions. Enrichment analyses was performed for RNA, proteomic and CNV, with package enrichGO and with annotation of the org.Hs.eg.db package. For all plots, R and the package ggplot2 were used. Statistical analyses were performed also using R, in particular the nonparametric Wilcoxon rank-sum test.

Results
The mitochondrial translation system related pathways for RNA sequencing, extracellular matrix related, metabolic process and immune response related pathways, for proteomics and plasticity related pathways for CNV analysis were found to be significantly increased in the HCN. HCN display, a higher number of gains (chromosomes 2, 4 and 12, $P<0.0001 – 0.004$) and lower number of losses (chromosome 3, $P<0.001 – 0.004$) when compared with the non-Hürthle group.

Conclusions
Our results revealed some significant differences between the two groups in the omics platform and in the CNV analyses. Our results suggest that HCNs vs mitochondrial-rich non-Hürthle thyroid tumours may be just “different phases” of a spectrum that ends with the Hürthle cell phenotype.

DO: 10.1530/endoabs.84.OP-07-33

OP-07-34
CDK4 phosphorylation status and rational use of CDK4/6 inhibitors in advanced thyroid cancers
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Endocrine Abstracts (2022) Vol 84
Introduction and objectives
The cyclin-dependent kinases CDK4 and CDK6 are key regulators of the cell cycle entry, by phosphorylating the onco-suppressor retinoblastoma protein (pRb). CDK4/6 inhibitors (CDKi) are already established as standard first-line treatment in advanced estrogen receptor-positive breast cancers. Some have emerged as novel drugs to treat various pRb-proficient chemotherapy-resistant cancers. Presence of activating T172-phosphorylation of CDK4 in breast tumors correlates with their sensitivity to the CDKi palbociclib (Roscup®; EORTC-C-EMBO Med Med. 2017; 9,1052-1066). The molecular characterization of metastatic differentiated (DTC), poorly differentiated (PDTC) and anaplastic thyroid carcinomas (ATC) suggests that CDKi could be considered for treating advanced thyroid cancers. We aimed to investigate the CDKi activation state in thyroid cancer and its relationship with the sensitivity to CDKi.

Methods and results
Sensitivity to three CDKi was assessed (by BrDU incorporation and viability assays) in 11 ATC-, 2 PDTC- and 7 WDTC-derived cell lines. All except 3 cell lines were sensitive to CDKi with either full or partial inhibition of DNA synthesis. CDKi post-translational modifications were investigated using 2D-gel electrophoresis. As seen previously in breast cancer, detection of CDKi T172-phosphorylation also predicted sensitivity to CDKi in thyroid cancer cell lines. The three resistant cell lines were characterized by barely detectable pRb phosphorylation and high expression of CDKi inhibitor p16, whereas in all sensitive cell lines, phosphorylated pRb was detected. A cohort of fresh-frozen primary tissues was also analyzed by 2D-gel electrophoresis. Consistent with their quiescent state, phosphorylated CDK4 could not be detected in 14 of 17 non-malignant thyroid tissues. CDKi phosphorylation was detected in 29 of 32 DTC, in 8 lymph node metastases, in 17 of 19 PDTC and in 12 of 20 ATC. Analysis by RNA-sequencing revealed that in comparison to tumors with CDKi-phosphorylated tumors without phosphorylated CDKi presented lower pRb levels and the tumors with high p16 levels. However, no pRb mutations were found in these samples. Palbociclib combination with MEK/RAF inhibitors as evaluated by clonogenic assay was highly effective, being able to completely arrest proliferation. The combined drugs were shown to prevent known resistance mechanisms, most notably Cyclin E/CDK2 activation, as observed by immunoprecipitation assays.

Conclusion
The presence of the phosphorylated CDKi (the actual CDKi target) and the inhibition of all ATC cancer cell lines supports CDKi as a very promising option to treat or control at least some ATC, which presently are incurable and lead to patients death within few months.

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OP-07-35
RET fusion genes in a large cohort of papillary thyroid carcinomas
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Objectives
RET fusion genes are known driver mutations in papillary thyroid carcinomas (PTCs) and have been described mainly in pediatric PTCs, in which they represent the most common genetic alteration. The aims of this study were to identify RET fusion genes in PTCs (from pediatric as well as adult patients), to correlate them with clinical and histopathological features and to determine the prognostic significance of RET fusion genes based on long-term follow-up of patients with PTC harboring this mutation.

Methods
The cohort consisted of 920 PTC samples (fresh frozen tissues) from pediatric and adult patients. Based on the detected mutation, samples were triaged. Samples positive for the BRAF, HRAS, KRAS, NRAS or NTRK fusion gene mutations were excluded from the further RET fusion gene analyses. Samples were analyzed for the presence of RET fusion genes using Real-Time PCR (LC480, Roche) or using the FusionPlex Comprehensive Thyroid and Lung panel ( ArcherDx) by next generation sequencing (MiSeq, Illumina).

Results
RET fusion genes were detected in 108 (11.7%) PTCs, from which 34/121 (28.1%) were from pediatric and adolescent patients (7-20 years old) and 74/799 (9.3%) were from adult patients. The mean age of diagnosis was 33.0 ± 17.1 years. A total of 20 types of RET fusions were found, including the following partner genes: CCDC6, NCOA4, PKEKL1, SQSTM1, HRAS, BASH2, PPP, ACROS5, RUFY2, BBIP1, APAF1, 12, AKAP13, TRIM27, SPECC1L, FBXO41, GOLGA5, SSRP2, ZMY2, ERC1, KIAA1217. The RET fusion-positive carcinomas were associated with infiltrative tumor growth, numerous intra-thyroid micrometastases, psammoma bodies, lymph node and distant metastases. Lymph node metastases were found in 31/34 (91.2%) pediatric cases and in 52/71 (73.2%) adult patients. Distant metastases were identified in 9/34 (26.5%) pediatric patients and in 11/69 (15.9%) adult patients. Patients responded well to radiodine treatment, radiodine-refractory PTCs harboring RET fusions were rare. Three patients (2.8%) died of the disease, in two cases was carcinoma positive for NCOA4/RET and in one case for CCDC6/RET with a TERT C250T co-alteration.

Conclusion
In summary, RET fusion genes are an important genetic marker in PTCs associated with aggressive tumor behavior and frequent metastases. RET fusions occurred approximately three times more frequently in pediatric and adolescent patients, in which carcinomas were more advanced, than in adult patients. In conclusion, the genetic molecular testing of RET fusions is important for patient’s diagnosis and prognosis and also for possible targeted therapy.

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OP-07-36
Loss of tumor cell MHC class II expression as driver of relapse to dabrafenib and trametinib in mouse BRAF-mutant anaplastic thyroid cancer
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Objectives
BRAFV600E, anaplastic thyroid carcinomas (ATCs) show remarkable responses to dabrafenib and trametinib (dab/tram) in an effect that may be in part immune-mediated. Murine BRAFV600E-ATCs regress upon BRAF inhibition. We find that recurrences are frequent and associated with loss of Mhc class II (MHCII) expression. Our goal was to investigate the mechanisms of loss of antigen presentation by tumor cells and whether this contributes to disease recurrence.

Methods
We developed primary ATC cell lines from mouse dox-inducible Braf-ATCs (TPO-Crel;LSL-rTA, GPPt Tet-O-myc.BRAFV600E;p53flx (BRAFp53) as well as ATC lines derived from recurrent tumors arising in mice after dox-withdrawal. A syngeneic orthotopic model with BrafV600E/Tp53– (TBP7343) ATC cells was developed. RNAseq of Braf/p53 ATC cells from mice treated with or without dox and from dab/ tram or vehicle treated TBP7343 ATCs was performed.

Endocrine Abstracts (2022) Vol 84
Oral Session 8: Basic 2  
OP-08-37  
Resistance to thyroid hormone alpha: molecular, biochemical and physiological approach to diagnosis and therapy

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BRAF V600E in ATC cells but the combination fails to induce MhcII in recurrences. Dox withdrawal or dab/tram treatment resulted in ATC infiltration by CD4 helper cells and increased MhcII expression in tumor cells. RNAseq of ATC cells showed activation of IFNγ transcriptional output and of the antigen presentation pathway (MhcII > MhcI). IFNγ induced MhcII expression in primary cell lines upon MEK inhibition with trametinib but this was ineffective in recurrent cell lines. Loss of induction of MhcII in recurrences was not due to incomplete ERK pathway inhibition or to interference with upstream IFNγ signaling. Recurrent cell lines had markedly attenuated basal and IFNγ induced expression of Ciita, the master transcriptional regulator of genes in the MhcII signaling pathway. We developed homozygous CRISPR KO of Ciita in TPB3743 cells to study the impact of Ciita loss in vivo. Ciita KO cells lost expression of MhcII in vitro and in vivo, which did not impact tumor growth but rendered the Ciita+ TPB3743 cells completely refractory to dabrafenib treatment.

Conclusions (i) IFNγ induction of MhcII expression requires MEK inhibition in primary BRAFV600E-ATC cells but the combination fails to induce MhcII in recurrences. (ii) Absence of MhcII expression is associated with attenuated Ciita expression. (iii) In Ciita GniezKO TPB3743 ATC cells MhcII expression is absent and Ciita+ ATCs are resistant to dabrafenib in vivo.

Objectives
THRA mutations cause Resistance to Thyroid Hormone α (RTHα), an under-diagnosed disorder with hypothyroid features but near-normal thyroid function tests (TFTs). We developed a pathway, combining molecular analyses, new biomarkers and physiological measurements, to better diagnose and treat this disorder.

Methods
Structural and functional analyses of THRA variants, discovered by next generation sequencing in specific projects (eg 100K Genome, Deciphering Developmental Delay, Genetics of Obesity study) or unbiased investigation of patients, identified an RTHα cohort (n = 32). In this cohort, we measured plasma metabolites or proteins and analysed facial images using artificial intelligence (AI) to differentiate RTHα from controls. We measured resting energy expenditure (REE) during thyroxine therapy of the disorder.

Results
17 different, heterozygous THRA variants, in individuals investigated for diverse causes (growth retardation, developmental delay, autism, dysmorphic facies) localised to the hormone binding domain of TRα, with 14 being homologous to THRβ mutations causing RTHβ. Varying transcriptional impairment or morphological and skeletal abnormalities when variants were expressed in mammalian cells or developing zebrafish and reduced THRA expression in specific projects (eg 100K Genome, Deciphering Developmental Delay, Genetics of Obesity study) or unbiased investigation of patients, identified an RTHα cohort (n = 32). In this cohort, we measured plasma metabolites or proteins and analysed facial images using artificial intelligence (AI) to differentiate RTHα from controls. We measured resting energy expenditure (REE) during thyroxine therapy of the disorder.

Conclusions
Different, heterozygous THRA variants, in individuals investigated for diverse causes (growth retardation, developmental delay, autism, dysmorphic facies) localised to the hormone binding domain of TRα, with 14 being homologous to THRβ mutations causing RTHβ. Varying transcriptional impairment or morphological and skeletal abnormalities when variants were expressed in mammalian cells or developing zebrafish and reduced THRA expression in specific projects (eg 100K Genome, Deciphering Developmental Delay, Genetics of Obesity study) or unbiased investigation of patients, identified an RTHα cohort (n = 32). In this cohort, we measured plasma metabolites or proteins and analysed facial images using artificial intelligence (AI) to differentiate RTHα from controls. We measured resting energy expenditure (REE) during thyroxine therapy of the disorder.
OP-08-38

Brain effects of combined levothyroxine (T4) and 3-iodothyronamine (T1AM) replacement therapy in a murine model of hypothyroidism

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Adult-onset hypothyroidism is associated with cognitive dysfunction, and a significant fraction of hypothyroid patients still shows persistent disturbances despite standard T4 replacement therapy. Experimental results showed that tissue levels of T4 metabolites, particularly T1AM, are decreased in hypothyroidism and remain low after T4 replacement. Thyroid hormones are important for the promotion of neurogenesis and neuron migration to different areas of the cerebral cortex, including hippocampus, and it is known that hippocampus-dependent memory is impaired in the hypothyroid mice. We aimed to evaluate the effects of hypothyroidism and different replacement treatments on neurogenesis in the subgranular zone of the dentate gyrus (SGZ). Six-week-old C57BL/6J male mice were given methimazole and potassium perchlorate (0.20 mg/g/day and 0.30 mg/g/day) in drinking water for 49 days while the control littermates received water. At day 21 mice were implanted with subcutaneous ALZET® osmotic pumps delivering replacement treatments for 28 days. Animals were divided in 4 groups: euthyroid; hypothyroid; hypothyroid treated with T4 (0.04 µg/kg BW/die); hypothyroid treated with T4 + T1AM (0.04 µg T4 & 0.004 µg T1AM/kg BW/die). Specific markers were used to quantify cell proliferation (Ki67) and the presence of neuroblasts/immature neurons (doublet/cortin-DCX) through immunofluorescence analysis performed in the SGZ. Then, following hippocampal RNA isolation, we analyzed gene targets involved in neurogenesis pathway using a PrimePCR pre designed 96-well collection panel (BioRad). A 49-day period of adult-onset hypothyroidism induced a reduction of around 20% in the number of DCX-positive newly generated cells. Compared to hypothyroidism, T4 treatment increased the number of cells by 45.58% (mean diff = -106.9; P < 0.05) while the T4 + T1AM treatment produced a 58.20% increase (mean diff = -141.6; P < 0.01). One-way ANOVA revealed a global significant effect among the 4 groups (P = 0.003). Real time PCR highlighted significant changes in the expression of genes related to neurogenesis as ANOVA revealed an upregulation in the expression of Ngf, Kdr, Nif1, Mapk1/3 and Neurog2 genes in T4 + T1AM treated mice compared to T4 treated mice (P < 0.05). Our results indicate that cognitive dysfunctions related to adult-onset hypothyroidism could be due in part to impaired hippocampal neurogenesis. Cellular markers and gene expression analysis suggest the presence of underlying molecular mechanisms activated only by the combination of T4 and T1AM. Further investigations are required to elucidate the potential pathophysiological and clinical relevance of these findings.

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OP-08-39

Stochastic epigenetic mutations as possible explanation for phenotypical discordance among twins with congenital hypothyroidism

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Congenital Hypothyroidism (CH) is the most common congenital endocrine disorder and one of the leading cause of intellectual and motor disability and abnormal thyroid function tests. The critical, particularly during the first half of pregnancy when the fetal thyroid gland is immature. Transcellular transport of thyroid hormones (TH) is facilitated by TH transporters. Monocarboxylate transporter 8 (MCT8) is a specific TH transporter that is crucial for transport of TH with a prominent expression at the blood-brain barrier. MCT8 deficiency is a rare disorder consisting of severe intellectual and motor disability and abnormal thyroid function tests. The transporter facilitating trans-placental TH transport is unknown. With the blood-brain barrier maturing around 18 weeks, the placental barrier may be as relevant as the blood-brain barrier for regulation of TH bioavailability for the fetal brain. We hypothesized that, should MCT8 be relevant in the placenta (a fetoplacental barrier), defective trans-placental transport of TH in MCT8 deficiency could be another additive mechanism of the disease, which might be overcome by the 3,5,3′-triiodothyronine (T3) analogue 3,5,3′-triiodothyroacetic acid (TRIA3). Methods We tested T4 transport in human term placentas using an ex vivo placental perfusion model. We added 10 µM silchristin (a MCT8-specific inhibitor) to

Endocrine Abstracts (2022) Vol 84
mimic MCT8 deficiency or vehicle as control, together with 100 nM T4 in the maternal circulation of the perfusion system. Samples were taken from both maternal and fetal circulations at different time points during a 3-hour perfusion. Next, we tested whether 100 nM TRIAC was able to cross silychristin-treated (‘MCT8-deficient’) placentas. T4 and reverse T3 (rT3) concentrations in perfusates were measured by radioimmunoassays. TRIAC concentrations were measured by liquid chromatography-mass spectrometry (LC-MS/MS).

Results

Maternal-to-fetal T4 transfer was substantially reduced in the presence of silychristin (with 4.2 ± 1.2 nM vs 10.6 ± 0.6 nM (control) (P < 0.01) fetal T4 after 3h-perfusion). TRIAC maternal-to-fetal transfer was achieved with TRIAC appearing in the fetal circulation (0 nM to 17.1 ± 2.5 nM after 3h-perfusion).

Conclusions

MCT8 has a major role in maternal-to-fetal T4 transport. Possibly, impaired transport of T4 across the placenta in MCT8 deficiency is a key element in disturbing early fetal brain development. TRIAC is efficiently transported across the placenta and may provide preclinical support for future clinical studies of TRIAC treatment in mothers carrying fetuses with MCT8 deficiency.

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OP-08-41

BOREALIN/CDC8A is necessary for an adequate thyroid morphogenesis and aging

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Background

Previously, we identified a novel gene, BOREALIN/CDC8A in congenital hypothyroidism. Patients with BOREALIN mutations had thyroid dygenesis, from asymmetric lobes to athyreosis (Carré et al. Hum Mol Genet 2017). Borealin is a major component of the Chromosomal Passenger Complex, an essential regulator of mitosis. We demonstrated a new feature of BOREALIN: involvement in the adhesion and the migration of the thyrocytes.

Objective

Further understand the role of Borealin in thyroid development and function.

Methods

Borealin+/- mice were studied during development, at 4 and 18 months. Borealin/- mice were not available because they die at E5.5. We documented thyroid morphology, performed immunohistochemistry with thyroid markers (Nkx2-1, Thyroglobulin, T4) and we analyzed the thyroid function. We used a well-established model with antithyroid drug induced hypothyroidism which was applied to the Borealin+/- and wild-type mice.

Results

First of all, Borealin+/- mice did not develop hypothyroidism at the adult stage (4-month-old) but they were significantly more sensitive to antithyroid drugs with a more profound hypothyroidism (T4: 41% less for Borealin+/- vs wild-type, P < 0.001). Four month-old Borealin+/- showed more hyperplasia with larger follicles surfaces in comparison with wild-type thyroid (P < 0.005). Thus, the Borealin+/- mice remain euthyroid at the expense of developing goiters. For elder mice, thyroid morphology of Borealin+/- was altered with heterogeneity in size of follicles with predominantly very large follicles and thyroids significantly more hyperplastic compared with wild-type (0.34 mg/g thyroid weight/animal weight vs 0.23 mg/g, P < 0.05). We found that thyroids of Borealin+/- were significantly hyperplastic at E9.5 in comparison with wild-type, and hypoplastic from E11.5 to E17.5 (P < 0.05). Thyroid development thus was abnormal in Borealin+/- compared to wild-type. In addition, transcriptome analysis of thyroids were performed at different stages. Specific pathways were disturbed in Borealin+/- thyroids at E13.5, at 4 and 18 months, mainly adhesion and motility pathways. At 18 months, Borealin+/- thyroid are enriched in cytoskeleton, cell cycle and thyroid cancer gene sets compared to wild-type.

Conclusions

Borealin is involved in crucial steps of the thyroid lifetime cycle. These data demonstrate the involvement of Borealin in the structural organization of the thyroid gland and consolidate the role of Borealin in thyroid development and function, which supports its involvement in thyroid dysgenesis of patients with congenital hypothyroidism. Impaired Borealin function plays also a role in morphologic deregulation in thyroids along time.

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OP-08-43

Novel somatic mutations in sporadic MTC (spMTC); clinical utility of NGS in precision medicine

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Objectives

Childhood papillary thyroid cancer (CPTC) often presents with advanced disease but rarely causes specific mortality (CSM). Controversy remains regarding optimal management and association with non-thyroid second primary malignancies (NSPM). We analyzed outcome in 189 CPTC patients and assessed the influence of radioiodine remnant ablation (RRA) and the utility of the American Thyroid Association risk-groups (ATA-R) in predicting tumor recurrence (TR).

Methods

All patients were operated by specialist surgeons. 88% had bilateral thyroidectomy (BT); at first surgery 86% had neck nodes removed, 17% had pT4a tumors and 78% were pN1, 58% with 5 or more regional metastases (RM). During 1951-2020 RRA was given to 43% of TNM stage I patients having BT with curative intent. Mean follow-up was 29 yr (range 1-71). TR and CSM details were derived from a computerized database and analyzed as previously described (WJS 43: 329, 2018).

Results

During 1936-50, 9/19 died from cancer; one from PTC and 8 from NSPM (7 having received radiation therapy); 15 died from all causes, as compared to expected 6 (P < 0.001). During 1951-2000 none of 170 patients died of PTC but 3 died of NSPM.13 died from all causes, as compared to 13 expected (P = 0.97). In 169 patients operated with curative intent 25-yr TR rate was 37%; 57 patients (34%) had recurrence:81% RM and 19% distant metastases (DM). Patient ages <11 and pT4a tumors were significantly (P < 0.05) associated with postop RM; tumor size >4 cm and pT4a tumors with postop DM (P < 0.002). BT + RRA did not significantly improve the 20-yr TR rates of 28% and 3% seen with BT alone for RM (P = 0.75) and DM (P = 0.99). We applied the ATA-R to 167 patients who had no DM at presentation and had complete tumor excision. 61 were classed as ATA high-risk, 49 as intermediate and 57 as ATA high-risk. 25-yr TR rates for low, intermediate, and high-risk groups were 24%, 34% and 53% (P = 0.0015). 25-yr rates for RNM and DM for the 3 risk groups were 19, 34 and 40% (P = 0.005) and 0, 4 and 19% (P < 0.001).

Conclusions

During the 11th era (1951-2020), we have noted no excess all-causes mortality in CPTC but we have not found that RA reduces postop TR after BT. Given that 78% present with pN1 disease, persistent/recurrent disease within RNM may be expected. The ATA-R high-risk group seems capable of predicting DM; perhaps in future years many CPTC patients classed as low-risk may require less than BT.

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OP-09-42

Childhood papillary thyroid carcinoma: long-term postoperative outcome and prediction of recurrent disease in 189 patients consecutively treated at the mayo clinic during 1936 through 2020

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Dynamic risk stratification in long-term clinical outcome of papillary thyroid cancer patients

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Introduction and Objective

The initial assessment of differentiated thyroid cancer (DTC) patients is based on the American Thyroid Association (ATA) risk stratification criteria. Dynamic risk stratification (DRS) of DTC patients takes into consideration the response to initial treatment being reassessed at 1–2 years and revealed significant shifts in the risk categories of DTC patients. We aimed to evaluate the long-term outcome of papillary thyroid cancer (PTC) patients according to the ATA risk class and DRS at the first follow-up.

Methods

We retrospectively evaluated 704 patients with low (n = 372) and intermediate (n = 332) risk PTC. At the first follow-up patients were divided in four subgroups according to the response to the initial therapy: excellent response (ER) 320/372 (86%), biochemical incomplete response (BIR) 31/372 (8.5%), indeterminate response (IR) 11/372 (3%), and structural disease (SD) 10/372 (2.7%) in low-risk group and ER 202/332 (60.8%), BIR 51/332 (15.4%), IR 23/332 (6.9%), SD 56/332 (16.9%) in intermediate-risk group.

Results

After a median follow-up of 9 years in the excellent subgroup of PTC patients, persistent remission was observed in 98.8% of low-risk patients and in 93.1% of intermediate-risk patients, while recurrent disease was observed in 1.2% of low-risk patients and in 6.9% of intermediate-risk patients (P = 0.005). The BIR patients showed an excellent response in 58% of cases in low-risk group and in 33.3% of cases in intermediate-risk group (P = 0.038). The rate of persistent disease (BIR + SD) was significantly higher in intermediate-risk patients than in low-risk patients (66.7% vs 42%, respectively) due to the higher rate of SD in intermediate-risk than in low-risk patients (15.7% vs 6.5%, respectively).

All patients with IR had an excellent response at the last follow-up, regardless of the initial ATA risk class. Finally, in patients with SD, after additional treatments, the rate of excellent response was only slightly not statistically significant between low and intermediate risk group (80% vs 46.4%, respectively) (P = 0.08).

Conclusions

The long-term outcome according to the dynamic risk stratification of PTC patients is still poorly characterized. In our study we found a better clinical outcome of low-risk PTC patients for each subgroup of response to initial therapy, suggesting that the initial ATA risk class should be taking into account in the long-term management of PTC patients.

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OP-09-45

The phenotype correlated with RET V804 germine mutation is characterized by the presence of medullary thyroid cancer alone

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Background

Genotype-phenotype correlations between various RET mutations and clinical manifestations of MEN 2 syndrome are well established. A discussion is still open if the FMTC phenotype really exists or if it is just a MEN2A variant. Aim of this study was to verify if the phenotype corresponding to the V804M germline mutation is restricted to FMTC.

Methods

During the last 25 years, we have identified 200 families with a hereditary form of MTC and 993 subjects have been studied for the presence of a RET germline mutation. Among these families, 43 had a Cys634 mutation, 32 had a Cys mutation in exon 10, 15 had the M918T mutation and 110 cases had a RET mutation at non cysteine codons. Among these latter 54 families had a V804M/1 germline mutation. All patients were annually submitted to clinical and biochemical examinations (e.g., abdomen ultrasound, plasma and urinary
epinephrine and norepinephrine, serum parathyroid hormone, vitamin D and calcium measurements) to ascertain any parathyroid and adrenal gland involvement.

Results
A total of 226 subjects have been screened: 54 subjects were index cases, 97 were RET gene carriers and 75 were negative for the presence of any RET germline mutation. Only 3 families showed the presence of additional endocrine neoplasia. In one family there was 1 subject with parathyropharyndysis that was cured with the surgical removal of one single parathyroid adenoma. In another family, a second germline mutation of TMEM127 was found correlating with the presence of pheochromocytoma even in family without RET germline mutations. The third family showed several cases with both MTC and pheochromocytoma but the genetically analysis did not find any other gene alteration in genes commonly involved in familial pheochromocytoma. However, the genealogic tree clearly showed a strict segregation of MTC and pheochromocytoma in one branch of the family while the other had only MTC.

Conclusions
These data strongly support the possibility that in these 3 families MTC was incidentally associated with other endocrine neoplasia. If this the case, the V804 mutation correlates with MTC and there is no reason to screen gene carriers for pheochromocytoma and hyperparathyroidism.

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OP-09-46
Interim outcome analysis of prospective ATA recurrence risk (RR) stratification for postoperative treatment and follow up of differentiated thyroid cancer (DTC)
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Objective
The 2016 ATA RR assessment recommendations for patients with DTC were based on retrospective studies. We present the first outcomes of a prospective assessment of thyroid cancer management according to the ATA RR stratification.

Methods
Using the Calgary prospective thyroid cancer database, we identified 612 patients with differentiated thyroid cancer (DTC) treated at our centre between April 2017 and December 2021. Each case was reviewed by the thyroid cancer (endocrinology) triage group and patients were prospectively assigned a modified ATA recurrence risk and AJCC 8th edition stage. Initial risk stratification guided the indication of radiodine dose and other adjuvant therapies. Patients were assessed for their response to treatment (RRT) at 6, 12, and 24 months postoperatively.

Results
The 612 patients of our study cohort comprise 435 (71%) females and 177 (29%) males with a median age at diagnosis of 48 years. Of these patients, the ATA recurrence risk was as follows: low-risk n = 323 (55%), intermediate-risk n = 178 (29%), high-risk n = 111 (18%), 280 patients (46%) received total thyroidectomy (TTX) and radiodine (RAI), 230 (38%) received TTX only, and 102 (17%) received lobectomy alone. 542 patients (89%) had at least 1-year follow-up. The RRT at 1 year was excellent response to treatment (IERT) in 86% of patients with lobectomy, 75% for patients with TTX only, and 53% for TTX & RAI (Table 1). Among the patients who were initially deemed to be low risk of recurrence, 79% had ERT, 17% had undeterminate response (IERT), 3% had biochemical incomplete response (BIR), and 1% had structural incomplete response (SIR). These are significantly better interim outcomes compared to the intermediate-risk group, which showed 60% ERT, 26% IERT, 7% BIR and 7% SIR. Lastly, the high-risk group had the worst outcomes, with 42% ERT, 18% IERT, 11% BIR, and 29% SIR.

Conclusions
The 2015 ATA risk stratification system is a useful tool for predicting disease status at 1-year post-treatment in patients with DTC. The 2015 ATA guidelines and modified ATA recurrence risk stratification treatment recommendations reduce thyroid cancer overtreatment by including lobectomy as a definitive treatment option for low-risk thyroid cancers and selective use of RAI for intermediate and high-risk patients.

Table 1. RRT at 1-Year Evaluation for 542 Patients who had TTX/lobectomy and one-year follow-up

<table>
<thead>
<tr>
<th>Patients Number</th>
<th>TTX + RAI</th>
<th>TTX only</th>
<th>Lobectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERT</td>
<td>363 (67%)</td>
<td>126 (23%)</td>
<td>157 (75%)</td>
</tr>
<tr>
<td>IRT</td>
<td>107 (20%)</td>
<td>59 (22%)</td>
<td>38 (18%)</td>
</tr>
<tr>
<td>BIR</td>
<td>30 (6%)</td>
<td>21 (9%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>SIR</td>
<td>42 (8%)</td>
<td>34 (14%)</td>
<td>7 (3%)</td>
</tr>
</tbody>
</table>

All 542 240 (44%) 209 (39%) 93 (17%)

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OP-10-47
Putative protective role of anti-nuclear antibodies in Graves’ orbitopathy
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Objectives
A sporadic association between thyroid and non-organ-specific autoimmunity has been reported, which could be relevant for Graves’ orbitopathy (GO), an autoimmune disease affecting orbital connective tissue. We investigated whether there is an association between GO and anti-nuclear antibodies (ANAs).

Methods
We performed a cross-sectional investigation in 265 consecutive patients with Graves’ disease (GD) who came to our observation over 36 consecutive months to undergo radioiodine treatment. One-hundred and fifty-eight of them had GO, whereas 107 had no GO. The primary outcome was the prevalence of ANAs in patients with GO vs those without GO. The secondary outcomes were: 1) relationship between ANAs and GO features; 2) prevalence of ANAs in GD patients with GO vs those without GO. The secondary outcomes were: 1) relationship between ANAs and GO features; 2) prevalence of ANAs in GD compared with nonautoimmune hyperthyroidism, namely 78 consecutive patients with toxic nodular goiter (TNG) who came to our observation over the same period to undergo radioiodine treatment.

Results
ANAs were detected in 212 (80%) GD patients, in all cases at low titres, namely 1:80 (98 patients, 46.2%) and 1:160 (114 patients, 53.7%). The prevalence of detectable ANAs did not differ between patients with GO (79.7%) and those without GO (80.3%); OR 0.95; 95% CI from 0.51 to 1.77 (P = 0.88). However, the prevalence of patients with higher ANA titres (1:160) was greater in GD patients (51.5 vs 38.3%), although the difference was only nearly statistically significant (OR 0.58; 95% CI from 0.33 to 0.9; P = 0.077). Within GO patients, proptosis was significantly lower in ANA-positive patients (mean difference -1.42; 95% CI from -2.51 to -0.32; P = 0.0011). Although CAS and eyelid aperture were lower in ANA-positive patients, the difference was only nearly statistically significant (OR 0.58; 95% CI from 0.33 to 1.02; P = 0.059). Within GO patients, proptosis was significantly lower in ANA-positive patients (mean difference -1.42; 95% CI from -2.51 to -0.32; P = 0.0011).

Conclusions
Within GD, ANAs are not more frequent in GO. However, they seem to exert a protective role on GO severity and on thyroid autoimmunity in general. A possible explanation is that ANA-related autoimmunity has an immunological phenotype different from the one of thyroid autoimmunity, in which ANA-positive patients may...
have a switch of the T-cell population that could result in a milder clinical GO picture. Further studies are needed to investigate the mechanisms underlying our observations.

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OP-10-48
ABSTRACT WITHDRAWN

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OP-10-49
TSH-receptor antibodies among 1,024 early pregnant women in the north denmark region: cut-off, prevalence, and follow-up

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Objectives
Measurement of TSH-receptor antibodies (TRAb) in hyperthyroid, pregnant women is an important tool when distinguishing between the autoimmune Graves’ disease and the physiological gestational hyperthyroidism. Evidence to support a cut-off for TRAb during early pregnancy is needed along with information on the frequency and follow-up of TRAb-positive as opposed to TRAb-negative hyperthyroidism.

Methods
Within the North Denmark Region Pregnancy Cohort (2011-2015), TRAb was measured (BRAHMS TRAK Human, Kryptor Compact, Thermofisher Diagnostics) in stored blood samples from the early pregnancy among all women with low TSH (Table). TRAb-positive women had lower TSH, TSH, and TRAb-negative women had higher TSH, higher free T4, and lower β-hCG, and they less often terminated the pregnancy with live birth. Among women with low TSH and no known thyroid disease (n=414), maternal follow-up after the pregnancy showed that diagnosis of thyroid disease was more frequent among TRAb-positive (52.5%) as compared to TRAb-negative women (8.4%).

Conclusions
In a large cohort of Danish pregnant women, most women with low TSH in early pregnancy were TRAb-negative and rarely later diagnosed with thyroid disease. The results warrant further studies on TRAb in early pregnancy to substantiate a cut-off for TRAb in early pregnancy and to extend the findings on prevalence and follow-up.

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OP-10-50
Outcomes of lenvatinib therapy in poorly differentiated thyroid carcinoma

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Introduction and objectives
Poorly differentiated thyroid carcinoma (PDTC) is a rare but aggressive thyroid tumor. PDTC frequently presents in advanced stages and conventional treatments are usually less effective than in differentiated thyroid carcinoma (DTC). Lenvatinib is a multi-kinase inhibitor approved for the treatment of radioiodine-refractory DTC, with significant improvement in progression free survival. Despite the inclusion of a minority PDTC patients in SELECT trial, specific studies have been scarce. We intend to share the results of real-world PDTC patients under lenvatinib therapy.

Materials and methods
Retrospective study of all PDTC patients treated with lenvatinib between 2019 and 2021 in our institution. Histological diagnosis were reviewed according to the Turin criteria. Stable disease (SD), partial and complete response (PR and CR) were assessed on computed tomography studies, performed every 3 months. The following clinical end-points were analyzed: median overall survival (OS), disease specific survival (DSS), progression-free survival (PFS), best overall response (BOR), disease control rate (DCR) and duration of response (DoR).

Thyroglobulin (Tg) levels were measured every 1-3 months.

Results
7 patients, 5 females, with median age at diagnosis of 58yr (IQR 12) and median age at lenvatinib start of 61yr (IQR 10). Two patients had inoperable disease and 6 had distant metastasis (lung, liver and bone). Previous treatments were performed in 5 patients: neck surgery and radioiodine therapy (n=5), neck radiotherapy (n=3) and sorafenib (n=2). The 2 patients with inoperable disease were treated with lenvatinib in neoadjuvant setting. Six patients had measurable Tg before treatment. Median follow-up was 22 months (IQR 19) and mean duration of lenvatinib therapy was 10.4 ± 6.9 months. Mean starting dose and mean overall dose were 15.1 ± 5.1 mg/day and 15.9 ± 4.6 mg/day, respectively (P=0.438). The median OS was 12 months (IQR 1) and DSS was 85.7% between 3 and 9 months and 66.7% at 12 months. Two patients died due to progression of disease.

The median PFS was 9 months (IQR 6) and mean Tg-based PFS was 8.8 months. The BOR was SD with a DCR and relative PFS of 100%, 60% and 50% at 3, 6 and 12 months of follow-up, respectively. The median DoR was 6 months (IQR 6) and mean Tg-based DoR was 7.8 months.

Conclusion
Lenvatinib has shown consistent results in radioiodine-refractory thyroid cancer. However, real-world analysis are still scarce. Our work specifically directed to PDTC revealed encouraging results in this otherwise orphan population. We encourage the design of prospective studies to evaluate multi-kinase inhibitors in the treatment of PDTC, which can increase therapy approaches and allow significant increase in outcomes.

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OP-10-51
Hypocalcemia is a frequent and life-threatening effect during lenvatinib treatment

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Early pregnancy hyperthyroidism (TSH < 0.1mIU/l)

<table>
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<th>Metric</th>
<th>Median</th>
<th>95% CI</th>
<th>Median</th>
<th>95% CI</th>
<th>p-value</th>
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<td>TSH (mIU/l)</td>
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<td>β-hCG (IU/l)</td>
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Endocrine Abstracts (2022) Vol 84
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**Objectives**

Lenvatinib treatment is responsible for several adverse events (AEs). Hypocalcemia has been described in the registration study in 7% of patients, being of grade ≥ 3 in 2.7% of cases. No real-life studies are available, and the actual impact of this AE during Lenvatinib treatment is still unknown. Aim of our study is to evaluate the frequency of hypocalcemia in our series of patients treated with Lenvatinib and the possible predictors of this side effect.

**Methods**

We included all patients who were treated with Lenvatinib for progressive radioiodine refractory thyroid cancer at our Institution. We excluded patients who had a follow-up of less than 6 months and for whom information about calcium levels was not available.

**Results**

We included 25 patients who received Lenvatinib treatment for a mean of 29 months (range 6-68 months). Hypocalcemia was recorded in 6/25 patients (24%) and it was of grade ≥ 3 in 2/25 patients (8%). Hypocalcemia occurred after a mean of 5 months (range 0.5-13 months) from the start of Lenvatinib. It was managed with calcium oral supplementation or intravenous treatment, when necessary, and Lenvatinib was transiently withdrawn in 2/6 patients. No significant differences were found among who developed and who did not develop hypocalcemia in terms of gender (females were 50% and 57.9% respectively), age at start of Lenvatinib (69.8 vs 65.9 years old), starting dose of Lenvatinib (mean dose was 17.7 mg vs 16.6 mg), length of treatment (mean duration was 23 vs 31 months), post-thyroideectomy hypoparathyroidism (16.7% vs 10.5%). All patients who had hypocalcemia and for whom a bone densitometry evaluation was available had osteoporosis (3/3), while among patients who did not experience hypocalcemia 4/6 (66.7%) had osteoporosis (P=0.28). Finally, 2 patients with normal post-surgical PTH levels, developed a grade ≥ 3 hypocalcemia with low (12.6 ng/l) or inappropriately normal (46.9 ng/l, n.v.13-64 ng/l) PTH levels during the hypocalcemic crisis.

**Conclusions**

Hypocalcemia is a frequent AE during Lenvatinib. Since it can be a life-threatening AE, monitoring of calcium levels following the start of treatment is mandatory and we recommend a particular caution during the first year of treatment. Oral calcium supplementation can correct hypocalcemia if promptly diagnosed; however, up to 10% of patients may have a severe hypocalcemia requiring intravenous treatment and Lenvatinib transient interruption. Further studies are needed to get more insights into the pathogenesis of hypocalcemia during Lenvatinib, though an inappropriate response of PTH to hypocalcemia has been observed.

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**OP-10-52**

**Outcome of sporadic medullary thyroid cancer (MTC) patients with a biochemical persistent disease after initial treatment**

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**Introduction**

MTC is a rare neuroendocrine tumor arising from thyroid parafollicular cells. After initial treatment, patients should be divided according to their clinical status in cured, biochemical persistence (BIO) and structural persistence (STR) of the disease. Concerning BIO patients less is known about the structural disease appearance rate and the time elapsed between the first evaluation after surgery and the appearance of structural disease.

**Method**

We retrospectively reviewed data of 592 consecutive patients with sporadic MTC, followed at the Endocrine Unit of the University Hospital of Pisa, from 2000 to 2018. After surgery, all patients were reclassified according to clinical, biochemical [basal (cT) or stimulated (sCT) calcitonin], neck ultrasound and, whenever indicated, other imaging procedures. When cT or sCT was above upper normal level according to gender thresholds, without evidence of structural disease, patients were considered BIO.

**Results**

After a median time of 5 months after surgery (IQR 3-8), 132/592 (22.3%) patients showed BIO. Among these, 89/132 (67.4%) and 43/132 (32.6%) patients were considered BIO for elevated cT or sCT, respectively. Median time follow-up of the BIO group was 103 months (IQR 50.5-152.5). The appearance of structural disease occurred in 60/132 (45.5%) patients, after a median time of 37.5 months (IQR 16-61.5). In patients who were considered BIO for the presence of elevated cT, the appearance of structural disease was more frequent than those with a positive sCT (56.2% vs 23.3%, P<0.001). This finding was still more evident when comparing patients with cT > 150 µg/ml to those <150 µg/ml (82.6% vs 37.6%, P<0.001). Neck was the most common site of structural disease appearance (41/60, 68.3%), followed by bone (9, 15%), liver (8, 13.3%), lungs (6, 10%) and mediastinal lymph nodes (5, 8.3%). Half of patients in whom structural disease appeared (30/60 – 50%), were submitted to other treatments and of these, 11/30 (36.6%) started systemic therapies.

**Conclusions**

In our large cohort of sporadic MTC patients with BIO, about half of them showed the appearance of a structural disease, prevalently located in the neck, after a median time of 3 years of follow-up. Patients with elevated cT at first evaluation, particularly those with cT > 150 µg/ml, had the higher risk of structural disease appearance.

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**OP-11-55**

**CD3⁺ CD8⁺ CD20⁺ T cells as a marker of the inflammatory phase in thyroid autoimmune and related polyautoimmune disorders: a pilot study**

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**Objectives**

Human CD3⁺ CD20⁺ T cells represents 3-5% of circulating T cells and may be detected in all lymphatic organs and in the cerebrospinal fluid. In healthy individuals CD3⁺ CD20⁺ T cells have been shown to produce higher levels of IL-17A and/or IFN-γ than those of CD3⁺ CD20⁻ T cells. Some reports described the role of CD3⁺ CD20⁺ T cells in autoimmune disorders such as multiple sclerosis and rheumatoid arthritis possibly due their ability to produce these inflammatory cytokines. This study is aimed at describing the behavior of CD3⁺ CD20⁺ T lymphocytes in patients in the most frequent autoimmune disorder i.e., Hashimoto’s thyroiditis, isolated or associated to further autoaggressive disorders in a frame of poly-autoimmunity.

**Methods**

The study group encompasses 65 patients bearing HT aged from 23 to 69 years (M=43; F=32), 42 of them associate another non-endocrine autoimmune disorder (16 with gastric atrophy (HT+GA), 15 with chronic myeloproliferative states (HT+V) and 11 with celiac disease (HT+CD)). Twenty sex- and age-matched healthy subjects act as control group (HD). The chronic use of interfering drugs, severe or chronic disorders, pregnancy and lactation were used as exclusion criteria. Whole blood samples (100 microliters) were stained with the fluorescent-labelled antibodies. Red blood cells were then lysed by adding 1 ml of hypotonic buffer and samples were acquired on a LSRs ARIA II Flow Cytometer (BD).

**Results/Conclusions**

The percentages of CD3⁺ CD20⁺ and that of CD3⁺ CD4⁺ CD20⁺ lymphocytes were similar in HD HT and poly-autoimmune patients. The subpopulation CD3⁺ CD8⁺ CD20⁺ was higher in the whole group of autoimmune patients as compared to HD (P=0.0089). Patients with isolated HT showed higher percentages of CD3⁺ CD8⁺ CD20⁺ than in HD patients although not reaching statistical significance. However dividing HT group based on thyroid function, hypothyroid patients showed a doubled CD8⁺ CD20⁺ percentages than HD patients (P=0.0115). The presence of associated autoimmune disorders did not change the CD8⁺ CD20⁺ cells subset but the co-presence of GA increased this cells percentage as compared to HD (P=0.0257) unlike the patients with H+CD all in gluten-free diet, in whom the CD8⁺ CD20⁺ subset was similar to the one in HD. These preliminary findings indicate that CD8⁺ CD20⁺ cells may behave differently in HT patients with or without poly-autoimmunity and may be a provisional marker of inflammatory phase of auto-aggressive disorders.

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**Endocrine Abstracts (2022) Vol 84**

44th Annual Meeting of the European Thyroid Association ETA 2022
OP-11-54
Study of target tissue-resident immune cells in Graves' disease and orbitopathy (star-GO): preliminary findings with a novel extensive immunophenotyping panel
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Background and Aims
Graves' disease (GD) and orbitopathy (GO) are characterised by the presence of pathological anti-thyrotropin receptor antibodies. In thyroid autoimmunity, especially GD and GO, a dysregulation of several T cell subpopulations has been proposed, especially T regulatory (Treg) and T helper 17 (Th17) cells, determining (auto)immunity inhibition and enhancement, respectively. T follicular cells (Tf) within germinal centres (GC: aggregates of lymphocytes within tissues) are also crucial, since supporting the maturation of GC-B cells that will later generate antibodies. The STAR-GO project aims to characterise immune signatures of GD/GO in relation with disease activity by analysing tissue-resident lymphocytes, more specific than those blood-derived.
Materials and Methods
Lymphocytes were derived from blood sampling and ultrasound-guided-fine-needle aspiration (US-FNA) of thyroid and neck lymph nodes (LNs) performed in the following patients: 6 GD early-onset (GD-E; newly diagnosed or recently relapsed) 2 active GO (GO-A; ongoing orbital inflammation), 3 inactive GO (GO-I; absent orbital inflammation) and 2 Hashimoto's thyroiditis (HT). Lymphocytes were immunophenotyped by flow cytometry (BD FASCSymphony®) with a 21 surface/intracellular staining panel.
Results
In the LNs analysis, B cells were more abundant in GD and GO, while T cells in HT. Among T cells, both GD and GO had increased Th17 cells compared with HT, while both GO-A and GO-I showed a peculiar increase of Th-helper cells (Thh). GC-B cells were highly abundant in GD-E, GO-A and especially in HT, while very low in GO-I, as a consequence GO-I patients had the lowest GC-B/GC-Thh ratio (0.1), compared with GD-E (0.62), GO-A (0.70) and HT (0.94). The immunophenotyping of PBMC and thyroid did not show particular differences among the patient groups.
Conclusions
Our preliminary results show that:
- Neck LN sampling with US-FNA is an effective tool for the immunophenotyping of patients with thyroid autoimmunity, more specific and informative than blood;
- GD and GO patients showed increased numbers of B cells, while HT patients of T cells, likely reflecting the different disease pathogenesis (predominantly humoral vs cell-mediated);
- Increased Th17 cells identify both GD and GO patients, while Thh cells seem particularly important for GO;
- As expected, GO during its inactive phase (GO-I) showed a low GC activity. We are currently increasing the number of subjects to verify our findings and further distinguish the different phases of GD/GO disease activity.
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OP-11-55
Role of NADPH oxidase 4 (NOX4) in resistance to metabolic iodine-131 radiotherapy in metastatic thyroid tumors carrying the BRAFV600E mutation
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Background: Radioiodine therapy (RAI) is a cornerstone of the treatment of distant metastasis from differentiated thyroid cancers (DTC), but is based on the expression of the iodine transporter NIS. The majority of DTC are papillary with BRAFV600E mutation in 45% to 60% of cases. This mutation is associated with RAI refractory DTC and low differentiation score. The absence of RAI uptake is a major challenge for the treatment of patients. A promising approach for the treatment of RAI-refractory patients is to re-enhance RAI uptake by promoting tumor reddifferentiation. We showed that BRAFV600E controls NADPH oxidase NOX4 expression and that NOX4-derived ROS contribute to NIS repression. Deletion of NOX4 promotes reactivation of NIS. This reversibility suggests a contribution of an epigenetic mechanism. Our hypothesis is that NOX4 generates specific oxidative DNA damage, promoting longer retention of epigenetic modifiers, such as DNMTs, at sites of DNA damage via the interaction with DNA repair proteins, contributing to stably preventing the transcription of genes from interfering with the repair process. Our objectives are 1- to determine the molecular and mechanistic events induced by NOX4-derived ROS that contribute to the reversible regulation of genes involved in differentiation/dedifferentiation process and 2- to evaluate the role of NOX4 in the resistance mechanism to BRAF/MEK inhibitors. Our data support a key role of NOX4 in oxidative DNA damage, which promotes the recruitment to chromatin of an epigenetic complex in which DNA methyl transferase 1 (DNMT1) and the DNA mismatch repair system (MMR) cooperate.
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OP-11-56
Focusing on the role of the enigmatic TRα2 isoform in modulation of thyroid hormone action
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1Universitätsklinikum Essen, Universität Duisburg-Essen, Institut für Humangenetik, Essen, Germany; 2University Hospital Essen, University of Duisburg-Essen, Department of Endocrinology, Diabetology and Metabolism, Essen, Germany; 3Universitäät Lübeck, Cbmbn / Med/ Cebmn, Molecular Endocrinology, Universität zu Lübeck, Lübeck, Germany, Lübeck, Germany
Thyroid hormones (TH) are important regulators of human metabolism and development, which modulate expression of target genes via nuclear thyroid hormone receptors (TRs). Different isoforms of these classical TRs including TRβ isoforms TRβ1 and TRβ2 as well as TRι1 were shown to be functional TH-responsive transcription factors and have been extensively studied. In contrast, the cellular function of TRα2, an alternative splice variant of TRα1, is poorly understood and it is even speculated whether the TRα2 protein is of biological relevance in vivo at all or the mRNA might only act as transcriptional sink to quickly regulate TRα1 production. Characterization of specific isoform functions has in particular been hampered by the lack of reliable antibodies. We aim to address the function and physiological relevance of the poorly characterised TRα2 isoform by using a tagged TRα2 variant. ChIP-sequencing analyses will be applied to generate genome-wide DNA binding profiles specific for both TRα isoforms, and different proteomic approaches will be used to identify isoform-specific protein interactions mediating TRα1 and TRα2 functions in gene regulation. These analyses will not only unravel the role of TRα2 for TH signalling but also elucidate whether this isoform may be a possible target to modulate TH action. To gain first insights into TRα2-specific functions, co-immunoprecipitation followed by mass spectrometric analysis of peptides bound by GFP-tagged TRα isoforms transiently overexpressed in HEK293 cells has been performed. In this analysis, well-known interacting proteins such as TR co-repressor NCOA1 were found, confirming the validity of the experimental approach. Moreover, novel putative shared as well as isoform-specific binding proteins have been identified that are suggesting a potential so far unknown specific function of TRα2. Interestingly, during first cellular analyses, we also observed different subcellular localisation of the two isoforms. While TRα1 appears to be evenly distributed in the cell nucleus, TRα2 accumulated in distinct nuclear speckles, which we will further investigate. To uncover cell-type specific functions of TRα2, protein interactions and DNA binding profiles will next be analysed in other cell types. Moreover, we aim to verify the identified DNA binding profile and protein interactions found for ectopic expression of TRα2 by performing the same analyses in different induced pluripotent stem cell-derived cellular models expressing endogenously tagged TRα isoforms.
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Endocrine Abstracts (2022) Vol 84
Monocarboxylate 8 transporter and deiodinase 2 deficiency impairs neurogliogenesis in the adult mouse subventricular zone leading to cellular and functional alterations
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Thyroid hormones (THs) play a crucial role orchestrating neurodevelopment, but also regulate adult brain function. Recently, the potent effects that THs exert in adult neurogenic niches have started to be uncovered in rodents. These include an important role in the modulation of progenitor generation, especially controlling whether a neural or glial (NSC) identity determines to become a neuronal or an oligodendroglial progenitor in the adult subventricular zone (SVZ), the largest NSC niche in the mammalian brain. A complex network of regulators tightly modulates TH availability and action, including transmembrane transporters, deiodinases and receptors. Among the TH-transporters, there is only one that is TH-specific, the monocarboxylate transporter 8 (MCT8). Deficiency of MCT8 leads to an ultra-rare but devastating disease, the Allan-Herndon-Dudley Syndrome (AHDS). Patients exhibit a plethora of endocrine and severe neurological disturbances and so far, no effective treatment for their neurological symptoms exists. Its complexity, along with its low prevalence and severe symptomatology, makes animal models and biomarkers of the disease a crucial step in the research for potential strategies to alleviate the patients’ severe conditions. Using a well-validated animal model of AHDS, the Mct8/Dio2 KO mice, we aimed to characterize how a reduced T3 availability structurally and functionally affected the neurogenic and gliogenic capacity of the adult SVZ-NSCs. To this end, we analysed the expression of cell markers by immunohistochemistry to study the balance between neurons and glia in the SVZ, both in vivo and using ex-vivo neurosphere cultures. These studies revealed severe alterations in the neurological balance, with an increase of the neuron/glia ratio in the SVZ in adult Mct8/Dio2 KO mice. We also observed that MCT8/DIO2 deficiency reduced NSC proliferation two-fold and hampered migrating of proliferating neuronal progenitors. Moreover, we tested the effects of administering exogenous THs and TH-agonists on neurosphere prepared from dissected SVZs. Neither the neuron/glia balance, nor proliferative activity responded to TH treatment in MCT8/DIO2 deficient neurospheres. Also, biochemical confinements of the observed NSCs alterations were studied in the olfactory memory and odour discrimination tests, as potential non-invasive biomarkers of the disease. These tests revealed that Mct8/Dio2 KO mice did not recognize new odours and failed to memorize them. Altogether, these results indicate that MCT8/DIO2 deficiency severely affects the regulation of adult SVZ-neurogliogenesis and suggest potential biomarkers for future preclinical studies.

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Integrated genomic, phenomic, functional and structural mapping of variants in thyroid hormone transporter MCT8
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Objectives
- To systematically integrated genetic, clinical and biochemical data from 371 patients with MCT8 deficiency, accrued through combination of data from our well-phenotyped global cohort and meta-analysis of all reported cases. We assessed the impact of common genetic variation in MCT8 on TFTs in ~70k individuals. We evaluated impact of 108 patient mutations and 304 MCT8 variants in a full alanine-scanning by TH transport assays. We linked three distinct LoF classes (mild, moderate, severe) to phenotypic outcomes and mapped all variants onto our homology model. Utilizing these data and conservation analyses, an MCT8 deficiency-specific variant classifier was constructed using artificial intelligence methods.

Findings
- Linking the different LoF classes to phenotypic outcomes, we observed a clear genotype-phenotype relationship across a range of disease features. Functional impact of variants strongly associated with survival of patients (median survival mild LoF: 71yrs; moderate LoF: 60yrs; severe LoF: 21.4yrs). Similar observations were noted for developmental (e.g. motor function), clinical (e.g. seizures and biochemical (e.g. T4, but not T3) features. Beneficial effects of the TH analogue Triac on several disease outcomes were independent of LoF category. By cross-referencing functional alanine-scanning data with patient mutants, we could infer the underlying mechanisms for the majority of variants. Our MCT8-specific classifier largely outperformed (AUC 0.95) commonly used prediction tools. Common genetic variation in MCT8 was associated with lower serum T4, but not with TSH or T3 concentrations, resembling the genotype-phenotype relationships in patients.

Interpretations
- The combination of deep phenotyping data from patients with MCT8 deficiency with a battery of functional and computational tests and with outcomes in population cohorts, enabled us to: (i) understand the divergent clinical phenotypes of MCT8 deficiency, (ii) assess therapy effectiveness, (iii) advance structural insights of MCT8, (iv) create a high-quality disease variant classifier, together also leveraging information on the role of MCT8 in non-affected individuals in the population.

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OP-12-59
Autonomously functioning thyroid nodules present intermediate malignancy risk according to european thyroid imaging and reporting data system; a comprehensive clinical, cytological and molecular characterization
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Objectives
- To systematically characterize autonomously functioning thyroid nodules (AFTN) by clinical, biological and imaging methods, cytology and histology when indicated.

Endocrine Abstracts (2022) Vol 84
Design
Prospective, single-center study conducted from March 2018 until September 2021, in 901 consecutive patients with 67 AFTN evaluated.

Methods
Enrolled patients underwent 99mTcO4 scintigraphy evaluation of thyroid function, ultrasound (US) using European Thyroid Imaging and Reporting Data System (EU-TIRADS), 123I scintigraphy in case of normal serum TSH, and fine needle aspiration (FNA) biopsy with molecular analysis and surgery when indicated.

Results
The median serum TSH of patients with AFTN evaluated was 0.41 (0.03-0.97) mIU/l and more than half of the patients were euthyroid. The median AFTN size measured by US was 27.0 (21.1-35.0) mm. 28.3% of AFTN were classified as mU/l and more than half of the patients were euthyroid. The median AFTN size was 3 and 72.7% as EUTIRADS score 4, indicating that the malignancy was detected at final histology (n=12), but one non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIIFP) was observed.

Conclusions
AFTN frequently present with normal serum TSH, intermediate malignancy risk according to US, and yield indeterminate FNA results. No malignant AFTN was detected in this study, but further prospective studies addressing the risk of malignancy of AFTN as a primary outcome are needed.

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OP-12-60
Population study on thyroid nodule ultrasound (TUS) reports quality with adherence to guidelines
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Objectives
To date, there has been no population-wide data looking at the adherence to published TUS reporting guidelines for thyroid nodule malignancy risk assessment. In our health care region in 2018, two radiology groups worked closely with endocrinologists to improve the quality of their TUS reports by adhering to the 2015 ATA or the 2017 TIRADS guidelines. We aim to present the improvement in TUS reports quality with these dedicated changes.

Methods
We analyzed the TUS reports of 981 patients from two prospective databases covering a population of 1.5 million people. We measured the reports' utility score (US; range 0-6), which is calculated based on the number of nodule characteristics provided in the report, and rate of ATA or TIRADS classification given by TUS, to assess the TUS report quality. The TUS report quality of the two radiology groups and other radiology groups were compared to each other. Since the two radiology groups implemented their adherence to guidelines in 2018, we then divided the databases into pre-2018 TUS reports and 2018-onwards reports and compared each group's later reports to its earlier ones.

Results
The two groups that implemented strict adherence to ATA or TIRADS guidelines had significantly higher US compared to other groups among the 2018-onwards reports. There was also a significant improvement in the US of the guideline-adhering radiology groups when comparing their TUS reports from pre-2018 vs those from 2018 onwards (Table 1). Additionally, the two groups also had higher rates of including an ATA or TIRADS classification in their report. In general, they had a substantially higher likelihood of providing TUS reports with both a clinically useful US of 4 or greater and an ATA or TIRADS classification. This allows for clinicians to better estimate the risk of malignancy of thyroid nodules.

Conclusions
Our data indicates that with dedicated adherence to the ATA or TIRADS guidelines, radiology groups can significantly improve the quality and utility of their TUS reports to better help clinicians manage thyroid nodules in a risk stratified manner, and to also help avoid unnecessary anxiety and additional testing and surgery.

Table 1. Mean US and percentage of reports with an ATA or TIRADS classification for pre-2018 TUS reports vs 2018-onwards TUS reports.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Number of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATA or TIRADS</td>
<td></td>
</tr>
<tr>
<td>pre-2018</td>
<td></td>
</tr>
<tr>
<td>Radiology group 1</td>
<td>3.62 (40.5%)</td>
</tr>
<tr>
<td>Radiology group 2</td>
<td>2.8 (11.5%)</td>
</tr>
<tr>
<td>Other radiology groups</td>
<td>2.49 (32.2%)</td>
</tr>
<tr>
<td>2018-onwards</td>
<td></td>
</tr>
<tr>
<td>Radiology group 1</td>
<td>5.77 (97.0%)</td>
</tr>
<tr>
<td>Radiology group 2</td>
<td>5.58 (93.3%)</td>
</tr>
<tr>
<td>Other radiology groups</td>
<td>3.28 (61.8%)</td>
</tr>
</tbody>
</table>

Conclusion
The aim of this prospective study was to compare the diagnostic performance of 99mTc-sestaMIBI SPECT scintigraphy (sestaMIBI), 18F-fluorocholine PET/CT or PET/MR (FCH) for preoperative localization of hyperfunctioning parathyroid gland. Materials and Methods: 60 patients with biochemical evidence of primary (n = 57) or tertiary (n = 3 kidney transplanted patients) hyperparathyroidism were imaged prospectively with dual phase/dual tracer 99mTc-sestaMIBI SPECT/CT (early FCH (FCHc) acquired by PET/CT (n = 60) and late FCH (FCHl), acquired by PET/CT (n = 18) or by PET/MR (n = 36). All imaging were interpreted independently by two nuclear medicine physicians and two radiologists. The results were classified into 3 categories (positive, inconclusive or negative) based on the nodular aspect of tracer uptake and the visualization of corresponding nodules on the CT or MRI. The imaging results were confronted to the surgical and histopathological findings and the follow-up.

Results
FCHc was positive in 51/60 (85%) patients, inconclusive in 8 and negative in 1 compared to 48/54 (88.9%), 5 and 1 for FCHl and 41/60 (68%), 13 and 6 for sestaMIBI. FCHc (FCHc and FCHl) detected 15 additional positive foci and 18 additional inconclusive foci and it confirmed 19 inconclusive foci. 45 patients underwent surgery and 54 lesions were removed (34 adenomas, 20 hyperplasia and 4 normal glands). FCHl, FCHc and PET/CT and PET/MR correctly localised 48 lesions compared to 39 correctly localised by sestaMIBI. Per-lesion sensitivity was 88.88% for FCHc and 87.75% for FCHl with respectively sensitivity of 100% for accuracy by PET/CT and 82.85% for acquisition by PET/MR – vs 72.22% for sestaMIBI. At follow-up, 34 patients were considered cured after surgery, while 5 patients had a biological recurrence of hypercalcemia. Biological control is requested for 4 patients and 2 patients are lost to follow-up.

Conclusion
18F-fluorocholine with PET/CT or PET/MR appears to be superior to sestaMIBI for lesion detection and localization of hyperfunctioning parathyroid tissue, particularly in patients with multiple lesions.

Key words: Hyperparathyroidism; parathyroid adenoma; MIBI SPECT; 18F-fluorocholine; PET/CT; PET/MR.

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OP-12-62
Progressive diastolic dysfunction in survivors of pediatric differentiated thyroid carcinoma
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Background
Pertinent differentiated thyroid cancer (DTC) has an excellent prognosis, but has unknown late effects of treatment. Initial cardiac evaluation showed subclinical diastolic dysfunction in 20% of adult survivors. In this follow-up study, we determined the clinical course of this finding.

Methods
This multicenter study, conducted between 2018 and 2020, re-evaluated survivors 5 years after the first evaluation. The primary endpoint was echocardiographic diastolic cardiac function (depicted by the mean of early diastolic septal and early diastolic lateral tissue velocity [e’ mean]). Secondary endpoints were other echocardiographic parameters and plasma biomarkers.

Results
Follow-up evaluation was completed in 47 (71.2%) survivors. Of these 47 survivors (87.2%) were women, median age 39.8 years (range 18.8-60.3). The median follow-up after initial diagnosis was 23.4 years (range 10.2-48.8). Between the first and second evaluation, the e’ mean significantly decreased by 2.1 cm/s (SD 2.3 cm/s, P < 0.001). The median left ventricular ejection fraction did not significantly change (58.0% vs. 59.0%, NS). In the best explanatory model of e’ mean, multivariate linear regression analysis showed that body mass index and age were significantly associated with e’ mean (β coefficient -0.169, 95% confidence interval [CI] [-0.292; -0.047], P = 0.008 and β coefficient -0.177, 95% CI [-0.240; -0.113], P < 0.001, respectively). The TSH value was not significantly associated with the e’ mean.

Conclusions
In this relatively large cohort of survivors of pediatric DTC, diastolic dysfunction decreased significantly during 5 year follow up, possibly more pronounced than in normal ageing. This finding requires further follow-up to assess clinical consequences.

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OP 12-63
Real-world performance of a novel dual-component molecular assay in cytologically indeterminate thyroid nodules: a single institutional experience
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Objective
We developed a novel dual-component molecular assay as an ancillary method to improve clinical decision-making in patients with cytologically indeterminate thyroid nodules. The assay includes next-generation sequencing (NGS) based detection of mutations in 23 thyroid cancer-related genes and digital polymerase chain reaction (dPCR) evaluation of the expression levels of a microRNA strongly associated with thyroid cancer. The method was designed as a “rule-out” test and preliminary results in a surgical cohort showed a negative predictive value comparable to a negative diagnostic cytology (100%). The aim of this study was to describe the performance of this approach in a real-world cohort of patients undergoing thyroid nodule fine-needle aspiration cytology, whose treatment is defined by the current clinical practice and based on clinical and ultrasonographic data.

Methods
Patients with a cytologically indeterminate nodule (TIR3A and TIR3B according to the Italian Consensus for Thyroid Cytology) were prospectively enrolled from January 2017 to January 2022 in the thyroid cancer unit at Policlinico Umberto I of Rome. For each consenting patient, residual cytological material from thyroid nodule aspirates was collected washing the needle with a nucleic acid preservative solution, after the preparation of standard cytology smears, with no dedicated passes. The samples were stored at -20°C until molecular testing. Patients underwent either surgery or clinical monitoring based on cytology diagnosis, molecular test results, clinical features, and patient’s preference. Patients who did not proceed to surgery were monitored clinically for somographic evidence of growth, development of suspicious US characteristics, or suspicious lymph node appearance. Median follow-up of these patients was 34 months.

Results
In total, 326 cytologically indeterminate thyroid nodules were consecutively collected since January 2017. Molecular analysis was performed on 218 thyroid aspirates from 211 consenting patients (TIR3A, n = 163; TIR3B, n = 55), displaying a 58% of positive call rate. The benign call rate of the assay was significantly higher in TIR3A (60%) than in TIR3B (44%) nodules (P = 0.0411). Among the 63 patients undergoing surgery (cancer prevalence 56%), the molecular assay showed high sensitivity (96%) and negative predictive value (96%). There was only 1 false-negative test result, representing a low-risk neoplasia.

Conclusion
These data confirm that the used dual-component molecular test can increase the diagnostic accuracy of thyroid cytology similarly reducing the number of nodules that will be classified as indeterminate and increasing those that can be reliably classified as benign, thus avoiding a substantial number of diagnostic surgeries.

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Oral Session 13: Basic 3

OP 13-64
Metabolic and neuroinflammatory consequences of hypothyroidism in two mouse strains with different metabolic adaptability capacities, the C57BL/6j and the WS/EJi strains
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Thyroid hormones (TH), among their pleiotropic actions, play a central role in the regulation of metabolism and in cognitive functions. Indeed, hypothyroidism is associated with a decrease in energy expenditure and lipid metabolism, and an impairment of memory. Metabolic deregulations induced by a high fat diet (HFD) generate peripheral inflammation, which promotes the development of neuroinflammation in various brain regions. This inflammatory state can disrupt neuronal homeostasis, leading to the alteration of synaptic plasticity and to memory disorders. Furthermore, a link between hypothyroidism and the development of neuroinflammation has previously been shown, particularly in the hippocampus, a brain structure rich in TH receptors. Our objective was to evaluate whether...
metabolic deregulations induced by hypothyroidism favor the development of neuroinflammation and thereby promote memory deficits. We compared the response to induced hypothyroidism in two mouse strains, the wild-derived WSB/EiJ mouse strain characterized by an obesity resistance due to its high metabolic flexibility phenotype and the C57BL/6J mice, prone to HFD-induced obesity. Adult mice were fed with a low-iiodine diet supplemented with 6-n-propyl-2-thiouracil (PTU) for 7 weeks to induce hypothyroidism. Our results show that hypothyroidism, characterized by a decrease in serum T4 levels, led to metabolic deregulations, as an alteration of lipid metabolism in the liver of both strains. However, the decrease in hepatic lipid synthesis was compensated in WSB/EiJ mice by a mobilization of lipid reserves from white adipose tissue, but not in the C57BL/6J mice. No peripheral inflammatory response to hypothyroidism was observed in both strains. In the hippocampus of C57BL/6J mice treated with PTU, the decrease in intracellular T3 availability was accompanied by an activation of glial cells, a hallmark of neuroinflammation, associated with an impairment of spatial memory. In contrast, no inflammatory response was observed in the hippocampus of WSB/EiJ mice, which appeared to maintain their thyroid status by locally increasing T3 availability via compensatory mechanisms. Our results shed light on the fact that serum thyroid status does not always reflect central thyroid status. Moreover, they demonstrated that the described link between hypothyroidism and neuroinflammation does not seem to be the consequence of metabolic deregulations induced by hypothyroidism but rather of an unbalance in the central thyroid signaling. Thus, our results emphasize the importance of maintaining central thyroid homeostasis to protect against the development of neuroinflammation, and in extension, of neurodegenerative diseases, given that neuroinflammation favors cognitive and memory impairments.

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OP-13-65

3,3',5-triiodo-l-thyronine and 3,5-diiodo-l-thyronine differentially modulate hepatic mitochondrial quality control in hypothyroid rats

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Objective

The maintenance of healthy and functional mitochondrial network via mitochondrial quality control (QC) mechanisms, is critical throughout life to respond to physiological adaptations and stress. Due to their role in energy production, mitochondria are exposed to high amounts of reactive oxygen species making their DNA (mtDNA) particularly vulnerable to oxidative damage. Mitochondrial dysfunction causes altered QC mechanisms (i.e. altered biogenesis, dynamics, autophagy/mitophagy) and mtDNA damage and depletion, as well as, in some cases, mtDNA release. When this occurs, mtDNA released from mitochondria into the extracellular and cytosol environment plays a central role in the damage-associated molecular patterns (DAMPs) through the activation of cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway, acting as an inflammatory trigger. Both 3,5-diiodo-L-thyronine (3,5-T2) and 3,3',5'-triiodo-L-thyronine (T3) have been shown to influence the mitochondrial QC system. However, the underlying mechanisms are poorly understood and likely differentiated when comparing the two iodothyronines. Here, by using a rat model of chemically induced hypothyroidism, we investigated the effect of administration of either 3,5-T2 or T3 on some key factors related to inflammation, mtDNA damage and mitochondrial QC system in the liver.

Methods

Hypothyroidism was induced by propylthiouracil and iopanoic acid; 3,5-T2 and T3 were intraperitoneally administered to hypothyroid rats for 1 week at 25 and 15 μg/100 g BW, respectively. Factors linked to hepatic inflammation (i.e. cGAS-STING pathways) were investigated. The status of mtDNA damage/repair and mitochondrial QC mechanisms (biogenesis, dynamics, and mitophagy) were studied.

Results

We showed an increase in mtDNA damage in the liver of hypothyroid rats accompanied by a significant reduction of mtDNA copy number, suggesting a reduction in mitochondrial biogenesis. Moreover, in hypothyroid rats, we found increased protein expression of both cGAS and cSTING, indicating activation of DAMPs pathways. The administration of either 3,5-T2 or T3 affected QC mechanisms ameliorating mitochondria fitness. Both iodothyronines enhanced mitochondrial copy number, reduced the mtDNA lesion frequency and oxidative damage, induced mtDNA repair mechanism and mitochondrial biogenesis, being T3 more effective than 3,5-T2. Also mitochondrial dynamics and autophagy were influenced. Of note, 3,5-T2, but not T3, reverted the activation of inflammatory triggers.

Conclusion

The reported data highlight new molecular mechanisms underlying the effect elicited by the administration of naturally occurring iodothyronines to hypothyroid rats on liver pathways related to QC to preserve mitochondrial health.

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OP-13-66

Generation of human thyroid organoids from embryonic stem cells to rescue hypothyroidism

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Organoids are tiny, self-organized three-dimensional versions of an organ that are produced in vitro. Human organoids offer unique opportunities to model the development, physiology, and diseases of human tissues while complementing animal models and reducing the need for animal testing. In the thyroid field, there is a lack of a functional human in vitro thyroid model which allows to further explore various aspects related to thyroid development and disease. Thus, the ability to generate TH-producing human follicles from embryonic stem cells would open new perspectives for the human thyroid research field. Here, by transient overexpression of thyroid transcription factors, NKX2-1 and PAX8, in human embryonic stem cells (hESCs), followed by time-dependent treatment with CAMP, hrTSH, Dexamethasone and TGF-beta inhibitor, we aimed to recapitulate thyroid developmental stages and generate the first in vitro functional thyroid derived from human ESC. Stepwise transcriptomics and histological analysis evidenced that the generated protocol recapitulates the gland developmental steps, cell expansion and follicular organization, and finally results in T4 production. In addition, these in vitro-grown follicles were able to maintain histological organization, promote vascular formation, and synthesize and release THs after three weeks of transplantation into the renal capsule of hypothyroid mice. This model opens a new window to better understand thyroid development processes as well as mechanisms/variants causing congenital hypothyroidism. Also, it can be considered as screening tool to test the toxic effects of compounds, in particular endocrine disruptors. Finally, although this model still needs improvement to be therapeutically applicable, it provides a proof-of-concept that generating autologous human thyroid tissue to maintain TH levels is within reach.

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OP-13-67

A single cell atlas of the T3-responsive transcriptome during early cortical neurogenesis in human cerebral organoids

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Endocrine Abstracts (2022) Vol 84
Perturbation of thyroid hormone (TH) function during prenatal brain development can cause a spectrum of neurological disorders as evident in pediatric patients with untreated congenital hypothyroidism or patients with mutations in THRA and SLC16A2 genes. However, scarcity and inaccessibility of human brain tissue from early developmental stages has been a major roadblock for experimental approaches to decipher local TH action in early development. Advanced in vitro models including human cerebral organoids (hCOs) hold great promises of accelerating our understanding of early human brain development and the hormonal signals that govern the complex processes underlying cortical neurogenesis. In this study, we differentiated hCOs from human induced pluripotent stem cells (hiPSC) in media containing either 1.5 nM T3 (BASAL group) or 20 nM T3 (CHRONIC group) for 9 weeks. Starting at day 13 of differentiation, hCOs were harvested at various developmental stages and analyzed by single cell RNA-seq for T3 treatment effects on the transcriptome. In addition, a subset of hCOs from the BASAL group was acutely treated with 50 nM T3 for 48 h (PULSE) at various stages and similarly analyzed by single cell RNA-seq. To avoid hiPSC line-inherent bias, all treatments were replicated for three different hiPSC lines resulting in 27 multiplexed single cell libraries. Global analysis of all cells collected during this study identified 31 neural cell clusters. Following cluster annotation, we could assign more than 95% of all cells to a major lineage trajectory from neural stem cell state towards excitatory neurons. Our single cell atlas comprised major cortical cell types including various radial glia cell (RGC) populations, three intermediate progenitor (IP) subtypes, as well as nine excitatory neuron subtypes. We defined developmental and T3-responsive expression profiles for genes related to TH action with cell type-specific resolution. For a subset of genes, smFISH was used to correlate spatial mRNA expression patterns with the laminar cell type distribution. We identified partially overlapping gene signatures in response to acute and chronic T3 treatment. Cell type- and developmental stage-specific gene set enrichments highlighted T3 effects on metabolic pathways in RGC, cell cycle regulation in IP and synapse function in neurons. T3-induced gene signatures in hCOs showed limited overlap with published mouse data sets. Chronic T3 treatment did not cause differentiation of aberrant cell types but altered the relative proportion of neuronal cell types in late stage hCOs. This comprehensive atlas of the T3-responsive transcriptome will serve as a unique resource to propel the use of hCOs in delineating the regulatory logic of local TH action in human brain development.

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ABSTRACT WITHDRAWN

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Poster Presentations
Saturday, 10th September 2022
Poster Session 1: COVID & Thyroid Disease
PSI-01-01
Autoimmune and inflammatory thyroid diseases following SARS-CoV-2 vaccines: an update from a systematic review of the literature
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Since the emergence of the COVID-19 pandemic in 2019, a massive vaccination campaign has been undertaken around the world, and SARS-CoV-2 vaccines-induced thyroid diseases became more frequently described in the literature. Subacute thyroiditis is reported in 52 patients, mean age 45.5 ± 1.8 years, mainly in women (n = 39), after the first (62%) or the second (38%) dose of mRNA (60%), inactivated whole-virus (25%) and adenoviral-vectorized (13.5%) vaccines. The mean time to onset is 9.0 ± 0.8 days, and the most frequent symptom is neck pain (97%). Thyrotoxicosis is confirmed by increased free T4 (30.0 ± 2.8 pmol/l), free T3 (34.3 ± 10.8 pmol/l) concentrations, with high ESR (53 ± 3 mm/hour) and CRP (105 ± 14 mg/l), heterogeneous thyroid gland with hypoechoic areas and decreased blood flow, decreased uptake on thyroid scan, and in rare patients on post-surgical pathology (n = 1) or on cytology after FNA (n = 5). Patients were initially given NSAIDs (52%) and/or oral glucocorticoids (48%), 10% patients are followed without treatment. In most patients, thyroid function returns to normal and subacute thyroiditis does not relapse. Graves’ disease is more frequent in women (n = 22) than in men (n = 10), mean age 46.2 ± 2.6 years. Hyperthyroidism is reported as new onset, recurrent or exacerbation of well controlled disease, after the first (62%) or the second dose (34%) of mRNA (72%) or adenoviral-vectorized (28%) vaccines. Mean time to thyrotoxicosis onset is 12.7 ± 2.6 days and patients present palpitations (53%), weight-loss (34%), tremor (22%). Thyrotoxicosis is confirmed by increased free T4 (43.3 ± 4.0 pmol/l), free T3 (39.0 ± 2.01 pmol/l) concentrations, with positive anti-TSH-receptor or thyroid stimulating immunoglobulins, markedly increased uptake of the radiotracer activity and increased vascularity of normal sized or enlarged thyroid gland. Patients are treated with beta-adrenergic blockers (32%), antithyroid drugs (89%), and 11% have no treatment. The discussed underlying pathogenic mechanisms of SARS-CoV-2 vaccine-induced thyroid diseases are molecular mimicry (SARS-CoV-2 proteins sharing a genetic homology with a large heptapeptide human protein) or autoimmune/inflammatory syndrome induced by adjuvants (ASIA), usually occurring in genetically susceptible individuals. The benefits of SARS-CoV-2 vaccination far weight the potential vaccine-induced side effects, but clinicians should be aware of possible thyroid adverse-effects, and can advise patients to seek medical assistance when experiencing anterior neck pain, fever or palpitations after SARS-CoV-2 vaccination. Further studies are warranted to clarify the clinical features, predisposing factors, management, and to investigate the etiopathogenesis of SARS-CoV-2 vaccines-induced thyroid diseases.

PSI-01-02
Post covid-19 complication in patient with chronic autoimmune thyroiditis
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Introduction
The information on prognosis morbidity chronic autoimmune thyroiditis and relationship with coronavirus disease 2019 (COVID-19) is lacking but endocrine involvement has been increasingly reported. The symptoms of thyroid dysfunction can be due to relationship after SARS-CoV-2 infection. In addition, the patients with COVID-19 leading to an increased risk of post COVID-19 complications of chronic autoimmune thyroiditis. As such, post COVID-19 complications outcomes among people with autoimmune disorders remain poorly understood.

Case report
We present clinical case of patient with chronic autoimmune thyroiditis with severe hypothyroidism which developed few weeks after resolution of COVID-19 infection. We discuss clinical presentation, diagnostic evaluation and principle of treatment of post COVID-19 complication in patient with Hashimoto thyroiditis. A 58-year-old female with a past medical history of chronic autoimmune thyroiditis diagnosed two years ago after COVID-19 pneumonia who later manifested hypothyroidism. She was diagnosed with COVID-19 infection with nasopharyngeal reverse transcriptase polymerase reaction (RT-PCR) at an outpatient clinic 68 days ago. An IgG against SARS-CoV-2 was positive. After three weeks for the treatment of COVID-19 pneumonia the patient complaining of worsening depression, dry skin, hair loss extreme and fatigue. Laboratory examinations showed significant increased for thyroid-stimulating hormone (TSH) 108 mIU/l (range 0.27–4.2), free thyroxine (T4) level 0.01 ng/dL (range 0.93–1.7), anti-thyroid peroxidase antibodies > 800 IU/mL (normal less than 44) and anti-thyroglobulin antibodies > 1000 IU/mL (normal less than 4.0), After additional examination the patient with Hashimoto thyroiditis was diagnosed severe hypothyroidism. The patient was prescribed treatment with levothyroxine a starting dose of 25 µg/day followed by titration at a daily dose of 175 µg. After 3 months, the therapy resulted in patient’s improvement of the general conditions and compensation of hypothyroidism (TSH 4.1 mIU/L, free T4 = 1.0 ng/dL).

Conclusions
Our clinical case suggests that the temporal relationship between post COVID-19 complications and the severe hypothyroidism manifestations in the patients with Hashimoto thyroiditis. Further studies are needed to clarify the link between combined effects of SARS-CoV-2 infection on the thyroid gland and the immune system.

Endocrine Abstracts (2022) Vol 84

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PSI-01-03
Incidence of subacute thyroiditis and autoimmune thyroid disease during COVID-19 pandemic
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Objectives
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is causing coronavirus disease (COVID-19), enters host cells via the angiotensin-converting enzyme 2 receptor. Its expression is higher in thyroid gland than in lungs. In the literature, an association between SARS-CoV-2 infection and subacute thyroiditis/autoimmune thyroid disease has been implicated. Therefore, we aimed to explore the influence of COVID-19 pandemic on the incidence of subacute thyroiditis, Hashimoto’s thyroiditis and Graves’ disease.

Methods
In our retrospective study we reviewed medical records of all patients who were referred for the first time to our thyroid department from 1 April 2019 to 31 May 2019 (before COVID-19) and from 1 April 2020 to 31 May 2020 (during COVID-19). Our institution has a stable catchment area of 1,000,000 inhabitants. Therefore, number of new cases may be considered the incidence of the disease. In each patient, thyroid specialists performed clinical examination and thyroid ultrasound. Levels of thyrotropin (TSH), free thyroxine, free triiodothyronine, thyroid peroxidase antibodies, thyroglobulin antibodies and, if applicable, TSH receptor antibodies as well as sedimentation rate were measured.

Results
In the two months period before COVID-19, we examined 946 patients (224 men/722 women) with the mean age 52.0 ± 19.0 years, and in the two months period during COVID-19, we examined 576 patients (154 men/422 women) with the mean age 53.7 ± 18.3 years. Between the two periods, patients did not differ with respect to sex and age (P = 0.201 and P = 0.438, respectively). Before COVID-19, we found 8 patients with subacute thyroiditis (0.8% from all in that period), while during COVID-19, we found 10 patients with COVID-19 (1.7% from all in that period). The incidence of subacute thyroiditis did not differ significantly between the two periods (P = 0.189). Before COVID-19, we diagnosed 435 (46% from all) patients with Hashimoto’s thyroiditis and 51 (5.4% from all) patients with Graves’ disease, while during COVID-19, we diagnosed 273 (47.4%) patients with Hashimoto’s thyroiditis and 22 (3.8% from all) patients with Graves’ disease. Incidence of Hashimoto’s thyroiditis and Graves’ diseases did not differ significantly between the period before and during COVID-19 (P = 0.629 and P = 0.205, respectively).

Conclusions
Although we diagnosed absolutely and relatively more patients with subacute thyroiditis during COVID-19 than before, the results were not statistically significant and cannot be easily attributed to SARS-CoV-2 infection. A longer observation period would probably yield different results. In addition, we did not find any difference in the incidence of Hashimoto’s thyroiditis and Graves’ disease during COVID-19 pandemic.

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44th Annual Meeting of the European Thyroid Association ETA 2022
Subacute thyroiditis (SAT) is an inflammation of the thyroid gland characterized by varying degrees of severity regarding thyrotoxicosis, inflammation and the incidence of hypothyroidism. It has been found that 18 from 25 patients had been vaccinated via vaccines of Chinese production. 7 participants had not been vaccinated at all. 7 from 18 patients further had symptoms of Covid-19 and also developed Subacute Thyroiditis. Although 11 patients (61%) had not any complain after vaccination, during 4-6 weeks clinically SAT clusters had appeared. In case of subacute thyroiditis caused by Covid-19, it is more preferable to add antiviral drugs to the Glucocorticoid treatment in order to avoid the recurrence. After the Covid-19 viremia persists in the blood and it may cause a subacute thyroiditis (6-8 weeks later).

**PS1-01-06**

The peculiarities of the subacute thyroiditis treatment course during the COVID-19

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Subacute thyroiditis (SAT) is an inflammation of the thyroid gland characterized by varying degrees of severity regarding thyrotoxicosis, inflammation and the incidence of hypothyroidism. The present study aims to identify whether the severity of SAT depends on the causative agent involved and to identify what is the optimal therapy. To this purpose we retrospectively evaluated 402 patients referred to of the University Hospital of Pisa because of to a SAT from January 2011 to December 2020. 32 patients did not receive pharmacological treatments, 16 were treated with non-steroidal anti-inflammatory drugs (NSAIDs) and 354 with glucocorticoids; among these the most common initial dose (n = 286) was 25 mg of prednisone and most patients were treated for 90 days (n = 277). 88 patients experienced definitive hypothyroidism. Patients with higher levels of free thyroxine (FT4), C reactive protein (CRP), erythrocyte sedimentation rate (ESR) and thyroglobulin (Tg) experienced more frequently hypothyroidism at the end of inflammatory process. Patients treated with glucocorticoids experienced a shorter duration of neck pain (14 days, P <0.001) than patients treated with NSAIDs (28 days) and those not treated (28 days). The more adequate prednisone’s starting dose to obtain peak remission was 25 mg/day. The third quarter of the year was characterized by the highest number of cases compared to the other quarters in all years except in 2012 and 2015, when there was a high incidence of cases in the first quarter of the year, and in 2020 where most of the SAT cases occurred in the second and fourth quarters. In these same quarters SAT was more severe with regard thyrotoxicosis, inflammatory indices and incidence of hypothyroidism. In a previous study we observed that SAT clusters in 2020 occurred within a month of the Covid-19 waves. Therefore, similarly we have evaluated the Italian epidemiological situation of the winter seasons 2011-12 and 2014-15, in which an anomalous circulation of the influenza virus A/H3N2 emerged; therefore it might be responsible for SAT clusters in the first quarter of 2012 and 2015. We conclude that the differences about the severity of SAT depend on the different agent responsible and glucocorticoid therapy for SAT is effective even at lower doses than recommended by the latest guidelines.

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**PS1-01-05**

Subacute thyroiditis and COVID-19 vaccination

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Aim

The aim of this study is to find out whether Subacute Thyroiditis may occur after Covid-19 Vaccination.

Materials and methods

This investigation was designed and held in “Kanaker-Zeytun” Medical Center and “Muratsan” University Hospital. 25 women (age: 35±7) with proved diagnoses of Subacute Thyroiditis were included in the study. The detailed history of disease was collected in order to understand how many of them survived Covid-19, whether they have been vaccinated and which vaccine had been done.

Results

It has been found that 18 from 25 patients had been vaccinated via vaccines of Chinese production. 7 participants had not been vaccinated at all. 7 from 18 patients further had symptoms of Covid-19 and also developed Subacute Thyroiditis. Although 11 patients (61%) had not any complain after vaccination, during 4-6 weeks clinically Subacute Thyroiditis had appeared. In case of subacute thyroiditis caused by Covid-19, it is more preferable to add Arbidol to the treatment according to the following regimes: Arbidol 200 mg 1 piece x 2 for 5 days, 1 piece x 1 for 5 days. Patients treated with glucocorticoids experienced a shorter duration of neck pain (14 days, P <0.001) than patients treated with NSAIDs (28 days) and those not treated (28 days). The more adequate prednisone’s starting dose to obtain peak remission was 25 mg/day. The third quarter of the year was characterized by the highest number of cases compared to the other quarters in all years except in 2012 and 2015, when there was a high incidence of cases in the first quarter of the year, and in 2020 where most of the SAT cases occurred in the second and fourth quarters. In these same quarters SAT was more severe with regard thyrotoxicosis, inflammatory indices and incidence of hypothyroidism. In a previous study we observed that SAT clusters in 2020 occurred within a month of the Covid-19 waves. Therefore, similarly we have evaluated the Italian epidemiological situation of the winter seasons 2011-12 and 2014-15, in which an anomalous circulation of the influenza virus A/H3N2 emerged; therefore it might be responsible for SAT clusters in the first quarter of 2012 and 2015. We conclude that the differences about the severity of SAT depend on the different agent responsible and glucocorticoid therapy for SAT is effective even at lower doses than recommended by the latest guidelines.

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Graves' orbitopathy and subacute thyroiditis related to SARS-CoV-2 infection or vaccination: the experience of a single centre in Milan, Italy

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Background

The Covid-19 pandemic caused by the severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2) determined millions of deaths worldwide, thus at the end of 2020 a massive vaccination campaign has been launched. SARS-CoV-2 infection and vaccines have been associated with several thyroid disorders, especially subacute thyroiditis (SAT), Graves’ disease (GD) and orbitopathy (GO). We studied the occurrence of SAT and GO following SARS-CoV-2 infection or vaccination in our Centre.

Methods

We recorded all consecutive cases of SAT (new diagnosis) from February 2020 and GO (new diagnosis or sudden worsening) from June 2021 onwards, noting if occurred within 1 month after SARS-CoV-2 infection or vaccines.

Results

Up to March 2022 we have recorded 25 SAT and 28 GO. The onset of SAT occurred within 1 month from SARS-CoV-2 vaccination in 8/25 (32%) and from SARS-CoV-2 infection in 4/25 (16%). Among the 28 GO, 11 (39%) occurred within 1 month from SARS-CoV-2 vaccination (9 new diagnosis and 2 worsening) and 1 from SARS-CoV-2 infection (new diagnosis). Interestingly, 5 (18%) had a GO onset apparently unrelated to SARS-CoV-2 vaccination, however had developed GD hyperthyroidism within one month from it. The 19 patients developing SAT or GO after SARS-CoV-2 vaccination had received Pfizer (n = 12), Moderna (n = 3) or AstraZeneca (n = 4); symptoms developed following the first, second or third dose in 8 (42%), mean +13 days, 5 (26%), mean +17 days and 6 (31%) mean +10 days cases, respectively. A previous documented SARS-CoV-2 infection several months before the vaccination had occurred in 1/19 patients (5%). The mean age of patients was 54 ±18.17 years (range 21-83 years) and females were 14/19 (73%). A previous history of thyroid disease was present in 3/19 (16%): one subclinical hypothyroidism, one euthyroid nodular goitre, one euthyroid Hashimoto’s thyroiditis. A family history of thyroid disorders was present in 10/19 (52%) patients.

Conclusions

SARS-CoV-2 vaccines seem to be associated with the onset of SAT and the onset or worsening of GO. Possible mechanisms involve the interaction of the spike protein with the ACE-II receptor expressed in thyroid tissue, a cross-reactivity of the spike protein with thyroid self-proteins or an immune reaction induced by adjuvants (ASIA syndrome). Many patients had a positive family history for thyroid disorders, thus a genetic predisposition is likely involved. Until more safety data about SARS-CoV-2 vaccines will be available, caution and strict monitoring of injected individuals is suggested, especially those predisposed to thyroiditis or autoimmunity.

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Subacute thyroiditis after SARS-CoV-2 vaccine

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Introduction

Subacute thyroiditis (SAT) is an inflammatory disorder of thyroid associated with viral infections. Rarely, cases of SAT have also been described post-vaccination, but there are not many reports related to exposure to the COVID-19 vaccine. Here we present a case of subacute thyroiditis after receiving the first dose of a SARS-CoV-2 vaccine inactivated COVID-19 vaccine (Sinovac-CoronaVac), developed by Sinovac/China National Pharmaceutical Group.

Case report

A 36 -year-old male presented to our outpatient endocrinology clinic with complaints of anterior neck pain with irradiation to right ear, fever and fatigue. In his past medical history, he had mild Covid-19 infection in October 2020 and did not report any past medical history for thyroid disease or preceding upper respiratory system infection. He has received his first dose of COVID-19 vaccine 5 days previously. On his physical examination his heart rate was 90/min; body temperature was 37.5 °C. On palpation, the thyroid gland was painful and enlarged. The nasopharyngeal swab polymerase chain reaction (PCR) test for SARS-CoV-2 done twice was negative. At laboratory investigations, his thyroid function test was compatible with subclinical hyperthyroidism thyroid stimulating hormone - 0.1 IU/ml (normal range: 0.39-4.2 IU/ml); free thyroxine -1.65 nmol/l (normal range 0.8-2.0 nmol/l); Thyroid autoantibody levels were normal: anti-thyroglobulin antibody - 1.2 IU/ml (normal < 4 IU/ml), thyroid peroxidase antibody – 3 IU/ml (normal <20 IU/ml) and anti-TSH receptor antibody- 0.1 IU/l (normal range 0-1.5 IU/l). Levels of leucocyte sedimentation rate (ESR) and C-reactive protein were elevated (ESR 38 mm/h; CRP – 30 mg/l). Thyroid ultrasound revealed unilateral focal hypochroic areas with decreased blood flow. Based on clinical symptoms and laboratory examinations, the patient’s diagnosis was considered to be subacute thyroiditis. He was advised to rest, but there were not many reports related to exposure to the COVID-19 vaccine. However, the symptoms persisted. Metyldenisolone 24 mg was initiated, and symptoms rapidly improved after medication.

Conclusion

Post-vaccination SAT cases have so far been rarely reported despite mass vaccination programs in all countries. Roughly 58% of the world population has been already fully vaccinated against covid-19, and there are only a handful number of cases of SAT reported. The development of thyroiditis may occur within a few days, as opposed to more days in case of post-viral illness. Clinicians need to be aware that there is a possibility of SAT post-vaccination and must consider this as a differential diagnosis in a patient presenting with anterior neck pain or fever with a recent vaccination history for adequate patient management and cure.

Hypothyroidism

PSI-02-10

Modern study of life quality of women with subclinical hypothyroidism

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Objective

To study the life quality of patients with subclinical hypothyroidism by using questionnaire SF-36 before and after replacement therapy.

Methods

All patients were collected at the Department of Endocrinology 3rd clinics of Tashkent Medical Academy. The study included 55 women with subclinical hypothyroidism and GO (new diagnosis or sudden worsening) from June 2021 onwards, noting if occurred within 1 month from SARS-CoV-2 infection or vaccines.

Results

The first group of patients with subclinical hypothyroidism were obtained test results: TSH -6.9 free T4- 14.2, TPOAb - 87.6, thyroid gland volume V=24.8 cm³ ± 7.8 and a second group members TSH -1.7 mU/l free T4-15.6 pmol/l and TPOAb - 18.4. After replacement therapy in the first group, TSH and TPOAb levels were 1.9 mU/l and 24.6 respectively. Average thyroid gland volume in the first and second groups was V=19.8 cm³ ± 4.3 and V=14.6 cm³ ± 3.6 respectively. The most common cause of subclinical hypothyroidism was Hashimoto’s thyroiditis with 83.6%. In 26, 6% members of the second group were diffuse enlargement of the thyroid gland 1degree. Practically on all scales of the questionnaire SF-36 and ultrasound investigation of the thyroid gland (USi), conducted research analysis: thyroid hormone-binding free T4, TSH, and anti-thyroid peroxidase antibody.

Conclusion

In patients with subclinical hypothyroidism in almost all parameters the quality of life is worse subacute thyroiditis without thyroid disease, especially scales are worse, than in healthy women. While comparing the quality of life in patients with hypothyroidism the rates of role physical functioning, vitality, social functioning.
and psychological health of patients with hypothyroidism were significantly less compared with women with euthyroid goiter.

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PSI-02-11

Ventricular extrasystoles as a consequence of hypothyroidism
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Background
Hypothyroidism is a clinical condition caused by a deficiency of thyroid hormones or a decrease in their biological activity. Premature ventricular contractions (PVCs) are early depolarizations of the myocardium originating in the ventricles. Rhythms with frequent and apparently idiopathic PVCs are considered to be a benign condition that can be managed with conservative measures. Beta blockers are considered to be quite effective.

Objective
To demonstrate the positive effect that the compensation of hypothyroidism had on the “treatment” of PVC.

Methods
The study, which lasted for six months, involved 73 women (aged 19y-53y), who were diagnosed with PVCs after 48 hours of Holter monitoring. In addition, TSH and FT4 levels in the blood were checked. TSH levels were ranging from 3.7-6.2 IU/ml, however FT4 levels were normal, therefore the patients were also diagnosed with hypothyroidism. They were treated with Levothyroxine exclusively (no Beta blockers were prescribed). Medication doses were calculated individually based on the patient’s body weight.

Result
Approximately 15 days after the start of Levothyroxine administration, the patients started experiencing significantly less tachycardia. Moreover, according to the second Holter monitoring, which was performed after 2 months, PVCs were either absent or considerably decreased.

Conclusion
We can conclude from this research that besides compensating hypothyroidism, Levothyroxine is highly likely to also “treat” benign ventricular extrasystoles.

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PSI-02-12

Characteristics of specialists delivering clinical care for hypothyroidism in europe: the “THESIS” study (treatment of hypothyroidism in europe by specialists: an international survey)
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Objectives
Some hypothyroid patients are critical of their care, although this appears to vary between countries. The quality of thyroid care delivered, and the perceived patient experience may be influenced by characteristics of specialists such as age, sex, experience, and workplace setting. Here, we aimed to explore geographical differences in thyroid specialist characteristics.

Methods
THESIS is a large European questionnaire survey of thyroid specialists treating patients with hypothyroidism. Participants were reached via the endocrine societies of 26 European countries plus Israel and Turkey. The questionnaire included questions about respondent demographic characteristics. Geographic regions were defined according to the UN Statistics Division definition (Eastern Europe, Western Europe, Northern Europe, Southern Europe, Western Asia). Data on gross national income per capita (GNIPC) in US dollars from the World Bank were used.

Results
A total of 16,733 invitations yielded 6,058 responses (93% endocrinologists). The median response rate was 43.5% and differed significantly between countries (6.8%-95.2%, P < 0.01). The mean age, the proportion of female respondents, and GNIPC were not associated with response rates. The proportion of females ranged between 36.6-93.9% (median 63.7%). The lowest proportion of females was in Northern Europe (45.6%) and the highest in Eastern Europe (77.2%). The proportion of females differed between regions (moderate association, P < 0.001, Cramer’s v 0.21). GNIPC was inversely associated with the proportion of female respondents (P < 0.001, r2 = 0.42). An inverse correlation was noted between respondent age and proportion of females (Cochran-Armitage test for trend, P < 0.001, two-sided). The sample included 794 (16.2%) respondents working exclusively in private practice. The distribution of respondents in private practice differed between countries with a strong association (P < 0.001, Cramer’s v 0.40). Decreasing GNIPC with an increasing proportion of respondents working privately (P < 0.011, r2 = 0.23). The proportion of respondents who reported treating over 100 hypothyroid patients/year was 62.1%. As GNIPC increased the percentage of respondents who treated more than 100 patients/year decreased (P < 0.01, r2 = 0.36).

Conclusion
Differences in characteristics of specialists who treat hypothyroid patients exist both at the country and the regional levels, with the greatest differences noted between Northern and Eastern Europe. The most significant determinant for these differences is GNIPC, although other factors, not addressed in this survey (organization of healthcare, culture) may also play a role. These differences may influence the management of hypothyroidism and patient satisfaction.

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PSI-02-13

Sex hormones levels and chronic autoimmune thyroiditis in a cohort of obese male patients
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Introduction and Aim
Obesity is associated with an increased risk of hypothyroidism and chronic autoimmune thyroiditis (AIT). However, little is known about the underlying pathogenic mechanisms. Recently it has been evaluated the role played by sex hormones in the onset of AIT and, analysing the data from a large cohort of normal/overweight males, a positive correlation between an increased ratio of estradiol/testosterone levels (E2/T) and AIT was found. Since obese males are more likely to have decreased testosterone and increased circulating estradiol levels, we investigated whether there was a causal relationship between an imbalance of the E2/T ratio and AIT in obese male patients.

Patients and Methods
We retrospectively evaluated anthropometric data (weight, height, BMI), thyroid assessment (thyroid ultrasonography and TSH, FT3, FT4, TgAb, TPOAb levels) and gonadal hormones [total testosterone (T), estradiol (E2), gonadotropins] of 337 obese male patients (age: 50 ± 11.5 years, BMI: 46 ± 7.6 Kg/m2). AIT was defined in different ways: the serum TPOAb and/or TgAb positivity (organ specific autoantibody positivity > 10 IU/mL), hypotalamic-pituitary axis dysfunction (with FSH/LH < 0.36), and/or characteristic US features (diffuse parenchymal hypoechogenicity and/or heterogeneous echogenic pattern of the thyroid gland) and/or hypothyroidism.

Results
AIT prevalence in our cohort was 6.5%. The prevalence of AIT did not correlate with age (P = 0.9), BMI (P = 0.9), hyponogonadism (P = 0.7), E2 (P = 0.1) and T (P = 0.4) levels, while an increased E2/T ratio was observed in subjects with AIT, although this difference was not statistically significant (P = 0.07). By ROC curve analysis (AUC 0.614; CI 95%:0.51-0.73, P = 0.045) we identified a E2/T ratio cut-off value significantly associated with AIT: 63.6% of subjects with E2/T ≥ 18.8 had AIT while this was observed only in 36.4% of subjects with a E2/T ratio < 18.8 (P = 0.035). This cut-off also predicted the absence of AIT with an excellent diagnostic accuracy (96% NPV). Then we carried out a multivariate statistical analysis and the E2/T ratio ≥ 18.8 was confirmed as a parameter independently associated with AIT (OR 2.80; CI 95%:1.17-7.21, P = 0.024).

Conclusions
Our results suggest that higher E2/T ratios were significantly associated with AIT among obese male patients. Since estrogens and androgens play an important role...
PS1-02-14

A case of late-onset dyshormonogenic goiter with hypothyroidism due to a homozygous mutation of SLC26A7 gene
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Introduction
Congenital hypothyroidism (CH) is the most common neonatal endocrine disorder, affecting up to one in 1500 to 2000 newborns, if mild forms of hypothyroidism with euthyroid and normal-sized thyroid gland are included. It is caused by either dysgenesis or dysmorphogenesis. Recently a novel iodide transporter, SLC26A7 (a member of the SLC26 transporter family), whose dysfunction affects thyroid hormogenesis in humans, has been identified. The main purpose of this study is to present a case of dyshormonogenic CH due to a homozygous mutation of SLC26A7 gene (c.1883delC, p.P628Qfs*11), which has never been described before.

Case Report
Here we report a case of a 19-year-old young Tunisian male, who presented with severe hypothyroidism and a voluminous diffuse goiter appeared 2 months after his arrival in Italy at the age of 18. No other signs and symptoms of hypothyroidism, mental retardation or delayed growth were observed. Neck US confirmed the presence of diffuse goiter and no nodules or lymphadenopathies were documented. Autoimmune and infiltrative thyroid diseases were excluded and no iatrogenic/toxic causes were detected. The perchlorate discharge test showed a partial organification defect and a hormone replacement therapy was started, leading to an overt reduction of the goiter size (thyroid volume from 93.98 ml to 41.43 ml). With LT4 therapy, a rapid increase of serum FT3 compared to serum FT4 levels was observed. After stopping LT4 therapy for 2 weeks, 1 mg of iodine was administered but worsening of hypothyroidism was observed. NGS analysis showed a not yet identified homozygous mutation of SLC26A7 gene (c.1883delC, p.P628Qfs*11), which results into a stop codon in position 639 and the synthesis of a truncated protein.

Conclusions
In literature, most of CH patients with homozygous mutations of SLC26A7 were detected by neonatal screening or within the first years of life. We describe the first case of CH due to a homozygous mutation of SLC26A7 gene diagnosed during late adolescence, when the patient was 19 years old. Although the neonatal screening test was not available, the absence of intellectual retardation and his harmonic growth suggest a late onset of hypothyroidism. The administration of 1 mg of iodine for 2 weeks did not correct hypothyroidism. We suppose that other environmental factors or genetic polymorphisms of other genes involved in thyroid hormone synthesis might influence the transport of iodine into the lumen of the thyroid follicles and might have a role on the timing of onset and on severity of hypothyroidism.

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PS1-02-15

Use of iodine in the treatment of congenital hypothyroidism with an in situ thyroid gland and of non-autoimmune subclinical hypothyroidism
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Introduction
Congenital hypothyroidism (CH) with in situ thyroid gland (GIS) and non-autoimmune subclinical hypothyroidism (NASI) are functional defects of thyroid gland occurring at birth and after birth, respectively. In recent years, a higher incidence of these disorders has been documented. The etiology remains unclear, with only an almost 50% of cases attributable to mutations in known dyshormonogenesis-associated or TSH-receptor genes. Although replacement therapy with levothyroxine (L-T4) is the treatment of choice for hypothyroidism, previous studies have reported an improvement/normalization of thyroid function in some cases of dyshormonogenetic CH after iodine administration. The objective of this study was to evaluate the effect of treatment with physiological doses of iodine in a group of children with CH and GIS and NASI.

Patients and Methods
34 children, 17 with CH and GIS (mean age 10.22 ± 3.15 years) and 17 with NASI (mean age 10.70 ± 4.36 years) were given iodine for 9 months, after stopping for 4 weeks L-T4, when taken. 3 children with CH and 1 with NASI had mutations of DUOX2, whereas the etiology was unknown in the remaining children. Iodine treatment was initiated with a daily dose of 50 μg, increasing to a maximal 150 μg/d. At the beginning of the study, all patients presented serum TSH between 4 and 12 μU/mL, free thyroid hormones within the normal range, undetectable anti-TG and anti-TPO antibodies and a thyroid of normal size and normoechogenic pattern at ultrasound. The same parameters were evaluated every 3 months for 12 months.

Results
Treatment with iodine failed to normalize TSH. Under the lowest dose of iodine, TSH did not change as compared to the baseline in both groups. After increasing the daily dose, there was a progressive increase in serum TSH in both groups, that became statistically significant (P = 0.038) when basal TSH values of whole group of patients were compared with those after 150 μg/d of iodine. Other parameters of thyroid function did not change after treatment in both groups. None of children developed serology and ultrasound markers of thyroid autoimmunity.

Conclusions
This study shows a failure of treatment with physiological iodine doses to correct CH with GIS and NASI. These results, which are apparently in contrast with the data reported in the literature, are probably due to the lower doses used in our study. Moreover, the increase of serum TSH levels observed during treatment may reflect the spontaneous course of the disease rather than a detrimental effect of iodine.

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PS1-02-16

Evolution of congenital hypothyroidism with in situ thyroid gland in children and adolescents: Clinical and biochemical features at diagnosis and after retesting
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Background
In recent years, increasing cases of congenital hypothyroidism (CH) with in situ thyroid gland (GIS) are identified. Outcome of children affected from CH with normally sized thyroid of normal size is still unknown. The objective of our study is to describe the natural history of this specific form of CH.

Methods
We retrospectively evaluated clinical, biochemical and instrumental data of 89 patients with diagnosis of CH and GIS, referred to our center after positive neonatal screening. After 3 years of age, 48 patients performed a clinical reassessment after withdrawal of levothyroxine therapy (L- T4), through biochemical evaluation with thyroid function profile (TSH, fT3, fT4), imaging evaluation with neck ultrasound and, in most cases, a scintiscan with 123-I and perchlorate discharge test. We evaluated the need for L-T4 therapy at retesting and during follow-up.

Results
In the first year of follow-up, 15 patients showed a transient CH. Among the other 74 patients, 48 performed clinical reassessment: 10 had overt hypothyroidism (20,8%), 20 showed hyperthyrotopeinemia (41,7%) and 18 were euthyroid (37,5%) after L-T4 withdrawal for 4 weeks. 32 patients performed a scintiscan with 123-I and perchlorate discharge test: 6 patients presented a partial iodine organification defect, while 4 patients had a total iodine organification defect. 28 children (58,3%) resumed therapy immediately after clinical reassessment, while 20 (41,7%) suspended it. Follow-up data at retesting (median duration of 10,36 years) were available in 44 patients. Among children who had suspended therapy at retesting, 4 resumed therapy during follow-up, while in the group of children who had resumed therapy at retesting, 9 suspended it. At the end of follow-up, 22 patients (50%) were untreated and 22 (50%) were still taking L-T4 therapy. We
observed no statistical differences between children who suspended or continued L-T4, in first serum TSH levels, sex ratio, or birth weight. Serum TSH at clinical reassessment showed a significant difference between two groups (P < 0.01).

Conclusions

Over a third of patients with CH and GIS had a normal thyroid function off L-T4 therapy. Therefore, a clinical reassessment after 3 years of age should be performed to avoid potential prolonged treatment. However, it is not possible to predict whether these subjects will need therapy again, so long-term follow-up studies are needed to better understand natural history of disease.

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PSI-02-17
Isolated hypothyroxinemia - not only in pregnancy

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Isolated hypothyroxinemia is rarely and briefly mentioned in medical textbooks and seldom discussed at endocrine conferences. It is most often, but not exclusively encountered in pregnancy. The author presents cases of isolated hypothyroxinemia encountered at a private endocrine practice in Budapest, Hungary and a specialized medical practice in Berlin, Germany. In the last seven years the author encountered about thirty cases: app. 60% in women who were 17-85 years old and app. 40% in men who were 50-86 years old. Women with isolated hypothyroxinemia in fertile age had a long history of infertility, miscarriage, primary and/or secondary amenorrhea and psychiatric symptoms. Most of these patients responded well to thyroxin supplementation and their symptoms improved or disappeared. The majority of patients over 60 years of age did not show any symptoms. They were predominantly closely followed and received thyroxin supplementation only in a few cases. In summary, isolated hypothyroxinemia seems to be a rare entity which is easily dismissed. In women of fertile age isolated hypothyroxinemia should receive more attention. An FT4 value below the reference range should not be regarded automatically as laboratory error even if the TSH is adequate.

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PSI-02-18
Human cerebral organoids as in vitro platform to assess thyroid hormone system disrupting chemicals

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Thyroid hormones (TH) play a fundamental role in brain development. Changes on TH availability during pregnancy and early childhood can lead to neurological disorders. Accordingly, concerns are mounting that exposure to environmental compounds capable of interfering with TH action can disrupt neuronal development. Current approaches to categorize chemicals as thyroid hormone system disrupting chemicals (THSDC) are mainly based on determination of changes in circulating TH concentrations in vitro. Since such tests are not adequate to capture alterations at cellular and molecular levels during human brain development, there is an urgent need to establish and validate human in vitro models for THSDC assessment. Human cerebral organoids (hCOs) derived from recaptured pluripotent stem cell (hiPSC) present a promising model system as hCOs recapitulate tissue complexity and critical developmental processes while providing an infinite source of material. We used single cell hiCO transcriptome data to extract lists of TH-responsive genes to be used as molecular markers of TH action in RT-qPCR assays. Since hCOs show dynamic changes in cell composition during their development, these lists included broad response genes as well as cell type-specific markers. We analyzed expression patterns of marker genes following acute 48 h treatment of hCOs at different stages with T3 (3-300 nM). We further characterized expression profiles following co-exposure of hCOs to T3 and the MCT8 inhibitor silicrysthin (SC) or the phenoloxidase inhibitor iopanoic acid (IA). In addition, we established a sensitive LC-MS/MS method to determine basal TH concentrations in media and the TH metabolite pattern (T3, 3,3'-T2; 3,5-T2; 3-T1; T1) following TH treatment and co-exposure experiments. RT-qPCR assays of whole hiCOs showed significant gene expression changes in a TH concentration-dependent manner for most of the selected marker genes. SC co-treatment attenuated the T3-induced expression response for a subset of genes (i.e., CADM2, DBP and DIO3) in acute T3 treatment schemes. IA co-treatment enhanced T3-induced expression levels in longer-term T3 treatment schemes. Cell type composition (progenitors, neurons) had a clear influence on T3-induced expression responses as evident from comparison of T3 effects in early and late stage hiCOs. hCOs effectively metabolize T3 to 3,3’2. Notably, metabolic degradation of T3 was reduced upon co-treatment with either SC or IA. Thus, the reference compounds affected both molecular markers and local T3 metabolism. Our study demonstrates the utility of hiCOs as a promising platform for THSDC assessment, identifies critical aspects (validation, endpoints, reference compounds) and highlights pitfalls for the assay validation process.

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Thyroid Cancer CLINICAL 1

PSI-03-02

Is isthmic tumor location in papillary thyroid carcinoma a high-risk factor in comparison with tumor located in thyroid lobes?

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Introduction

Thyroid isthmus has lack of normal parenchyma, and it connects both of thyroid lobes with lymphatic drainage. It is known that isthmic papillary thyroid cancer (PTC) presents frequent extrathyroidal extensions (ETE), multifocality and lymph node involvement. Therefore, many surgeons prefer total thyroidectomy and central compartment neck dissection (CCND) for the radical treatment of PTC located in thyroid isthmus. The purpose of this study is to figure out the clinical implication of isthmic tumor location in PTC compared with PTC located in unilateral thyroid lobe.

Materials and Methods

A total 1500 patients with PTC who underwent total thyroidectomy and lymph node dissection were reviewed. 160 were isthmic PTC patients (isthmic cancer group), 1340 were patients with PTC located in unilateral thyroid lobe and 1.5 propensity score matching in age, sex and tumor size were performed. Finally, 800 patients (matched-unilateral cancer group) were selected to compare with isthmic cancer group.

Results

After matching, the median follow up period of total patients was 122 months. 10-year cumulative RFS rate were 99% for isthmic cancer group and 96% for matched-unilateral cancer group (P = 0.260), respectively. There were no differences in age, sex, tumor size, ETE tumor multifocality and the number of metastatic lymph node between two groups. However, the ratio of patients with lateral neck node metastasis was lower in isthmic cancer group (P = 0.032) and it mainly occurred bilaterally (P < 0.001) in comparison with matched-unilateral cancer group. The tumor location of isthmus did not increase the risk of ETE, lymph node metastasis and tumor multifocality in multivariate analysis. It did not worsen RFS in Cox regression, neither.

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Changes in clinical status after second 131I treatment in patients with differentiated thyroid cancer (DTC) not cured with the initial treatment

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Objectives
Currently, 131I treatment after surgery is suggested in selected intermediate-risk and in high-risk patients with DTC. In patients with radio-avid structural disease and in those with biochemical disease a second 131I treatment could be considered. However data about the impact of the second 131I treatment on clinical status remains controversial.

Methods
Clinical data of 231 DTC patients followed at the Unit of Endocrinology of the University Hospital of Pisa, who experienced the second 131I treatment for indeterminate/biochemical (BiR) or structural incomplete response (SiR), were collected.

Results
Most of patients were females (64.9%). Median age was 41 and median tumor size was 2.1 cm. Most of cases were pT1 according to TNM 8th edition (45.5%) and pN1 disease accounted for 51.5% of the cases. CV-PTC was the most frequent histology (59.3%). Multifocality and bilaterality were frequently observed (77.7%), like mETE (70%); while in 32.4% of the cases vascular invasion was diagnosed. All patients were submitted to the first 131I treatment either with low (61%) or high (39%) 131I activities. Eight patients (3.5%) performed neck surgery for lymph node metastases before second 131I treatment and, for this reason, were excluded from the study. Therefore 223 patients performed a second 131I treatment: 65.5% (n = 146) because of BiR and 34.5% (n = 77) because of SiR, either for radio-avid disease or for positive neck ultrasound. Regarding BiR patients (n = 146) the second 131I treatment led to excellent response (ExR) in 13.7%, while BiR persisted in 64.4%. In the remaining 32 patients (21.9%) a SiR was detected, either because radio-avid (40.4%) or for the identification of lymph node metastases by neck ultrasound (59.6%). Conversely in patients who performed the second 131I treatment for an initial SiR (n = 77), 6.5% showed an ExR, 15.6% a BiR and 77.9% a persistent SiR. During the follow-up, overall, 58.3% (n = 130) experienced further treatments, while 41.7% (n = 93) were followed-up without any other treatment. After a median follow-up of 9.6 years, ExR accounted for 22.9%, BiR for 48.8% and SiR for 28.7% of all study group.

Conclusions
Only 11.2% of patients can be cured by a second 131I treatment. Other treatments, any type, performed in about 60% of patients, increased the percentage of cured patients up to 23%, during a follow-up of about 10 years.

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Risk of structural recurrence in differentiated thyroid carcinoma (DTC) patients without evidence of disease after initial treatment: insights into risk factors and comparison with american thyroid association guidelines

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Background
The last American Thyroid Association guidelines (ATA-2015) defined the risk of structural recurrence in patients with DTC cured after initial treatment and according to the initial histology. However, these data resulted from several studies including different patients with different kinds of treatment. We retrosively evaluated a large population of patients with DTC, treated and followed in a tertiary referral center, with the aim to characterize the rate of structural recurrence, the clinical-pathological factors involved in the recurrence and to compare our results with those proposed by the ATA-2015.

Patients and Methods
We evaluated epidemiologic and clinical-pathologic data of 1331 consecutive patients between January 2010 and September 2012, followed at the Operative Unit of Endocrinology of the University Hospital of Pisa. Data were collected at the time of first 131I treatment after surgery for all patients, and thereafter during the follow-up according to the standard of care.

Results
At the first control after 131I treatment (median time 8 months), 36 patients (2.7%) were lost at follow-up and 82 patients (6.2%) showed a structural incomplete response and for this reason were excluded from the study. In the remaining (n = 1213) who showed an excellent, indeterminate, or biochemical incomplete response, only 34 patients (2.8%) (Group A) showed a structural recurrence during the follow-up (median 7 years). Compared to the patients who did not show any structural recurrence (Group B), patients of group A showed more frequently larger tumor size (> 4 cm), aggressive histology, minimal extrathyroidal extension, vascular invasion and a more advanced TNM stage. When compared with ATA-2015, the overall recurrence rate in our group is significantly lower, both if considering the histologic ATA-2015 categories and when classifying patients in the three groups according to initial histology and rate of recurrence reported (≤ 5%, 6-20%, > 20%).

Conclusions
In a large population of DTC patients without evidence of structural disease after the initial treatment, treated and followed with a uniform modality over time, the structural recurrence rate is a rare event (2.8%). However, several clinical and histologic factors were significantly associated with the risk of structural recurrence. The recurrence rate, in this series was lower than that proposed by ATA-2015. One possible reason is that these patients were followed-up at the same tertiary referral center with the same clinical strategy.

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Low risk differentiated thyroid carcinoma (DTC) can be safely treated with thyroidectomy alone: real-life experience in a medium-long term follow-up

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Background
Since 2006 according to the European consensus for the management of patients with DTC, in tumors ≤ 1 cm, treatment with thyroidectomy alone without 131I treatment was suggested. Therefore, in our institution, we applied this suggestion in clinical practice, although prospective studies were not still available. Aim of this study is to evaluate the rate of the events occurring in a medium-long term follow-up.

Patients and Methods
We evaluated clinical-pathologic data of 378 consecutive DTC patients at low risk of recurrence treated with total thyroidectomy, without lymph node dissection and 131I treatment after surgery, between 2006 and 2012. Events during the follow-up were defined as structural if abnormal findings at neck US appeared and were cytologically confirmed. Biologic events were defined in TgAb negative patients if LT4-Tg increased > 5 ng/ml or > 2 ng/ml in two consecutive evaluations, or TgAb appeared; conversely in TgAb positive patients if TgAb increased > 50% in two consecutive evaluations and if the increasing trend over time was constant.

Results
Females accounted for 75.4% of our study group median age was 50 (IQR 40.75-59). Mean tumor size was 0.45 ± 0.27 cm. Most of patients had a unifocal T1a tumor (98.9%), and 73.3% had CV-PTC, 24.1% FV-PTC, 2.4% aggressive variants of PTC and in 1 case an FTC was diagnosed. After a median follow-up of 7.7 years, no structural events occurred. Regarding biologic events, 16/378
(4.2%) were highlighted, 12 (3.2%) for increase in LT4-Tg values and 4 (1.1%) for the increase in TgAb values, over time. Mean detection time of biologic events was 41 months (median 17 months). No patients performed additional treatments, surgery or 131I treatment and currently were followed-up with active surveillance.

Conclusions

In a real-life experience in the management of low-risk DTC we obtained similar results than the recently reported prospective EStimABC 2 trial, although with a mean tumor size slightly smaller, but in longer follow-up time. These data confirmed that also in a medium-long term follow-up, low-risk DTC, particularly those with moderate risk features, has excellent overall survival.

Results

There was no statistically significant difference in recurrence between the mETE and gETE groups before propensity score matching (Z-score = 0.072). In inverse-probability weighted regression adjustment (IPWRA), by balancing the bias that I131-treated patients displayed a more aggressive behavior, with ongoing ATA risk stratification system. Treatment effect was assessed by Kaplan-Meier analyses demonstrated that higher LNR of central compartment with cut-off value of 0.56 reduced disease-free survival (log-rank P < 0.001).

Conclusions

Central LNR was an independent prognostic factor in N1b PTC patients.

Keywords: Papillary thyroid cancer, central lymph node, lymph node ratio, Disease-free survival

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PS1-03-23

Comparison between minimal and gross eTE for risk of recurrence in papillary thyroid carcinoma: a propensity score matching study

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Background

The presence of extrathyroidal extension (ETE) is associated with locoregional recurrence and distant metastases in papillary thyroid carcinoma (PTC). ETE is classified into gross ETE (gETE) and minimal ETE (mETE). The mETE was recently excluded from the T3 category in the TNM staging system. The purpose of this study is to compare the recurrence risk of mETE and gETE in PTC patients through propensity score matching analysis. And a comparison in the same way for papillary thyroid microcarcinoma (PTMC) in subanalysis was done.

Methods

We assessed 4452 patients with DTC who underwent thyroid surgery from January 2009 to December 2015 at Seoul St. Mary’s Hospital (Seoul, Korea). Clinopathological characteristics and long-term oncologic outcomes between mETE and gETE in PTC were compared using propensity score matching to reduce selection bias. The mean follow-up duration was 122.7 ± 22.5 months.

Results

There was no statistically significant difference in recurrence when comparing mETE group and gETE group before propensity score matching (P = 0.072). In multivariate Cox regression analysis, mETE and gETE were not associated with an increased risk of recurrence. After propensity score matching, there was no statistically significant difference in recurrence when comparing mETE group and gETE group (P = 0.668). Moreover, gETE did not show statistically significant comparison with mETE in univariate and multivariate Cox regression analyses. Lymphatic invasion features and positive lymph nodes were shown as independent risk factors for tumor recurrence. Similar results were shown in PTMC subanalysis.

Conclusions

There was no statistically significant difference in tumor recurrence and DFS between the mETE and gETE groups after propensity score matching. The results of this study suggest that, like gETE, PTC patients with mETE should be carefully followed up because of equal risk of recurrence. Furthermore, we might reconsider the T staging system classification.

Keywords: Minimal ETE, Gross ETE, Papillary thyroid carcinoma, Recurrence risk, Propensity score matching

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PS1-03-24

Central lymph node ratio predicts prognosis of N1B papillary thyroid cancer

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Background

To date, no staging system has been related to the number of metastatic lymph node or lymph node ratio. Lymph node ratio (LNR) was defined as the number of metastatic LNs divided by the total number of LNs dissected. The purpose of this study was to determine how central LNR had a prognostic value to predict recurrence in N1b papillary cancer.

Methods

This study included 331 patients who underwent total thyroidectomy with lateral neck dissection for N1b papillary thyroid cancer at Seoul St. Mary’s Hospital between January 2012 and December 2017. The mean follow-up duration was 82.1 ± 20.4 months. Hazard ratios of the cut-off LNR values for recurrence were calculated for relevant covariates using multivariate Cox regression analyses. Kaplan-Meier analyses were also utilized to assess the effects of estimated LNR cut-off values on disease-free survival (DFS).

Results

The patients enrolled was divided into two groups according to central lymph node ratio, and the cut-off value of 0.56 was determined by ROC curve. Age, sex, tumor size, lymphatic invasion, vascular invasion, the number of positive LNs, T stage, TNM stage, and recurrence were factors that statistically relevant to central LNR. Multivariate Cox regression analyses revealed that central lymph node ratio higher than 0.56 was an independent prognostic factor for recurrence in N1b papillary thyroid cancer (hazard ratio [HR]: 6.177, 95% confidence interval [CI]: 1.763-21.639, P = 0.004). In addition, tumor size was independently prognostic for recurrence (hazard ratio [HR]: 1.951, 95% confidence interval [CI]: 1.450-3.340, P = 0.0015). Kaplan-Meier analyses demonstrated that higher LNR of central compartment with cut-off value of 0.56 reduced disease-free survival (log-rank P < 0.001).

Conclusions

There was a statistically significant difference in recurrence when comparing mETE group and gETE group before propensity score matching (Z-score = 0.072). In inverse-probability weighted regression adjustment (IPWRA), by balancing the bias that I131-treated patients displayed a more aggressive behavior, with ongoing ATA risk stratification system. Treatment effect was assessed by Kaplan-Meier analyses demonstrated that higher LNR of central compartment with cut-off value of 0.56 reduced disease-free survival (log-rank P < 0.001).

Central LNR was an independent prognostic factor in N1b PTC patients.

Keywords: Papillary thyroid cancer, central lymph node, lymph node ratio, Disease-free survival

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PS1-03-25

Low-intermediate risk thyroid cancer: no benefit of postsurgical iodine?

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Objectives

Evaluate the benefit of postsurgical radioactive iodine (RAI) in patients with differentiated thyroid cancer (DTC) at low to intermediate risk of recurrent disease in whom routinary use of RAI is recommended

Methods

We retrospectively evaluated 1316 patients with DTC diagnosed between 2009-2015. ATA low (LR) and intermediate (IR) risk were included in the study (PTC: tumor size > 1 cm, microscopic extrathyroidal invasion, < 5 microscopic N1 (< 2 mm), > 5 N1 of <3 cm, aggressive histology, vascular invasion; FTC minimally invasive with tumor size > 1 cm). These patients were categorized into either treated or untreated with I-131. The response to therapy was evaluated by ongoing ATA risk stratification system. Treatment effect was assessed by inverse-probability weighted regression adjustment (IPWRA), by balancing the distribution of factors influencing treatment assignment between I131-treated or untreated patients.

Results

A total of 469 patients (119 males and 350 females) were selected. The mean age at diagnosis was 46.1±14.3 years old. 328 patients (69.9%) were treated with I-131 while 141 (30.1%) untreated. In the overall group, biochemical or structural disease was observed in 44 (9.4%) patients after a median time of 17.5 months from the diagnosis. Persistent/recurrent disease was more frequent in I131-treated than in untreated patients (12.5% vs 2.1%, respectively, P < 0.001). This result was in line with the bias that I131-treated patients displayed a more aggressive pathology at diagnosis. By the inverse-probability weighted regression adjustment (IPWRA) analysis, the estimated percentage of recurrent disease was 10% (95% CI = 6.3-12.9%) in I131-treated and 16% (95% CI = 11.1-20.71%) in untreated patients (P = 0.02). Hence, if all patients would be treated with I131, the estimated risk of relapse would be reduced by 40% (RR = 0.6; 95% CI = 0.40-0.92, P = 0.018). Multivariate logistic regression analysis identified
as factors independently associated with persistent/recurrent disease: pN1 (OR = 3.56; 95% CI 1.55-8.17), male sex (OR = 2.45; 95% CI 1.12-5.36) and microscopic extrathyroidal extension (OR = 3.28; 95% CI 1.5-7.15).

**Conclusion**
Radioiodine administration in LR and IR is frequently defined on a case-by-case basis as suggested by retrospective studies. To make the outcome conditionally independent of the treatment assignment, in our matching method we observed that treatment with I131 in low/intermediate DTC reduces the absolute risk of persistent/recurrent disease by 6%. Only prospective clinical trial may definitely answer the question whether consider or not consider I131 therapy for low-to-intermediate DTC. Until then, a careful evaluation of the whole range of “aggressive” features of the tumor should guide RAI decision making.

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**PS1-03-26**

**Age as a prognostic factor in at low and intermediate risk thyroid cancer patients**

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**Background and Aim**
American Thyroid Association (ATA) guidelines do not consider age at diagnosis of differentiated thyroid cancer (DTC) as a prognostic factor in the estimation of risk of recurrence and persistent disease. While age at diagnosis has already been assessed in high-risk patients, it remains to be established whether there is a correlation between age at diagnosis and long term outcome in DTC patients.

**Methods**
We retrospectively evaluated 863 DTC patients with a median follow-up of 10 years, 52% of them classified as low risk (449/863) and 48% as intermediate risk (414/863). For each ATA-risk class patients were divided into subgroups based on age at diagnosis (<55 or ≥55 years).

**Results**
Age had no impact on clinical outcome of ATA low risk patients. Intermediate risk patients ≥55 years had a higher risk of recurrence (P = 0.0125), death (P = 0.03) and worse long term outcome (P = 0.006) at univariate analysis. Multivariate analysis confirmed the impact of age on mortality together with T stage in intermediate risk patients (OR = 5.35, 95% IC 1.44-25.55, P = 0.02 and OR = 13.34, 95% IC 3.74-54.2, P = 0.01 for age and T stage, respectively). Age ≥55 years was the only independent risk factor associated with recurrences in intermediate risk patients (OR: 5.04, 95%IC 1.31-24.18, P = 0.02). Age at diagnosis was not confirmed as a long term outcome predictor at multivariate analysis in intermediate risk patients, where only T stage was significantly associated with final outcome (OR: 5.45, 95%IC 2.63-11.21, P < 0.001).

**Conclusion**
Age at diagnosis is a predictor of recurrence and death only in ATA intermediate risk patients. This finding suggests that age at diagnosis should be considered as an additional feature to improve the initial risk stratification.

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**PS1-03-28**

**Cardiometabolic risk factors in a cohort of Algerian thyroid cancer survivals**

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**Objectives**
Cardiovascular disease encountered the leading cause of death in thyroid cancer survivals exceeding death by cancer itself. Etiological factors are the therapy used and the duration of exposure to this it, the diagnosis of cancer itself, or the factors that led to this cancer. We aim to evaluate cardiometabolic risk factors in an Algerian cohort of thyroid cancer survivals.

**Methods**
The study includes a cohort of patients followed in the thyroid cancer register in the endocrinology department of Constantine University Hospital during the period between January 2020 and June 2021. Patients have received a complete examination in addition to an ECG and a fasting blood sample including fasting blood sugar, complete lipid profile, TSH, and FT4.

**Results**
33 patients have been included, mean age was 47 years (28-70), mean age at diagnosis of cancer was 42(25-64), 91% were women, type of cancer was 63.6% for papillary thyroid cancer and 27.3% of follicular variant of papillary thyroid cancer, 3% were follicular cancer and 6.1% were NIFTP. All patients underwent total thyroidectomy. Concerning TMM classification; 75.7% were T1 including 33.3% of Tla, 15% were T2 and 3% were T3. 15% were N1. According to the 8 AJCC staging system, 97% were stage 1 and 3% were stage 2. In accordance with the modified 2009 American Thyroid Association (ATA) risk stratification system 72.7% were at low risk, 21.2% at intermediate risk, and 6.1% at high risk. 60% of patients have received Radioiodine therapy. Concerning cardiometabolic risk factors, 36.4% had hypertension which was diagnosed after thyroid cancer surgery in 18.2%. 21.2% were diabetic or prediabetic with the diagnosis made after surgery in 6.2% of patients, dyslipidemia was diagnosed in 48.5% of patients and 78.8% of patients were overweight or obese. Just one patient was a current smoker.

**Conclusion**
In this cohort of Algerian thyroid cancer survivals, the risk of death by cancer is low in most cases, however, cardiometabolic risk factors are prevalent and more attention for cardiovascular prevention is needed for these patients.

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Thyroid hormone transporters and development

PS1-04-29
Cell-specific function of the thyroid hormone transporters MCT8 and Oatp1c1 in murine brain barrier cells

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Mice with combined deficiency in the thyroid hormone transporters Mct8 and Oatp1c1 (Mct8/Oatp1c1 dko mice) display a strongly diminished TH brain content and, consequently, a disturbed neuronal maturation and myelination as well as locomotor abnormalities while serum T3 levels are highly elevated. This phenotype can be explained by an impaired transport of T4 and T3 into the CNS in the absence of both transporters. Yet, the exact cell-specific function of Mct8 and Oatp1c1 in brain barrier cells remains to be investigated. To address this question, we generated mice lacking Mct8 and/or Oatp1c1 specifically in endothelial cells (= Endo del mice) by crossing conditional Mct8 flox and Oatp1c1 flox animals with mice expressing cre-recombinase under the constitutively active Tie2 promoter. In order to eliminate Mct8/Oatp1c1 specifically in astrocytes in the adult CNS (= Astro del mice), we took advantage of a Tamoxifen-inducible Aldh1l1CreERT2 line and crossed them with conditional Mct8/Oatp1c1 flox mice. Both Mct8/Oatp1c1 Astro del as well as Endo del mice were phenotypically indistinguishable from their wildtype littermates. Monitoring Cre recombination activity with a YFP reporter construct confirmed the cell-specific cre-mediated recombination in astrocytes and endothelial cells, respectively. Likewise, Mct8 protein expression was not affected in choroid plexus epithelial cells as well as in tanyocytes excluding off-target effects. Mct8 and Oatp1c1 mRNA expression further was studied by fluorescence in situ hybridisation (FISH). Indeed, in both mouse models, a decreased mRNA expression for both TH transporters could be observed. To evaluate the functional outcome of the respective genetic modification, Mct8/Oatp1c1 Astro del mice were subjected to locomotor tests and revealed only a mild coordination deficiencies in beam walk test whereas Mct8 Endo del mice showed a normal locomotor performance. To assess the cell-specific TH status in different brain cells, a first set of FISH experiments was conducted and already revealed normal THK transcript levels in hypothalamic PVN neurons of Mct8/Oatp1c1 Astro del mice whereas THK expression was found to be highly elevated in Endo del mice. Currently, further FISH studies are ongoing that include a variable of different TH-regulated target genes in different neural cell types and are expected to provide further information regarding the cell- and brain area-specific TH status. By this approach, we ultimately aim to clarify the function of Mct8 and/or Oatp1c1 in astrocytic vs endothelial TH transport.

PS1-04-31
The role of type 3 deiodinase in a human model for early brain development

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Background
Disrupted thyroid hormone (TH) homeostasis has devastating effects on human neurodevelopment. THs are critical signaling molecules in neurodevelopment, acting on differentiation of neural cells, migration, synaptogenesis and myelination, with deiodinases governing intracellular TH concentrations in a spatiotemporal manner. It is remarkable that fetal neural cells, while being key target cells of TH, exhibit strong activity of the TH inactivating enzyme DIO3. Currently, the molecular mechanisms underlying TH action in brain are mainly derived from animal models. We utilized human induced pluripotent stem cell (hiPSC) technology to investigate the role of DIO3 in a human model for early brain development.

Methods
We generated neural progenitor cells (NPCs) and neural networks from hiPSCs as a model for early human brain development. hiPSCs-derived neural cells contained all the key players in TH cellular signaling. We inactivated DIO3 in different neural cells using tetracycline (TetO) control, a small molecule that blocks DIO3 activity. Cells were cultured with different T3 concentrations (0-3.10 nM). We used immunocytochemistry, gene expression and DIO3 and metabolism assays as readouts.

Results
We observed a high DIO3 activity in NPCs and neural networks, being the highest in NPCs. Inactivation of DIO3 caused increased gene expression of T3-dependent genes such as KLF9 in neural progenitor cells and neural networks. We also examined the differentiation potential of neural progenitor cells to neural networks in absence of DIO3. Our preliminary immunocytochemistry data showed an increase in cells containing neuronal nuclear protein (NeuN), a biomarker for neurons, when the activity of DIO3 is diminished.

Conclusion
Our preliminary results suggest that impaired DIO3 activity may lead to excessive TH action in neural cells and therefore compromising normal brain development. We are currently investigating further to validate this findings. We also aim to inactivate DIO3 through genetic modification using the CRISPR interference technology. Our model represents a versatile tool to investigate cellular TH regulation and action for early human brain development.

PS1-04-30
Impact of thyroid hormone transport on the hippocampal gabaergic and glutamatergic system

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Patients with inactivating mutations in MCT8, known as Allan-Herndon-Dudley syndrome (AHDS), present a severe form of psychomotor retardation and, frequently, epileptic seizures of unknown etiology. These neurological symptoms are thought to arise due to an impaired transport of thyroid hormones (TH) across the blood brain barrier and/or into the neural cells. As a consequence of species-specific differences in the expression of the TH-specific organic anion transporter polypeptide 1c1 (Oatp1c1), the AHDS pathology is only replicated in Mct8/Oatp1c1 double knockout (M/O-dKO) mice. Here, we address the question whether alterations in the hippocampus, a brain area central in epilepsy disorder, underpin the seizure susceptibility of MCT8 patients. To this end, we first characterized the inhibitory GABAergic system and the excitatory glutamatergic system in the hippocampus at different postnatal stages using the M/O-dKO mouse model. At P12, immunofluorescence studies showed a severe decrease in Gad67 levels, a general GABAergic marker, in M/O-dKO mice. Likewise, numbers of GABAergic neurons positive for parvalbumin were strongly reduced, while there was a significant increase in somatostatin positive interneurons in M/O-dKO mice. These cellular changes are transient as at P120, no differences were visible in M/O-dKO mice any longer. In contrast, qPCR analysis of hippocampal homogenates at P12 and P120 revealed an increased expression of GABA transporters and GABA transaminase in adult M/O-dKO animals, indicating increased GABA reuptake and metabolism, respectively. On the other hand, the expression levels of kainite receptor subunits such as GluR6 or KA1 were increased in adult M/O-dKO mice, suggesting an abnormal glutamate signaling in the hippocampus. Together, these results point to an altered development of both the inhibitory and the excitatory system that can potentially impact seizure susceptibility in the absence of Mct8 and Oatp1c1.

PS1-04-32
Three-dimensional spheroids: a new approach for the identification and characterization of novel markers for tumor-initiating cells subpopulations in thyroid cancer

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Thyroid cancer (TC) is the most common endocrine malignancy, with an increasing number of diagnosis in the last decades. Of all TC histotypes, the
poorly differentiated and anaplastic TCs (PDTC and ATC) have a very poor prognosis because of their invasiveness and metastatic behavior, as well as their insensitivity to radioactive-iodine treatment. In the last years, the stem cell model has been developed to further explain TC carcinogenesis. According to this model, only a subset of cancer cells, identified as Cancer Stem-like Cells (CSCs) or Tumor Initiating Cells (TICs), give rise to progenitor cells that may drive tumor growth. These cells exert stem-like properties, tumorigenic potential and the ability to grow in non-adherent spheres. An aggregating candidate for the identification of putative TICs in TC, especially for the most dedifferentiated forms, is EpCAM (epithelial cell adhesion molecule), a transmembrane glycoprotein that is highly expressed in TICs of other tumors of epithelial origin, playing a role in balancing cell proliferation and differentiation. We are aiming to investigate the biology of putative thyroid TICs, by in vitro characterization of thyrosphere-forming cells. We’ve developed a standardized thyrosphere model, based on PDTC and ATC cell lines displaying different genetic background. The main methodologies applied to obtain the 3D cultures are the hanging-drop and coating with poly(2-hydroxyethyl methacrylate) non-adhesive substrate. In appropriate growth condition, all the cell lines tested were able to generate thyrospheres when seeded at clonal density. We applied the ELDA web-tool to estimate the frequency of TICs with potential stem-like properties able to generate the 3D spheres, and we observed the highest stem cell frequency on spheres derived from FRO (ATC cell line). The screening of eight cell lines by Western Blot revealed that only FRO express EpCAM. Immunofluorescence on FRO-derived 3D spheres have shown an increase in EpCAM cleavage according to a radial gradient, and a variable expression of Ep-cadherin, a typical epithelial marker, in EpCAM-expressing cells. Moreover, immunofluorescence on cryosections of healthy and pathological patient-derived tissue samples have shown homogenous expression and cleavage of EpCAM in the healthy epithelium, while only heterogeneous distribution is seen in tumor sections. To conclude, EpCAM displays a distinct expression among TC cell lines and human tissues, and appears to correlate with the ability to generate 3D spheres in vitro. This thyrosphere model is a promising approach to better investigate the biology of aggressive TCs, including the sensitivity of thyroid TICs to different anticancer drugs.

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PS1-04-33
Transcriptomic signature of human embryonic thyroid reveals transition from differentiation to functional maturation
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The human thyroid gland acquires a differentiation program as early as weeks 3–4 of embryonic development. The onset of functional differentiation, which manifests by the appearance of colloid in thyroid follicles, takes place during gestation weeks 10–11. By 12–13 weeks functional differentiation is accomplished and the thyroid is capable of producing thyroid hormones although at a low level. During maturation, thyroid hormones yield increases and physiological mechanisms of thyroid hormone synthesis regulation are established. In the present work we traced the process of thyroid functional differentiation and maturation in the course of human development by performing transcriptomic analysis of human thyroids covering the period of gestation weeks 7–11 and comparing it to adult human thyroid. We obtained specific transcriptomic signatures of embryonic and adult human thyroids by comparing them to non-thyroid tissues from human embryos and adults. Remarkable upregulations of signaling growth factors such as IGF1 and FGF, already found to be involved in analogous models of thyroid development, as well as proteins involved in the cAMP pathway regulation and activity were highlighted in this transcriptomic analysis of human fetal/embryonic thyroids. This gives clues to explain how this pathway, crucial for the differentiation of thyroid cells, is activated in the absence of TSH during embryonic/fetal development. We defined a non-TSH (thyroid stimulating hormone) dependent transition from differentiation to maturation of thyroid. The study also sought to shed light on possible factors that could replace TSH, which is absent in this window of gestational age, to trigger transition to the emergence of functional functions and propose a list of possible genes that may also be involved in abnormalities in thyroid differentiation and/or maturation, hence leading to congenital hypothyroidism.

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PS1-04-34
The dawning of deiodinases: an outer ring deiodinase activity in the social amoeba Dictyostelium discoideum with high affinity for reverse T3
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Background
Conservation of genes involved in TH transport, metabolism and action can reveal clues about the origins of TH signaling. A deiodinase homologue (DdDio) was previously identified in the social amoeba Dictyostelium discoideum (Singh, 2014). Dictyostelium cells live as single cell amoeba in soil where they feed on bacteria. However, upon starvation a developmental program is initiated that results in the formation of a multicellular fruiting body consisting of a stalk of dead cells that supports a sporehead in which 80% of the cell population survives as spores. DdDio knock-out cells are disturbed in aggregation and developmental gene expression, indicating a potential role for DdDio in development. In this study we determined whether Dictyostelium has deiodinating activity towards iodothyronines.

Methods
Lyases from Dictyostelium cells in the early culmination phase were prepared and measured for deiodinase activity using several radiolabeled iodothyronines as substrate.

Results
We found limited iodine release with T3 and T4, but efficient outer ring deiodination of rT3, 3,3'-T2 and 3',5'-T2. We did not detect any inner ring deiodination. For rT3 as substrate, we found a Vmax of 1.2 (± 0.1) pmol/min mg total lysate protein, a Km of 21 (± 2) nM, and an IC50 of 19 (± 0.5) nM in cis-inhibition studies. The Dictyostelium deiodinase activity is dependent on DTT as a co-factor andihuely was disturbed by 0.1 mM iopanoic acid, but not by 0.1 mM PTU.

Conclusion
Our results show that the Dictyostelium deiodinase has high affinity and activity towards certain iodothyronines. To our knowledge, this is the most distant species from humans in which iodothyronine deiodination has been found to date, pushing the root of iodothyronine metabolism back to at least 1 billion years. Future studies will have to reveal whether iodothyronines are produced and have signaling functions in Dictyostelium. Singh et al. Dev Biol 2014, 396: 256-68

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PS1-04-35
Spatiotemporal expression of the thyroid hormone transporter MCT8 during cortical neurogenesis in human cerebral organoids
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Thyroid hormones (TH) play a critical role during nervous system development and patients carrying coding variants of THRA or SLC16A2/MCT8 genes present a spectrum of neurological phenotypes presumably resulting from perturbed local TH signaling during early brain development. Mono-carboxylate transporter MCT8 is a well-characterized TH membrane transporter and MCT8 mutations have been associated with the Allan-Herndon-Dudley Syndrome. Recent advances in stem cell biology allow for generation of human cerebral organoids (hCOs) from induced pluripotent stem cells (hiPSC). By recapitulating many aspects of human neocortex development, hCOs provide a tractable model to probe local TH action during cortical neurogenesis. The primary aim of this study was to map the spatiotemporal expression of MCT8 during hCO differentiation. hCOs were generated from healthy hiPSC lines and cultured for up to 10 weeks to a stage

Endocrine Abstracts (2022) Vol 84
corresponding to human cortex development at midgestation. The developmental expression profile of MCT8 protein was analyzed by immunofluorescence staining of cryosections prepared from hCOs of different stages. Expression of SLC16A2 mRNA was analyzed by single molecule fluorescent in situ hybridization (smFISH) and quantitative RT-PCR. Already along with the initial formation of rosette-like structures containing neuronal progenitors, MCT8 protein was detectable in Sox2+/Nestin+ radial glia cells (RGCs). During subsequent development of the ventricular zone, MCT8 immunostaining in RGCs became enhanced in apical endfeet at the ventricular surface. MCT8 expression was also detected in EOMES+ intermediate progenitors and HOPX+ outer RGCs located in the inner and outer subventricular zone, respectively. In addition to the diverse progenitor cell types, we detected robust MCT8 protein expression in TBR1+/AHP2+ deep layer neurons and at later developmental stages in SATB2+ upper layer neurons. The spatial expression of SLC16A2 mRNA across cortical cell layers (detected by smFISH) was highly concordant with the MCT8 protein expression profile. When comparing the spatial expression profile of SLC16A2 and THRA mRNAs, we observed enhanced THRA probe staining in the cortical plate zone and smFISH confirmed that excitatory neurons express much higher levels of THRA mRNA than neuronal progenitors. Our study shows that MCT8 is expressed at comparable levels in both neuronal progenitors and excitatory neurons during early cortical neurogenesis in hCOs whereas THRA mRNA is clearly expressed at higher levels in neurons compared to progenitors. The similarity of expression profiles in hCOs and human embryonic cortex tissue suggests that hCOs provide a promising system for studies on neuronal effects resulting from targeted disruption of MCT8 function.

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PS1-04-36

Thyroid hormone signaling in a human cellular model for early brain development

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Background and Objective

Disrupted thyroid hormone (TH) signaling has devastating effects on human neurodevelopment. The molecular mechanisms underlying TH regulation and action are largely based on animal models. However, animal models are limited in revealing some of the most fundamental aspects of neurodevelopment that are unique to humans. We employed human induced pluripotent stem cell (iPSC) technology to study the effects of T3 on neurodevelopmental processes in a human model for fetal brain development.

Methods and Results

We differentiated iPSC-derived neural precursor cells into 2D neural networks, consistent 60:40 ratio of neurons to glia and mimicking fetal brain development. Neural networks were cultured in different T3 concentrations (0, 3, 10, 30 nM). We quantified T3-responsive gene expression (KL9) by qPCR, and differentiation potential and synaptogenesis by immunohistochemistry. Neuronal electrophysiological function was assessed by calcium imaging.

Results

This well-established model in the field of neuroscience expressed key players of TH signaling (e.g. MCT8 DIO3). We observed a dose-dependent upregulation of KL9 mRNA than neuronal progenitors. Our study shows that MCT8 is expressed at comparable levels in both neuronal progenitors and excitatory neurons during early cortical neurogenesis in hCOs whereas THRA mRNA is clearly expressed at higher levels in neurons compared to progenitors. The similarity of expression profiles in hCOs and human embryonic cortex tissue suggests that hCOs provide a promising system for studies on neuronal effects resulting from targeted disruption of MCT8 function.

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PS1-05-37

The solid study (simplification of low level internal dosimetry): preliminary findings

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Background

Diagnostic thyroid scans using technetium-99m pertechnetate are widely used to differentiate the causes of hyperthyroidism. Only 1-3% of the administered isotope is taken up by the thyroid after 20 minutes resulting in high background radioactivity.

Objectives

To determine the effective radiation dose and calculated organ doses after a standard administration of Technetium-99m pertechnetate in patients referred for diagnostic scans.

Methods

All patients participating in the study gave their written informed consent. We used SPECT imaging and 2D whole body imaging to determine the radiopharmaceutical retention within regions of specific uptake i.e. thyroid, stomach, bladder, salivary glands. IDAC 2.1 was used to determine effective doses.

Results

The effective dose calculated for the standard 78.4 MBq administration was 4.89 mSv. The highest organ doses expressed as tissue dose per administered activity (mGy/MBq) were observed in the thyroid (0.488) followed by salivary glands (0.018), oesophagus (0.011), bladder wall (0.009), reproductve system (0.007) and lymphatic nodes (0.006). Lowest organ doses were in the lenses (0.002) and skin (0.002).

Conclusions

These are preliminary results from the Simplification of Low Level Internal Dosimetry study (SOLLD). As more data are accumulated we hope to develop a simple method of determining tissue doses which will help guide clinicians ordering nuclear medicine scans.

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PS1-05-38

TSH is superior to T4 for the assessment of thyroid function

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Background

Morbidity and mortality are associated with thyroid hormone levels in populations. This has invited a debate on what is the better parameter for assessment of thyroid function: the controlling hormone thyrotropin (TSH) or peripheral thyroid hormone measurements (thyroxine (T4) and triiodothyronine (T3)).

Aim

To assess the ability of TSH and total T4 (T4T) to discriminate between subtle differences in thyroid function.

Methods

Monthly collection of blood samples over one year in 35 subjects leading to 420 samples and 15 euthyroid and 20 mildly hypothyroid subjects. The latter group was classified as subclinically hypothyroid (SH) by two independent tests of thyroid function prior to inclusion. None of the participants received current treatment for thyroid disease. We measured TSH and total T4 in serum. Reference ranges with our assays were 0.4-4.5 mU/l for TSH and 60-140 nmol/l for T4. Results

The true thyroid state was confirmed by the mean of 12 repeated measurements, which was 1.97±7.23 mU/l for TSH in the euthyroid/SH subjects and 106/85 mmol/l for T4. No single TSH measurement was above the upper limit of the reference range for TSH in the euthyroid group, and thus 100% of test results conformed to the euthyroid state. In the SH group, 86% of test results were in keeping with the true thyroid state while 14% were within the reference range. For
TT4, 99% of test results were within the reference range among euthyroid subjects while this was 96% for the SH group. An overlap between the two groups was markedly more pronounced for TT4 compared to TSH. Bootstrap estimates based on 1000 replications showed an estimated area under the curve of 0.999 (95% CI: 0.995; 1.000) for TSH and 0.853 (0.736; 0.935) for TT4. There was no confidence interval overlap between participant groups for TSH, and hence markedly better performance of TSH compared to TT4.

Conclusion
The two groups differed more clearly when evaluated by TSH than by TT4. The TSH measurements were outside the reference range for 86% of individuals with SH compared 4% of TT4 measurements. Thus, our findings point to a higher diagnostic power for TSH compared to TT4 for separating individuals with mild hypothyroidism, and TSH is the most sensitive and accurate index of thyroid status at an individual level.

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**PS1-05-39**
The effect of obesity-related allostatic changes on cardio-metabolic risk in euthyroid children
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Purpose
The hormonal thyroid changes related to obesity, even when in the euthyroid state, may contribute to the unfavorable cardio-metabolic profile of obese patients. In this retrospective study we aim to investigate the biochemical thyroid changes and the association between serum TSH, FT4, FT3 and cardio-metabolic risk factors in euthyroid obese youths.

Methods
Four hundred ninety-one Caucasian euthyroid obese children and adolescents aged 9.93 ± 2.90 years were recruited. Each patient underwent clinical and auxological examination and laboratory workup including an OGTT and the measurement of thyroid function and lipid profile. Homeostasis model assessment of insulin resistance (HOMA-IR), triglyceride to high density lipoprotein cholesterol ratio, total cholesterol to HDL ratio, atherogenic index of plasma, insulino-metric index, area under the glucose and insulin curve were calculated.

Results
We found that TSH was positively correlated with BMI-SD values, increasing insulinogenic index, area under the glucose and insulin curve were calculated. FT4 levels resulted negatively correlated with fasting plasma glucose and FT3 levels positively correlated with the area under the curve of insulin and negatively correlated with HDL levels.

Conclusions
Taken together, our data showed that thyroid hormones influence obesity, lipid and glycemic parameters in euthyroid youths. These findings could carry implications regarding optimal TSH levels in obese children and confirm the importance of evaluating the thyroid function as possible adjunctive cardio-metabolic risk factor related to obesity.

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**PS1-05-40**
Thyroid hormone variability and cardiovascular morbidity in hyperthyroid patients treated with long-term antithyroid drug therapy
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Analysis of thyroid function and thyroid-stimulating hormone (TSH) measurements were determined and evaluated in relation to baseline clinical factors. The associations of TTR variability and baseline clinical factors with CVD-associated hospital visits were assessed with logistic regression analyses.

Results
In the multivariable analyses, age (odds ratio [OR] 1.06, 95% confidence interval [CI] 1.02-1.09), median FT4 (OR 1.09, 95% CI 1.05-1.13) and median FT3 values (OR 1.34, 95% CI 1.09-1.65), and FT4-CV (OR 1.02, 95% CI 1.01-1.04) were independent risk factors for CVD morbidity, whereas baseline positive thyrotropin receptor antibodies (TRAb) protected from CVD morbidity (OR 0.29, 95% CI 0.13-0.66). When the patients with baseline TRAb positivity were studied separately, FT4-CV was associated with CVD morbidity (OR 1.03, 95% CI 1.00-1.05), but median FT4 or FT3 levels were not. The patients with positive baseline TRAbs or thyroid peroxidase antibodies (TPOAbs) had higher FT4-CV and median FT4 levels, compared to the patients with negative TRAb or TPOAb measurements (P = 0.002 and P = 0.024, respectively).

Conclusions
During long-term ATD therapy for hyperthyroidism, FT4 variability is associated with an increased CVD morbidity. Patients with autoantibody-related hyperthyroidism have a higher variability of FT4 values compared to patients without thyroid autoantibodies. Although positive TRAbs are associated with a lower CVD morbidity compared to hyperthyroidism with negative autoantibodies, the variability of FT4 is associated with CVD morbidity also in patients with positive TRAbs.

DOI: 10.1530/endoabs.84.PS1-05-40

**PS1-05-41**
I-131 treatment of patients with autonomously functioning thyroid nodules and normal TSH blood level
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Analysis of thyroid function and thyroid-stimulating hormone (TSH) measurements were determined and evaluated in relation to baseline clinical factors. The associations of TTR variability and baseline clinical factors with CVD-associated hospital visits were assessed with logistic regression analyses.

Results
In the multivariable analyses, age (odds ratio [OR] 1.06, 95% confidence interval [CI] 1.02-1.09), median FT4 (OR 1.09, 95% CI 1.05-1.13) and median FT3 values (OR 1.34, 95% CI 1.09-1.65), and FT4-CV (OR 1.02, 95% CI 1.01-1.04) were independent risk factors for CVD morbidity, whereas baseline positive thyrotropin receptor antibodies (TRAb) protected from CVD morbidity (OR 0.29, 95% CI 0.13-0.66). When the patients with baseline TRAb positivity were studied separately, FT4-CV was associated with CVD morbidity (OR 1.03, 95% CI 1.00-1.05), but median FT4 or FT3 levels were not. The patients with positive baseline TRAbs or thyroid peroxidase antibodies (TPOAbs) had higher FT4-CV and median FT4 levels, compared to the patients with negative TRAb or TPOAb measurements (P = 0.002 and P = 0.024, respectively).

Conclusions
During long-term ATD therapy for hyperthyroidism, FT4 variability is associated with an increased CVD morbidity. Patients with autoantibody-related hyperthyroidism have a higher variability of FT4 values compared to patients without thyroid autoantibodies. Although positive TRAbs are associated with a lower CVD morbidity compared to hyperthyroidism with negative autoantibodies, the variability of FT4 is associated with CVD morbidity also in patients with positive TRAbs.

DOI: 10.1530/endoabs.84.PS1-05-40
Conclusion This study shows that radiomucide therapy with I-131 in pts with AFTN and normal TSH blood level is a simple, cheap and very effective modality. The effect of the I-131 therapy on AFTNs can be evaluated with a thyroid scan 6 months after I-131 therapy. DOI: 10.1530/endoabs.84.PS1-05-41

PS1-05-43

Treatment of hyperthyroidism reduces the systemic oxidative stress load, as measured by biomarkers of rna and dna damage

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Background Increased oxidative stress has been linked to both hypo- and hyperthyroidism. Whole-body oxidative stress can be estimated by the oxidized guanine nucleosides, 8-oxo-7,8-dihydログuanosine (8-oxoGuo) and 8-oxo-7,8-dihydログ-2′-deoxyguanosine (8-oxodG), derived from RNA and DNA, respectively. These biomarkers have been associated with increased morbidity and mortality in several diseases but are not well explored in humans with thyroid disorders.

Methods We measured urinary excretion of 8-oxoGuo and 8-oxodG in 51 hyperthyroid patients (toxic nodular goiter (TNG), n = 30; Graves’ disease (GD), n = 21) before, or shortly after, initiation of therapy and when stable euthyroidism had been achieved for at least 12 months. Patients with TNG were older (mean: 59 ± 12.5 years) than those with GD (50 ± 8 years). Mean follow-up time was 17.2 ± 4.6 and 22.9 ± 8.9 months for TNG and GD, respectively. All patients with TNG were treated with radioiodine, except for one who underwent thyroidectomy. GD patients were treated with methimazole and two of whom also received radioiodine.

Results Both oxidative stress markers correlated positively with age (8-oxoGuo: P < 0.001; 8-oxodG: P = 0.003). After adjustment, the baseline urinary excretions correlated with the severity of the disease, reflected by the plasma levels of thyroxine (8-oxoGuo: P = 0.002; 8-oxodG: P = 0.021), and were significantly higher in GD than in TNG (P = 0.001 for both biomarkers). Treatment significantly affected the excretions of the oxidative stress markers. In TNG, 8-oxoGuo decreased from geometric mean (GM) 2.11 nmol/mmol (95% CI: 1.85-2.39) to 1.91 nmol/mmol (95% CI: 1.67-2.19), P = 0.001, while 8-oxodG decreased from 1.65 nmol/mmol (95% CI: 1.41-1.93) to 1.48 nmol/mmol (95% CI: 1.27-1.74), P = 0.026. In GD, 8-oxoGuo decreased from 2.25 nmol/mmol (95% CI: 1.95-2.59) to 1.79 nmol/mmol (95% CI: 1.63-1.97), P = 0.0003, while 8-oxodG decreased from 2.02 nmol/mmol (95% CI: 1.73-2.38) to 1.54 nmol/mmol (95% CI: 1.31-1.81), P = 0.001. When euthyroid, no between-group differences were found.

Conclusion Treatment of hyperthyroidism significantly decreased the systemic oxidative stress load by 10-25%, as measured by the urinary excretion of nucleic acid metabolites. The higher values in patients with GD could be due to the more severe hyperthyroidism seen in this condition. Our findings may signify a key factor, explaining the higher morbidity and mortality linked to patients with hyperthyroid diseases, as shown in observational studies. Link to publication: https://pubmed.ncbi.nlm.nih.gov/33901280/

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PS1-05-44

The effect of testosterone supplementation on the hpt axis in euthyroid hypogonadal adult men: a prospective observational study

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Background and Objective It is known that androgens decrease and estrogen increases TBB. In female to male transsexuals under testosterone replacement, decrease of TBB has been shown, but also an increased T3/T4 ratio despite stable free T4 and TSH, suggesting increased conversion to T3 by testosterone. We wanted to study the HPT axis in hypogonadal cis-males before and after testosterone replacement.

Method Prospective observational study in adult male patients with hypogonadism in the setting of an outpatient endocrine clinic. Serum samples were taken prior to (visit

Endocrine Abstracts (2022) Vol 84
1) and at the first consultation (visit 2) under testosterone replacement. Males with history of thyroid disorder, having abnormal thyroid function at visit 1, treated with betaHCG, or taking drugs at baseline or during follow-up knowing to affect thyroid function were excluded. Paired t-test or Wilcoxon matched-pairs signed rank test was applied where appropriate.

**Results**

A cohort of n = 24 hypogonadal male patients was studied. Mean age was 52.9 +/- 15.4 years, n = 17 patients were treated for structural hypogonadism (n = 8 hypogonadotropic, n = 9 hypogonadotrophic), n = 7 patients were treated for functional hypogonadism. Median time between visit 1 and 2 was 2.53 months (range 1.15-11.5). As expected, total and free testosterone increased significantly (see Table). TSH was not different, but T4 (total and free) decreased. Total T3 was not different, and T3/T4 ratio increased between visit 1 and 2.

**Conclusion**

In euthyroid hypogonadal cis-males, testosterone replacement did not alter TSH, decreased total T4 and free T4, but not total T3. The increased T3/T4 ratio suggests increased conversion and/or differential binding to TBG.

**Table 1**

<table>
<thead>
<tr>
<th>Testosterone (ng/dL)</th>
<th>TSH (mIU/l)</th>
<th>Total T4 (ng/dL)</th>
<th>Free T4 (ng/dL)</th>
<th>Total T3 (ng/dL)</th>
<th>T3/T4 ratio</th>
</tr>
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<tbody>
<tr>
<td>Visit 1</td>
<td>Visit 2</td>
<td>n</td>
<td>p value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>249.1 [15.1-649.1]</td>
<td>368.3 [122.9-1297]</td>
<td>24</td>
<td>0.0003</td>
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<td></td>
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<tr>
<td>3.95 [0.20-7.30]</td>
<td>6.45 [2.20-16.90]</td>
<td>24</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.54 +/-0.85</td>
<td>1.46 +/-0.74</td>
<td>24</td>
<td>0.6490</td>
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<td></td>
</tr>
<tr>
<td>1.32 +/-0.16</td>
<td>1.24 +/-0.19</td>
<td>18</td>
<td>0.0337</td>
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<td></td>
</tr>
<tr>
<td>117.5 +/-30.4</td>
<td>123.2 +/-24.5</td>
<td>24</td>
<td>0.1010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.35 [8.94-22.34]</td>
<td>16.15 [11.56-27.71]</td>
<td>24</td>
<td>0.0101</td>
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</table>

**DOIs:** 10.1530/endoabs.84.PS1-05-44

**PS1-05-45**

**ABSTRACT WITHDRAWN**

**PS1-05-46**

**Body composition determinants of thyroid function and volume in euthyroid patient with obesity**

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The aim of our study was to investigate the relationship between anthropometric and body composition parameters and thyroid function (measured with TSH and free T4), as well as thyroid volume, in patients with obesity.

**Methods**

This is a cross-sectional study including patients with obesity consecutively referred to our tertiary endocrine center for diverse pathologies. TSH and free T4 was measured in all patients and thyroid ultrasound was performed by an experienced investigator, to estimate thyroid volume. Whole body DXA scans were available to evaluate total and regional body composition (lean and fat mass). We excluded from our analysis patients with abnormal thyroid function (TSH > 10 or < 0.5 mIU/l).

**Results**

In our group of 221 patients (147 women) mean BMI was 37.03 ± 7.37 kg/m² and mean age was 51.9 ± 18.95 years. As expected, TSH positively correlated with BMI (r = 0.142, P < 0.05), while free T4 was negatively associated with total lean mass (r = -0.143, P < 0.05), legs lean mass (r = -0.136, P < 0.05) and total fat-free mass (r = -0.169, P < 0.05). Thyroid volume was significantly higher in men (P < 0.01) and correlated with total lean mass (r = 0.353, P < 0.001), %fat mass (r = -0.213, P = 0.0002), weight (r = 0.179, P < 0.05) and height (r = 0.225, P < 0.01), but not with BMI. Lean mass remained positively associated with thyroid volume in a multivariate linear regression analysis which also included age, gender and %fat, together explaining about 41% of its variation.

**Conclusions**

In patients with obesity, lean mass is a factor independently associated with thyroid volume.

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**PS2-06-47**

**Prescription of levothyroxine and concurrent use of anti-arrhythmic and bone-anti-resorptive drugs in Belgium: retrospective study in a large population sample**

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Background and objective

Increased prescription of levothyroxine (LT4) has been observed in the USA and countries in Europe and has been related to increased thyroid function screening and a lower treatment threshold, increasing risk for overtreatment and overtreatment. We wanted to study the evolution of LT4 prescriptions in Belgium, and compare the use of anti-arrhythmic drugs (AAD) and bone-anti-resorptive drugs (BAD) between LT4-users and non-LT4-users.

**Method**

Retrospective study, using reimbursement data from the largest health insurance company (Christelijke mutualiteit/Mutualité Chrétienne), representing 42% of all Belgian residents during years 2001 to 2018. Individuals with history of thyroid surgery or concurrent use of thiamazole drugs were excluded (2.1% of cohort).

**Data extracted:** age, gender, socio-economic status (SIES, defined by right for increased reimbursement), number of persons with at least one package of reimbursed LT4 that was delivered in the public pharmacy, dose, BAD, AAD.

**Results**

Whereas 2.1% of individuals were prescribed LT4 in year 2001, this rose to 5.1% in year 2018 (2.5-fold increase). The increase was most pronounced for individuals aged ≥65 and especially ≥80yo (11.2% in year 2018 vs 4.3% in year 2001). Furthermore in year 2018 and for the total cohort, the proportion of LT4-users was higher in females (8.2% vs 1.9% in males, year 2018) and higher in individuals with increased reimbursement (7.4% vs 4.7%, year 2018). In 10.9% only the lowest commercially available dose of LT4 (25 µg) was prescribed, with highest proportion (14.4%) in the ≥80yo subgroup. Finally, in individuals aged ≥65yo in year 2018 use of AAD was higher among LT4-users than non-LT4-users (7.4% vs 50.4%; OR = 1.39; P < 0.00000). Also use of BAP was higher among LT4-users, especially in males (2.6% vs 1.9%; OR = 1.3; P < 0.0001; females: 10.4% vs 9.8%; OR 1.03; P = 0.026).

**Conclusions**

In a large representative Belgian sample, we confirm increasing prescription of LT4, most pronounced in the elderly, raising concerns regarding potential overtreatment. The high proportion of lowest LT4 dose and higher concurrent use of anti-arrhythmic and bone-anti-resorptive drugs among older LT4-users could point to overtreatment, but warrants further study.

**DOIs:** 10.1530/endoabs.84.PS2-06-47

**PS2-06-48**

**Pseudomalabsorption of levothyroxine: munchausen’s syndrome, compliance defects or fraud?**

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**Endocrine Abstracts (2022) Vol 84**
Objective

Factitious disorder imposed on self or Munchhausen’s syndrome (MS), is a psychiatric disorder in which physical symptoms are intentionally produced without any practical benefit. Patients with MS represent a diagnostic dilemma as laboratory and clinical results can be inconsistent with the history and physical exam. The aim of this study was to evaluate the role of the levothyroxine overload test to differentiate MS from malabsorption and to address life-threatening hypothyroidism.

Methods

1 mg of levothyroxine was administered to patients referred to our Department for severe hypothyroidism and suspect malabsorption. TSH, FT4 and FT3 were measured at baseline, after 360 minutes and 2 to 7 days.

Results

We studied 9 hypothyroid patients (1 male and 8 females, mean age 46.2±14.8 years). Three female had Hashimoto’s thyroiditis while the remaining patients had undergone thyroidectomy for cancer (n = 5) or goiter (n = 1). Although at referral all patients had TSH >100 mU/L with low or even undetectable FT4/FT3, at the time of testing three of them had TSH 4.5, 23.6 and 39.1 mU/L, respectively. All patients adequately absorbed levothyroxine as shown in the table (data expressed as mean ±SD). The huge variability of results depended on the severity of their hypothyroidism, as we observed that the rate of change of FT4/FT3 was positively and that of TSH negatively correlated with baseline TSH levels (P <0.01; r² = 0.69, 0.67 and 0.62), while did not correlate with patients’ weight or BMI.

In patients with baseline TSH >200 mU/L, the TSH did not change significantly at 360 minutes, but declined few days after the overload (range 32-62%). In 5/9 patients additional levothyroxine loads were administered to achieve euthyroidism. None of the patients had adverse events or reported side effects. Three patients fulfilled the criteria for MS and were referred to a Psychiatrist. In 3 patients we suspected malingering, as they were asking for social assistance for disabled people; 10 female had Hashimoto’s thyroiditis while the remaining patients had undergone thyroidectomy for cancer (n = 5) or goiter (n = 1).

Conclusions

Despite the low number of patients, typical of a pilot study, this is the first characterization of faecal microbiota composition of hypothyroid patients with the specific focus on T4 requirement.

DOI: 10.1530/endoabs.84.PS2-06-49

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PS2-06-50

TSH levels assessment in hypothyroid patients treated with liquid or tablet L-thyroxine

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Objective

Tablet levothyroxine (L-T4) is the common used therapy for hypothyroidism. In order to assess a good compliance to the therapy, treated patients are monitored with the execution of annual thyroid hormonal test. The stability of TSH levels in hypothyroid patients (with no malabsorption issues), treated with liquid L-T4, compared to that of the patients treated with tablet L-T4, remained a poorly understood topic. This study has the purpose to deepen this issue.

Methods

We selected patients who reported the following criteria: a) normal serum TSH levels at the basal evaluation; b) no malabsorption or drug interference issues; c) in treatment with liquid or tablet L-T4. Hypothyroid patients (matched by gender and age) were compared according to the used drug formulation; 653 subjects were in treatment with liquid L-T4, and 329 subjects with tablet L-T4. We performed a two year follow-up, during which the serum TSH, FT3, FT4 levels were annually measured.

Results

Gender, age, body mass index, history of chronic autoimmune thyroiditis, initial TSH level, and L-T4 dose were the parameters evaluated at the first abnormal TSH value. These parameters, at the time of initial normal TSH, were not associated significantly with time to abnormal TSH values. After 1 year, TSH values were normal in 86% of the patients who were in treatment with L-T4 liquid formulation, whereas only in 80% of patients who followed a tablet L-T4 therapy. After 2 years, normal TSH values were registered in 84% of patients who were treated with L-T4 liquid formulation, while only in 74% of patients who received tablet L-T4 (P < 0.05).

Conclusion

These data showed that in the long term follow-up, liquid L-T4 can permit to maintain more efficiently normal TSH levels in hypothyroid patients, than tablet L-T4.

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PS2-06-51

ABSTRACT WITHDRAWN

DOI: 10.1530/endoabs.84.PS2-06-51
PS2-06-05
The effect on serum tsh levels in patients with newly diagnosed hypothyroidism
Poupaq Fathali1, Silvia Martina Ferrari2, Giusy Elia3, Francesca Ragusa3, Sabrina Rosaria Paparo3, Valeria Mazzi1 & Alessandro Antonelli1
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Objective
The treatment with proton pump inhibitors (PPI; omeprazole, pantoprazole, lansoprazole) used for gastritis, gastric ulcer, etc. could lead to L-thyroxine (LT4) malabsorption issues, that is induced by the increased gastric pH. Many factors like age, way of assumption (during breakfast or with food), other drugs interferences, drug-kinetics, adherence to therapy, could impair the LT4 absorption.

Methods
The study involved 27 hypothyroid patients in treatment with LT4 tablet formulation. All patients were switched to an oral liquid LT4 formulation, maintaining the same dosage of LT4.

Results
We showed that circulating thyroid-stimulating hormone (TSH) levels could be normalized or decreased, after the switch from LT4 tablet to a liquid formulation, at the same dose. Furthermore, a worsening of TSH levels, with a relapse in the hypothyroid range, was recorded in 15% of the patients who, for different reasons, were switched back to take LT4 in tablets, with the same dosage.

Conclusion
Finally, our study suggests that the LT4 malabsorption issue caused by PPI could be solved with the assumption of the LT4 in a liquid formulation. However, this field needs to be further investigated involving also other conditions of altered LT4 absorption.

DOI: 10.1530/endoabs.84.PS2-06-05

PS2-06-03
Whole-body oxidative stress measured by biomarkers of RNA and DNA damage is higher in hypothyroid women, even after treatment, than in healthy individuals, measured by biomarkers of RNA and DNA damage
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Introduction
Hyptothyroidism has been associated with oxidative stress. Urinary excretion of oxidized RNA and DNA damage is a marker of oxidative stress. In healthy individuals, the excretion of 8-oxo-7,8-dihydroguanosine (8-oxoGuo) and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), respectively, represent whole-body DNA and RNA oxidation. While these biomarkers have been associated with increased morbidity and mortality in various diseases, they have been only sparsely explored in patients with thyroid disorders.

Methods
In 45 women with newly diagnosed hypothyroidism (overt: n = 23; subclinical: n = 22), urinary excretions of 8-oxoGuo and 8-oxodG, corrected for creatinine and smoking status between patients and controls. In the patients, none of the biomarkers changed significantly by achievement of euthyroidism. Thus, the geometric mean of 8-oxoGuo was 1.63 (95%CI: 1.39-1.92) nmol/mmol creatinine at baseline and 1.67 nmol/mmol (95%CI: 1.51-1.83) at euthyroidism (P = 0.39), while 8-oxodG was 1.28 nmol/mmol (95%CI: 1.14-1.44) and 1.32 nmol/mmol (95%CI: 1.18-1.48), respectively (P = 0.47). In the control group, the geometric mean of 8-oxoGuo was 1.23 nmol/mmol creatinine (95%CI: 1.07-1.42), while 8-oxodG was 1.04 nmol/mmol creatinine (95%CI: 0.88-1.23). Thus, the patients at euthyroidism, compared with control subjects, showed a significantly higher level of both 8-oxoGuo (P < 0.001) and 8-oxodG (P = 0.03). Among patients, a multiple regression analysis demonstrated a negative correlation between TSH and 8-oxoGuo, and a positive correlation between free T4 and 8-oxoGuo, at baseline. A positive correlation between baseline free T4 and 8-oxodG was also demonstrated.

Conclusion
In hypothyroid women, no significant effect of LT4 treatment was demonstrated on the oxidative stress biomarkers 8-oxoGuo and 8-oxodG. The excretion of these biomarkers was significantly higher in patients than in healthy individuals. It is speculated whether the increased oxidative stress burden reflects the impact of thyroid autoimmunity per se.

Endocrine Abstracts (2022) Vol 84
Conclusions
For UK endocrinologists, the role of combined levothyroxine + liothyronine in treatment of hypothyroidism remains a live issue for further research, brought into focus recently by the cost-led withdrawal of access to liothyronine in many regions. The importance of facilitating efficient dissemination of research findings in the UK is highlighted by the proportion of respondents who would currently consider prescribing thyroid hormone treatment in euthyroid female infertility with high titre antibodies, an indication for which evidence of efficacy is lacking.

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PS2-06-55

Free T3 levels and clinical status of patients with levothyroxine-compensated primary hypothyroidism: can we do better?

Objectives
To evaluate the relationship between free T3 (FT3) levels with symptoms suggestive of thyroid dysfunction, and quality of life (QoL) outcomes, in patients with compensated primary hypothyroidism (PH).

Methods
Cross-sectional study encompassing Portuguese levothyroxine-treated patients for PH who presented Thyroid-stimulating hormone (TSH) and free T4 (FT4) within the normal range. Pregnant women, patients with central hypothyroidism and/or with significant comorbidities (Charlson Comorbidity Index) were excluded. Blood samples for thyroid function tests were collected at the time of clinical evaluation. The Portuguese versions of the “Quality of Life Questionnaire for Patients with Thyroid Disease” (ThyPRO-39b) and the “MOS Short Form Health Survey 36 item v2” (SF-36v2) were applied.

Results
Two hundred and one patients were included, 176 (87.6%) were female, with a median age of 5 (minimum;maximum: 19;87) years. Chronic autoimmune thyroiditis was the most common cause of PH (n = 89[44.3%]). The median daily dose of LT4 was 100 µg (1.51µg/kg/day; minimum; maximum: 25; 250 µg).

Globally, the most reported symptoms were asthenia (n = 134[66.7%]), cutaneous xerosis (n = 127[63.2%]) and muscle fatigue (n = 107[53.2%]). In the ThyPRO-39b questionnaire, 138 (68.6%) patients did not attribute a detrimental effect on their QoL, to PH. Asthenia (n = 114[56.7%]), depressed mood (n = 112[55.7%]) and cutaneous xerosis (n = 94[46.8%]) were the most frequent complaints. With regard to the SF-36v2 questionnaire, most patients did not describe significant physical disability in activities of daily living. Around a third reported decreased vitality and energy, and approximately half of the patients described stability, compared to their health status in the previous year. Patients with complaints of constipation (P = 0.010) and depressed mood (P = 0.039) had significantly lower FT3 levels than patients without these symptoms.

The same trend was observed in patients with asthenia, muscle fatigue, cutaneous xerosis, periorbital edema, dysphonia, weight gain, cold intolerance and memory loss, although without statistical significance.

Conclusions
Most patients with normal TSH and FT4 do not have a negative impact on their QoL, at least significantly. Despite the restoration of “euthyroidism”, there are a number of symptoms with high titre antibodies, an indication for which evidence of efficacy is lacking. Many patients do not describe significant physical disability in activities of daily living. Around a third reported decreased vitality and energy, and approximately half of the patients described stability, compared to their health status in the previous year. Patients with complaints of constipation and depressed mood had significantly lower FT3 levels than patients without these symptoms. A number of symptoms with high titre antibodies, an indication for which evidence of efficacy is lacking.

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PS2-06-56

Polychlorinated biphenyl congeners PCB 118 and PCB 126 induce upregulation PD-L1 expression in human thyrocytes through aryl hydrocarbon receptor (AhR) pathways
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Objectives
Polychlorinated biphenyls (PCBs) are persistent organic pollutants that have been reported to cause a variety of toxic effects, including inflammation and cancer, through binding to the aryl hydrocarbon receptor (AhR). In turn, AhR promotes xenobiotic detoxification and antioxidant defense, by up-regulating specific responsive genes, the so-called “AhR gene battery”. AhR is also involved in modulation of immune response, by regulating programmed cell death 1 (PD-1) ligand (PD-L1) levels. PD-L1 has an important role in regulating immune responses by binding to PD-1 on immune cells, contributes to maintaining immune tolerance by down-regulating T-cell immune responses and cytokine production, and might favor the escape from immune surveillance of cancer cells. The aim of this study is to investigate the effects of PCBs on PD-L1 expression on thyroid cells.

Methods
Primary thyrocytes were obtained from patients undergoing surgery for benign thyroid disease (solitary thyroid nodule). Cultured cells were exposed for 24 h to increasing concentrations (2.5 and 5 µM) of 2 dioxin-like PCBs: the 2,3',4,4',5'-pentachlorobiphenyl (PCB 118) and the 3,3',4',4',5-Pentachlorobiphenyl (PCB 126). Gene silencing of AhR was performed by using a specific siRNA. mRNA and protein levels of PD-L1, AhR, IL-1beta and IL-6 were evaluated by real-time qPCR, ELISA and Western Blot.

Results
In cultured thyrocytes, exposure to PCB 126 and PCB 118 at 2.5 and 5 µM concentrations significantly induced the increase of both mRNA and protein levels of AhR and PD-L1 (P < 0.01 and P < 0.001, at 2.5 and 5 µM respectively for mRNA expression and P < 0.05 at 5 µM for protein levels). On the contrary, the knockdown of AhR before PCBs treatments reduced PD-L1 mRNA and related protein levels, indicating the involvement of this receptor in the regulation of PD-L1 enhanced by PCBs. In the same in vitro model, PCB exposure induced the increase of both mRNA and protein levels of inflammatory cytokines IL-1beta and IL-6 (P < 0.01 and P < 0.001, at 5 and 10 M respectively for mRNA expression; P < 0.05 and P < 0.01 at 5 and 10 M for protein levels).

Conclusion
Our data demonstrated that PCB 118 and PCB 126 may promote PD-L1 expression in thyrocytes. Such effects can be partially attributed to the activation of the AhR. These results suggest that the PD-1/PD-L1 pathway is activated in thyrocytes in the context of inflammatory/toxic stimuli and point to a new mechanism that need to be further deepened to understand the effect of PCBs on thyrocytes.

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Graves’ Disease I

PS2-07-57

Post-alemtuzumab graves’ disease remitting after switch to ocrelizumab
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Objectives
Graves’ hyperthyroidism is a frequent complication of alemtuzumab treatment in MS. We present the case of an MS patient who developed clinically and biochemically overt alemtuzumab-induced Graves’ disease, remitting 6 months after treatment with ocrelizumab and methylprednisolone pulse-therapy.

Methods
A 49-year-old man diagnosed with active multiple sclerosis who had undergone alemtuzumab treatment, and developed Graves’ hyperthyroidism which remitted after ocrelizumab and pulse-therapy with methylprednisolone. Clinical symptoms

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of Graves’ disease and thyrotropin antibody titres were frequently evaluated as well as multiple sclerosis clinical and paraclinical parameters.

Results
Several months after the second alemtuzumab course the patient developed a symptomatic Graves’ hypothyroidism with very high thyrotropin antibody titres, which was treated with anti-thyroid drugs. Two years later ocrelizumab was started along with methyprednisolone in pulse-therapy due to a multiple sclerosis relapse, with subsequent remission of the hyperthyroidism. Six months later the antibodies decreased and the anti-thyroid drugs were stopped. 24 months later he remains euthyroid.

Discussion
This case highlights the possibility of remission of post-alemtuzumab Graves’ disease after methyprednisolone pulse-therapy and ocrelizumab with avoidance of further medical or surgical treatment.

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PS2-07-58
High IgG4 serum levels in Graves’ disease compared with nonautoimmune hyperthyroidism
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Objectives
A role of IgG4 in Graves’ disease (GD) has been proposed, although the available data are conflicting. In addition, an association between Graves’ orbitopathy (GO) and IgG4-related disease has been postulated, but no firm demonstration has been obtained. Thus, the aim of the present study was to investigate the role of IgG4 in GD.

Methods
We performed a cross-sectional investigation in 351 consecutive patients (F: 284, M = 67; age 48.2 ± 15 yr.), of whom 306 had Graves’ disease and 45 had toxic nodular goiter (TNG). All patients came to our observation over 36 consecutive months to undergo radioiodine treatment. IgG4 were measured in all patients. The primary outcome was the level of IgG4 in GD patients compared with TNG. Secondary outcomes were: 1) the prevalence of IgG4 levels above the upper limit of normal range (66 mg/dL); 2) the prevalence of IgG4 levels above the cut-off value considered diagnostic for IgG4-RD (135 mg/dL); and 3) within GD patients, the levels of IgG4 and the prevalence of high IgG4 (≥66 mg/dL or ≥135 mg/dL) in patients with and without GO.

Results
IgG4 concentrations in GD patients (53 mg/dL; IQR: 26-94.7) were significantly greater than those in patients with TNG (56 mg/dL; IQR: 25-59; Mann Whitney U: 5.41; P = 0.02). In addition, the prevalence of patients with IgG4 levels above the upper limit of normal range was greater in GD (112/306, 36.6% vs 8/45, 17.7% in TNG; OR: 2.67, 95%CI from 1.2 to 5.9; P = 0.016). The prevalence of patients with IgG4 levels above the cut-off value diagnostic for IgG4-RD was nearly statistically significantly greater in GD patients (46/306, 15% vs 2/45, 4.4% in TNG; OR: 3.8, 95%CI from 0.89 to 16.2; P = 0.071). Limited to GD patients, IgG4 levels and prevalence of high values (≥66 mg/dL or ≥135 mg/dL) did not differ between patients with GO and those without GO.

Conclusions
IgG4 serum levels are higher in patients with GD compared with nonautoimmune hyperthyroidism, with an apparent greater prevalence of values that can be considered relevant. The possible clinical implications of our findings remain to be investigated.

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PS2-07-59
TPO antibody status prior to first radioactive iodine therapy as a predictive parameter for early hyperthyroidism in Graves’ disease
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Introduction
Several studies identified pre-treatment parameters that could help in the prediction of the thyroid functional outcome after radioactive iodine therapy (RAI) in Graves’ disease. However, the role of the thyroid peroxidase antibody (TPO Ab) status is not well studied.

Objectives
We investigated if a positive TPO Ab status before radioactive iodine (RAI) therapy in patients with Graves’ hyperthyroidism is a predictive factor for developing hypothyroidism post RAI.

Methods
We performed a retrospective study of patients with Graves’ hyperthyroidism with known TPO Ab status, receiving a first administration of RAI. Patients from four thyroid outpatient centres in Belgium receiving a first RAI therapy between the years 2011 and 2019 were studied. Clinical, laboratory, imaging, and treatment data were recorded from medical charts. Hypothyroidism and cure (defined as combined hypo- and euthyroidism) were evaluated in period 1 (≥2 and ≤9 months, closest to 6 months post RAI) and period 2 (>9 months and ≤24 months post RAI, closest to 12 months post RAI).

Results
One hundred fifty-two patients were included of which 105 (69%) were TPO Ab positive. Compared to TPO Ab negative patients, TPO Ab positive patients were younger, had a larger thyroid gland, and had more previous episodes of hyperthyroidism. There was no difference in TSH receptor antibody titer at diagnosis, pre-treatment with anti-thyroid drugs or administered RAI activity. In period 1, 89% of the TPO Ab positive group developed hypothyroidism vs 72% in the TPO Ab negative group (P = 0.007). In period 2, the observation was similar: 88% vs. 72% (P = 0.019). Cure rate was similar in both groups in period 1 (91% vs. 85%, P = 0.238) and in period 2 (94% vs 86%, P = 0.146).

Conclusion
A positive TPO Ab status in patients with Graves’ hyperthyroidism receiving a first administration of RAI is associated with a higher risk of early hypothyroidism. The underlying mechanism warrants further investigation. Future studies investigating pre-treatment parameters affecting outcome after RAI in patients with Graves’ disease should incorporate TPO Ab status as a variable.

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PS2-07-60
Polymorphisms in proinflammatory cytokines’ genes and lipid profile in patients with graves’ disease
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Objective
Graves’ Disease (GD) is one of the most common autoimmune disorders. Some SNP in pro-inflammatory cytokines have already been linked to an increased susceptibility of developing GD. Thyroid hormones are crucial modulators of lipid metabolism. A pro-inflammatory state, may contribute several metabolic changes, including disturbances in lipid metabolism. Our aim was to evaluate if SNP in pro-inflammatory cytokines also contribute to disturbances of lipid profile in GD patients.

Methods
Lipid profiles (total cholesterol [TC], high density lipoprotein [HDL], low-density lipoprotein [LDL] and triglycerides [TG], apolipoprotein A-I [Apo A-I], apolipoprotein B [Apo B] and lipoprotein (a)) were assessed in a case-control study comprising 98 Graves’ disease patients treated with methimazole. Genetic variants in IL6-174 G/C (rs1800795), TNFA-308 G/A (rs1800629), IL1B-511 C/T (rs16944), and IFNGR1-56 T/C (rs2234711) were discriminated by real-time PCR.

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using TaqMan SNP genotyping assays. The associations of genetic variants with lipid profile were evaluated with analysis unadjusted and adjusted for age and sex.

Results
Within our sample of 97 patients with GD, 91.8% were females, with a mean age of 44.4 ± 15.1 years. The mean TSH level of our population was 0.4 (0.0-1.3) mU/L, and the mean levels of FT3 and FT4 were 3.0 (2.6-3.5) ng/mL and 1.1 (0.9-1.4) ng/mL, respectively. Seven subjects (9.2%) had diabetes and thirty-three patients (43.4%) had prediabetes. The mean level of total cholesterol was 193.7 (149.1-238.3) mg/dL, the mean level of HDL cholesterol was 59.9 (43.5-76.3) mg/dL, and the of LDL cholesterol’s level was 117.1 (84-150.2) mg/dL. The A allele in TNFA-308 G/A was associated with significant lower levels of HDL cholesterol (P = 0.037). TNF-α A allele also had higher levels of fasting insulin (0.042). IL1B-511 C/T (rs16944), IL6-174 G/C (rs1800795) and IFNGR1-56 T/C (rs2234711) polymorphisms showed no association with lipid profile.

Conclusions
In patients with GD, we found lower levels of HDL among those with A allele in TNFA-308 G/A. This polymorphism may contribute to a higher atherogenic risk in patients with GD.

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PS2-07-61
Management of graves' disease among endocrinologists in russia
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Objective
We aim of the study was to investigate the clinical approach to Graves’ disease (GD) treatment among endocrinologists in Russia.

Materials and methods
An online questionnaire survey was conducted among doctors from Sept till Dec 2021. The questions covered the principles of diagnosis, treatment and dynamic observation of adults with GD.

Results
104 endocrinologists participated in the study. 99% of respondents chose the thyrotropin receptor antibody (TRAb) test to clarify the etiology of thyrotoxicosis, while 60.6% chose thyroid scintigraphy. Antithyroid drug (ATD) treatment was chosen as the first-line treatment by 88.5% of respondents, radioactive iodine (RAI) by 13.5%. Titration ATD regimen is preferable compared to the “block-replace” 72.1% vs 28.8%. Most doctors (95.2%) initiate therapy with moderate doses of thiamazole (20-30 mg). Most of them perform dynamic monitoring of the level of transaminases (57.7%) and complete blood count (78.8%). ATD treatment is prescribed for a period of 12-18 months by 88.5% of doctors, up to 24 months by 10.6%. 89.4% of respondents monitor thyroid hormones, 82.7% of respondents TRAb and 49% perform thyroid ultrasound before ATD withdrawal. Repeated courses of ATD treatment are prescribed by up to 61.5% of respondents. About 65.5% of the surveyed doctors stated difficulties with referral to radical treatment due to the limited number of specialized institutions. The main limiting factors in RAI are the patient’s unwillingness and planning pregnancy (81.6%) and doctors’ fear of developing complications (49%).

Conclusion
The results of the study demonstrated that in their practice, doctors, as a rule, follow international recommendations for the treatment of GD. This study is unique in its kind, since no similar work has been carried out in Russia before.

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PS2-07-62
Multifocality in sporadic and familiar medullary thyroid cancer: analysis of prevalence and possible predictive roles
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Endocrine Abstracts (2022) Vol 84

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Aims
Surgery is the only curative treatment for medullary thyroid cancer (MTC) patients and the gold standard practice is still represented by total thyroidectomy and prophylactic central neck compartment lymphnode dissection. As it happened for differentiated thyroid cancer, in the last years some authors proposed less aggressive and extent surgical modality as hemithyroidectomy and ipsilateral neck compartment dissection in unilateral and solitary sporadic MTC cases. Few studies are available regarding the prevalence of multifocality in MTC and its pre and postsurgical role. Aims of this study were to assess the prevalence of multifocality in familiar and sporadic MTC patients and to correlate the presence of multifocality with clinical and pathological parameters.

Patients and Methods
We retrospectively analyzed data from 389 consecutive MTC patients followed-up at our department from 2005 to 2018. Multifocality was defined as the presence of at least more than one tumor focus both in the same thyroid lobe or in the contralateral one. Independent sample t-test and chi-squared were used for correlations. A p-value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using 22.0 SPSS statistical package

Results
Multifocality was found in 89/389 cases (22.9%), particularly in 45/311 (14.5%) of sporadic cases and 44/78 (56.4%) of familiar ones. All multifocal tumors were also bilateral in familiar cases, while tumor bilateralarity was present in half of sporadic cases (8.7%). When we correlated the presence of multifocality with clinical and pathological features we found a strong correlation with mutated RET (P < 0.001), advanced stage II/IV (P < 0.001), tumor extrathyroidal extension (P < 0.001), presence of neoplastic emboli (P = 0.001), tumor bilateralarity (P < 0.001), presence of central neck compartment lymphnode metastases (P < 0.001), younger age at MTC diagnosis (P < 0.001), younger pre-surgical calcitonin levels (P = 0.01). When we analyzed separately the group of familial and sporadic cases, we found almost the same associations, with the exception of age at MTC diagnosis in both group (P = 0.1 in sporadic and P = 0.3 in familiar cases) and of pre-surgical CT levels in familiar one (P = 0.06). In this last group a correlation was also found between multifocality and with bigger tumor dimension (P = 0.01).

Conclusion
According to our data, as expected, the majority of hereditary cases were multifocal and bilateral, while sporadic cases were multifocal in a rather low percentage of cases (14.5%) and only in a subgroup they were bilateral (8.7%). In the era of personalized medicine, we could start to propose lobectomy in sporadic MTC patients with single intrathyroidal lesions.

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PS2-07-63
Corticosteroids and mycophenolic acid have a synergistic effect on chemokines secretion in orbital cells from patients with graves' ophthalmopathy
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Objective
An enhancement of the response rate has been recently showed in patients with Gravess’ ophthalmopathy (GO) treated with corticosteroids and mycophenolic acid. In GO, retro-orbital cells showed a cytokine-induced secretion of Th1 and Th2 chemokines. Since no data are present in literature about the effect of corticosteroids and mycophenolic acid on the chemokines secretion in GO orbital cells, we aim to deepen out this topic.
Methods
We established primary cultures of myoblasts, preadipocytes and fibroblasts obtained from GO patients, and we tested increasing concentrations of mycophenolic acid or corticosteroids in order to study the effect on the secretion of either the Th1 (CXCL10) and Th2 (CCL2) chemokines.

Results
As regard the Th1 chemokines, we observed that CXCL10 was undetectable in the supernatants of the retro-orbital primary cultures cells, while IFNγ induced its release in a dose-dependent manner, and TNFα alone had no effect. By contrast, CCL2, whose amount is low in basal conditions, while IFNγ alone had no effect on the CCL2 secretion. The combination of TNFα and IFNγ had a synergistic effect on the CXCL10 and CCL2 secretion. Increasing concentrations of mycophenolic acid or corticosteroids (in a pharmacological range), were able to reduce the chemokines secretion in a dose-dependent manner, even in the presence of the IFNγ and TNFα stimulation. In addition, in presence of IFNγ and TNFα, the combination of corticosteroids and mycophenolic acid had a higher effect on the inhibition of the release of chemokines.

Conclusion
Our investigation showed the important role of mycophenolic acid and/or corticosteroids in the inhibition of the secretion of both Th1 (CXCL10) and Th2 (CCL2) chemokines. These findings suggest a possible therapeutic role of these drugs.

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**PS2-07-65**

Hyperthyroidism in Graves’ disease and subacute thyroiditis and association with cardiovascular events
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Objectives
Overt hyperthyroidism is reported to be associated with an increased mortality risk and an increased risk of cardiovascular (CV) complications such as an acute coronary syndrome requiring percutaneous coronary intervention, ischemic and non-ischemic stroke, atrial fibrillation and venous thromboembolism. Increased rate of acute CV events in the course of hyperthyroidism is well documented in Graves’ disease (GD) but not in subacute thyroiditis (ST). Last year we reported three patients with an acute CV event in the course of ST. The aim of this study was to systematically compare the characteristics of hyperthyroidism and the incidence of CV events in patients with GD and ST.

Methods
Our retrospective study included 505 patients that were evaluated for overt hyperthyroidism due to GD or ST in a tertiary referral center from January 2019 to December 2020. The diagnosis of GD and ST was based on clinical evaluation, laboratory tests including measurement of TSH receptor antibodies and/or sedimentation rate, and on thyroid ultrasound. In selected cases, thyroid scan and fine needle aspiration biopsy were also performed. Continuous data are presented as mean (±SD).

Results
Table 1 presents the characteristics of patients with GD or ST.

**Table 1. Clinical characteristics of patients with hyperthyroidism due to Graves’ disease or subacute thyroiditis.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Graves’ disease</th>
<th>Subacute thyroiditis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female/male; % female)</td>
<td>301/89 (77.2%)</td>
<td>81/33 (70.4%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.6 (± 15.8)</td>
<td>46.0 (± 10.6)</td>
<td>0.91</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.6 (± 6.3)</td>
<td>24.8 (± 4.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Arterial hypertension (%)</td>
<td>51 (13.1%)</td>
<td>5 (4.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>108 (27.7%)</td>
<td>9 (7.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free T₄ (pmol/l)</td>
<td>43.0 (± 27.9)</td>
<td>36.5 (± 15.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Free T₃ (pmol/l)</td>
<td>18.5 (± 6.6)</td>
<td>12.3 (± 6.3)</td>
<td>&lt;0.001</td>
</tr>
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</table>

In the GD group, 13 (3.3%) patients suffered a CV event within 3 months before or after the diagnosis of GD (acute coronary syndrome in 6, atrial fibrillation in 4, pulmonary thromboembolism in 2 and cerebrovascular accident in 1 patient). No CV events were registered in the ST group.

Conclusions
The patients in the GD group were significantly more hyperthyroid; in this group, there were significantly more patients with hypertension and smokers. In our cohort of patients with overt hyperthyroidism, CV events were registered only in the GD group. Acute CV events in the course of ST seem to be an extremely rare complication.

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**PS2-07-66**

Influence of thyroperoxidase and thyroglobulin antibodies on the presentation and the evolution of medically treated Graves’ disease
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Influence of thyroperoxidase and thyroglobulin antibodies on the presentation and the evolution of medically treated Graves’ disease

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Introduction
Thyrotropin receptor stimulating antibodies (TRAb) are responsible for Graves’ disease (GD) manifestations. Other thyroid antibodies, namely thyroperoxidase (TPOAb) and thyroglobulin (TGAb) antibodies are highly prevalent in GD, but their roles in GD presentation and evolution are controversial.

Methods
We retrospectively analysed TPOAb and TGAb levels and evolution in 88 consecutive patients with newly diagnosed GD between 2000 and 2018. The patients were treated with anti-thyroid drugs (ATD) in a block-and-replace regimen for at least 12 months and followed-up after ATD discontinuation for at least one year or until disease relapse.

Results
The mean age at diagnosis was 41.4 ± 12 years, 67/88 (76.1%) of patients were women and 16/88 (18.2%) of patients were smokers. Thyroid eye disease (TED) was observed in 21/88 (24%) patients. Mean duration of medical treatment and follow-up were 24.6 ± 13.2 months and 80.3 ± 58.2 months, respectively. During follow-up, 51/88 (58%) of patients relapsed. At diagnosis, 61/88 (73%) of patients were TPOAb positive and 45/88 (51%) of patients were TGAb positive. The presence of TPOAb or TGAb antibodies at diagnosis did not influence the relapse (P = 0.356 and P = 0.641, respectively). There was less TED in patients TGAb positive at diagnosis than in patients without TGAb (15.6% vs. 32.6%, P = 0.061). Logistic regression showed that the absence of TGAb at diagnosis increased the risk of TED by a factor 2.6, without reaching statistical significance (P = 0.066). TRAb and TGAb were both positive in 39/88 (44%) of patients, 25/88 (28.5%) of patients had only TPOAb, 6/88 (7%) of patients had only TGAb, and neither antibody was positive in 18/88 (20.5%) of patients. There was no difference in terms of GD relapse (56.4%, 65.4%, 40% and 55.6% respectively, P = 0.722) or TED occurrence (P = 0.119) between the four groups. The positivity of TPOAb and/or TGAb at treatment discontinuation or at the last visit before relapse was not predictive of relapse. We observed lower titers of TGAb during treatment in patients who relapsed, TRAb, TPOAb and TGAb significantly decreased during the treatment and increased after ATD discontinuation until relapse.

Conclusion
TPOAb and/or TGAb positivity and evolution were not significantly associated with GD presentation or relapse after a first course of ATD. There is a non significant trend of more recurrence of GD in patients with low levels of TGAb but a slight non significant protection against TED in cases of TGAb positive at diagnosis.

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PS2-08-68
NOX-derived oxidative stress is high in neoplastic thyroid lesions and correlates with a tumor risk in papillary thyroid cancer
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Oxidative stress (OS) can have an impact both in the pathogenesis and in the progression of TC, as it has been shown to induce oncogenes and inhibit tumor suppressors. The main source of cellular ROS is represented by NADPH oxidases (NOXs). Aims of the study were to investigate the NOX-derived OS in TC samples, benign nodules and corresponding normal tissues, and to correlate the level of OS with histological classification, genetic profile and clinical and prognostic features of patients. Twenty-four papillary (PTCs), 6 follicular (FTCs) and 3 anaplastic thyroid tumors (ATCs), 4 nonnvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFPTs), 8 follicular adenomas (FAs), 4 Hurtle adenomas (HAs) and contra-lateral normal tissues were included in the study. H2O2 generation by NOXs in the cytoplasmic fraction of tumoral and normal tissues was measured using the fluorescent Amplex Red Reagent. The molecular profile of tumor samples was characterized by a custom AmpliSeq DNA/RNA NGS panel (illumina) in which the most common mutations/fusions found in TC are included. The medical of H2O2 generation considering all tumors and benign lesions was significantly higher than that obtained in all normal tissues analyzed. When compared with the corresponding normal tissues, differences in H2O2 production were found only in PTCs and FTCs (P = 1.2*10^-6, 5.8*10^-5, respectively). Interestingly, when we stratified PTCs for genetic variants, only PTCs with mutations in TERT and BRAF or BRAF alone showed an increased H2O2 generation compared with the corresponding normal tissues (P = 0.03 and 6.1*10^-5, respectively). Moreover, H2O2 production in FTCs resulted higher compared to FA and to FTCs (P = 0.003). Finally, the
H2O2 production in PTCs with high/intermediate ATA risk resulted significantly higher compared with that obtained in low ATA risk PTCs (p = 0.02). In conclusion, our data indicate that thyroid tumors are exposed to a higher OS compared to normal tissues. Moreover, the level of NOX4-generated ROS correlates with BRAF and TERT mutations and with worst tumor presentation in PTCs. The high OS associated with thyroid tumors may have diagnostic, prognostic and therapeutic relevance.

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**PS2-08-69**

Use of long noncoding rnas for molecular diagnosis of thyroid cancer

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**Objective**

Improved molecular testing for common somatic mutations and the identification of mRNA and microRNA expression classifiers are promising approaches for the diagnosis of thyroid nodules. However, there is a need to improve the diagnostic accuracy of such tests in identifying thyroid cancer. Recent findings have revealed a crucial role of lncRNAs in gene modulation. Thus, we aimed to evaluate the diagnostic value of selected lncRNAs from The Atlas of Noncoding RNAs in Cancer (TANRIC) thyroid cancer dataset.

**Methods**

lncRNAs in TANRIC thyroid cancer dataset that have significantly increased or decreased expression in thyroid cancer tissues were selected as candidates for thyroid cancer diagnosis. Surgical specimens from patients who underwent thyroidectomy were used to determine the separation capability of candidate lncRNAs between malignant and benign nodules. Fine needle aspiration samples were obtained and screened for candidate lncRNAs to verify their diagnostic value.

**Results**

lncRNAs LINC02471, LINC02082, UNC5B-AS1, LINC02408, MPPED2-AS1, LINC01217, LINC02082, and LINC010019219 were selected as the candidate lncRNAs. Multiplex immuno-fluorescence indeed confirmed the recruitment of abundant macrophages among thyroid cancers and BRAF V600E genetic alteration is found in 60% of this endocrine cancer. BRAFV600E+ tumors are associated with poor prognosis resistance to radioiodine therapy and tumor progression. Histological follow-up by anatomo-pathologists reveals that 2/3 of surgically-removed thyroid do not present malignant lesions. Continued fundamental research into the molecular mechanisms of thyroid cancer downstream of BRAF V600E remains thus central to better understand the clinical behaviour of tumours, to improve differential diagnosis between thyroid cancer subtypes, to propose new therapies, and to avoid unnecessary surgery. To study PTC we used a mouse model in which we aimed to describe biochemical and cluminant macrophages among which a population of CD206+/lyve-1−/Stab-1+ was dramatically increased. We decided to focus on this subpopulation of alternatively-activated macrophages by genetically inactivating the gene coding for the scavenger receptor Stabilin-1. We will present the results of our inactivation of Stabilin-1 in the context of in situ BRAFV600E+ dependent thyroid cancer and of the expression of Stabilin-1 in human thyroid cancers and other thyroid pathologies.

**Conclusion**

This retrospective study on the insTTCTdelG-RET666 variant, which is the largest to date, suggests that this variant is pathogenic and associated with low risk MTC/CCH and rarer other A2A manifestations.

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**PS2-08-70**

Biochemical and clinical characteristics of belgian families with germline insTCTdelG mutation affecting codon 666 of the ret gene: a retrospective cohort study

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**Objective**

Papillary thyroid carcinoma (PTC) is the most frequent histological subtype of thyroid cancers and BRAFV600E+ genetic alteration is found in 60% of this endocrine cancer. BRAFV600E+ tumors are associated with poor prognosis.

**Methods**

Recent findings have revealed a crucial role of lncRNAs in gene modulation. Thus, we aimed to evaluate the diagnostic value of selected lncRNAs from The Atlas of Noncoding RNAs in Cancer (TANRIC) thyroid cancer dataset.

**Results**

lncRNAs LINC02471, LINC02082, UNC5B-AS1, LINC02408, MPPED2-AS1, LINC01217, LINC02082, and LINC010019219 were selected as the candidate lncRNAs. Multiplex immuno-fluorescence indeed confirmed the recruitment of abundant macrophages among thyroid cancers and BRAF V600E genetic alteration is found in 60% of this endocrine cancer. BRAFV600E+ tumors are associated with poor prognosis resistance to radioiodine therapy and tumor progression. Histological follow-up by anatomo-pathologists reveals that 2/3 of surgically-removed thyroid do not present malignant lesions. Continued fundamental research into the molecular mechanisms of thyroid cancer downstream of BRAF V600E remains thus central to better understand the clinical behaviour of tumours, to improve differential diagnosis between thyroid cancer subtypes, to propose new therapies, and to avoid unnecessary surgery. To study PTC we used a mouse model in which we aimed to describe biochemical and cluminant macrophages among which a population of CD206+/lyve-1−/Stab-1+ was dramatically increased. We decided to focus on this subpopulation of alternatively-activated macrophages by genetically inactivating the gene coding for the scavenger receptor Stabilin-1. We will present the results of our inactivation of Stabilin-1 in the context of in situ BRAFV600E+ dependent thyroid cancer and of the expression of Stabilin-1 in human thyroid cancers and other thyroid pathologies.

**Conclusion**

This retrospective study on the insTTCTdelG-RET666 variant, which is the largest to date, suggests that this variant is pathogenic and associated with low risk MTC/CCH and rarer other A2A manifestations.

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**PS2-08-71**

Stabilin-1 Macrophages in thyroid cancer microenvironment

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**Objective**

Papillary thyroid carcinoma (PTC) is the most frequent histological subtype of thyroid cancers and BRAFV600E+ genetic alteration is found in 60% of this endocrine cancer. BRAFV600E+ tumors are associated with poor prognosis resistance to radioiodine therapy and tumor progression. Histological follow-up by anatomo-pathologists reveals that 2/3 of surgically-removed thyroid do not present malignant lesions. Continued fundamental research into the molecular mechanisms of thyroid cancer downstream of BRAF V600E remains thus central to better understand the clinical behaviour of tumours, to improve differential diagnosis between thyroid cancer subtypes, to propose new therapies, and to avoid unnecessary surgery. To study PTC we used a mouse model in which we aimed to describe biochemical and cluminant macrophages among which a population of CD206+/lyve-1−/Stab-1+ was dramatically increased. We decided to focus on this subpopulation of alternatively-activated macrophages by genetically inactivating the gene coding for the scavenger receptor Stabilin-1. We will present the results of our inactivation of Stabilin-1 in the context of in situ BRAFV600E+ dependent thyroid cancer and of the expression of Stabilin-1 in human thyroid cancers and other thyroid pathologies.

**Conclusion**

This retrospective study on the insTTCTdelG-RET666 variant, which is the largest to date, suggests that this variant is pathogenic and associated with low risk MTC/CCH and rarer other A2A manifestations.

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Thyroid cancer (TC) is the most common endocrine tumor and its incidence has increased faster than in any other malignancy. Although TCs are usually well differentiated, disease recurrence or persistence is high, because of local and distant metastasis and therapeutic resistance. As in other cancer types, despite the promising results obtained in pre-clinical studies, the efficacy of Targeted Therapy is highly variable and therapy resistance is not uncommon. This may be due to a lack in the understanding of the complex signaling pathways and feedbacks that cancer cells with a specific genetic background exchange with all the other components of the tumor microenvironment, such as immune cells, fibroblasts, endothelium, and extracellular matrix (ECM). The aim of the present study is to unravel the mechanisms by which cancer associated fibroblasts (CAFs) and ECM can influence the tumor response to different anticancer drugs and to identify new potential druggable pathways. For these purposes, we developed an in vitro model in which a panel of 12 thyroid cancer cell lines with different genetic background is used to activate fibroblast and generate ECMs. The ECMs are then used as culture substrate for the different thyroid cancer cell lines. We used this model to compare how the ECMs produced under different conditions can influence TC cells response to different TKI currently used in clinical practice, such as vemurafenib, lenalidomide and dabrafenib. First, our experiments confirmed that the genetic background of TC cells can significantly influence the degree of activation of CAFs and the type and amount of ECM that they produce. Moreover, the various ECMs differentially influence TC cells growth and their degree of activation of CAFs and the type and amount of ECM that they produce. After logistic regression we build mathematical diagnostic models based on the expression of miR145 and miR7. The AUC value for model was 0.99 (96.9-100), the sensitivity (Se) was 98.1% (89.9-100), the specificity (Sp) was 96.6% (88.1-99.6).

Conclusion
The expression of miR145 and miR7 has a high diagnostic value in detecting of thyroid cancer

Key words: thyroid cancer, molecular genetic testing, miRNA

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PS2-08-74

EIF1AX gene variants in the context of thyroid tumorigenesis

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Objective
EIF1AX gene variants in the context of thyroid tumorigenesis have been reported in malignant as well as benign thyroid nodules and their clinical significance is still unclear due to their low prevalence. The aim of this study was to identify EIF1AX variants in a large cohort of different types of thyroid nodules and to correlate them with clinical and pathological data.

Methods
The study consisted of 904 thyroid nodule samples. The cohort included 577 patients with thyroid nodules. In about 1/3 cases FRA and cytological examination shows indeterminate diagnosis. Deregulation of miRNA expression has been described in several diseases, including thyroid cancer, molecular genetic testing, miRNA. The expression of miR145 and miR7 has a high diagnostic value in detecting of thyroid cancer.

Key words: thyroid cancer, molecular genetic testing, miRNA

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PS2-08-73

MiR-145 and miR7 as a potential diagnostic markers of thyroid cancer

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Objective
Thyroid nodules are the most common thyroid disease and preoperative differentiation of benign and malignant lesions is an important diagnostic purpose. In about 1/3 cases FRA and cytological examination shows indeterminate diagnosis. Deregulation of miRNA expression has been described in a variety of tumors, including thyroid cancer. The aim of our study is to evaluate the association between miRNAs expression and risk of thyroid cancer in patients with thyroid nodules.

Methods
In retrospective case-control study we have studied 112 patients with suspected thyroid cancer (FNA Bethesda III-VI). All patients underwent thyroidectomy with histological verification of the diagnosis. The expression of miR144, miR145, miR146, miR155, miR183, miR199, miR221, miR331, miR551, miR375, miR545 and miR7 were determined using quantitative real-time PCR. Logistic regression and receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic efficacy and build mathematical diagnostic models.

Results
Study group included 54 patients with thyroid cancer and control group of 58 patients with benign nodules. In our study up-regulation of miR146, miR221, miR155, miR375, miR331, miR551 and down-regulation of miR7 and miR145 were significantly associated with thyroid cancer. The most diagnostic value has been expression of miR145 with an area under the ROC curve (AUC) value of 0.982 (95%CI: 0.953-1.0), miR146 – 0.945 (95%CI: 0.896-0.994), miR375 – 0.931 (95%CI: 0.895-0.971) and miR7 (95%CI: 0.863-0.906). After logistic regression we build mathematical diagnostic models based on the expression of miR145 and miR7. The AUC value for model was 0.99 (96.9-100), the sensitivity (Se) was 98.1% (89.9-100), the specificity (Sp) was 96.6% (88.1-99.6).

Conclusion
The expression of miR145 and miR7 has a high diagnostic value in detecting of thyroid cancer.

Key words: thyroid cancer, molecular genetic testing, miRNA

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thyroid tissues was used for preparation of libraries using the Nextera XT DNA Library Prep Kit (llumina, USA) and analyzed using next-generation sequencing (MiSeq, Illumina, USA). Variants in the EIF4X gene (exons 1, 2, 5, 6) were visualized in Integrative Genomics Viewer (Broad Institute, USA) and evaluated by VarSome platform (Saphetor SA, Switzerland).

**Results**

**EIF4X** gene variants were detected in 18 of 904 thyroid samples (2%) - 2 ATCs, 3 FTCs, 2 FT-UMPs, 1 oncocytic adenoma and 6 other benign nodules. The most frequent **EIF4X** A113 splicing variant was found in 6 of 18 (33.3%) positive samples (1 ATC, 2 FTC, 1 FTA, 1 FT-UMP and 1 goiter). Variants in codon 90 (G90W, G90D) of **EIF4X** gene were found in 3 benign nodules and 1 ATC, in which coexisted with variants of TERT, TP53 and NRAS genes. The coexistence of **EIF4X** variants with mutations in other genes (5× TERT, 9× RAS – 4 × simultaneously) was found in a total of 10 of 18 cases, and often correlated with more aggressive disease. On the other side, 8 **EIF4X**-positive samples which did not possess other driver mutations were benign nodules, FTCs or FT-UMPs.

**Conclusion**

In summary, **EIF4X** gene variants were detected in 18 cases. In most cases, the **EIF4X** variants co-occurred with known variants of other genes and were associated with more aggressive tumor behavior. In accordance with literature, distinct **EIF4X** variants may be related to different types of thyroid tumors and extension of the positive cohort could provide more accurate insight into the understanding of this gene. Supported by AZV N2U-1-00448 and MH CR RVO 68027761.

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**PS2-08-75**

**PD-L1 and MCL-1 markers and the relationship with prognostic characteristics of differentiated thyroid carcinoma**

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**PD-L1 AND MCL-1 MARKERS AND THE RELATIONSHIP WITH PROGNOSTIC CHARACTERISTICS OF DIFFERENTIATED THYROID CARCINOMA**

**Objectives**

MCL-1 and PD-L1 proteins are related to carcinogenesis mechanisms in differentiated thyroid carcinoma (DTC). Tumor antigens stimulate the expression of PD-L1 in immune cells, which binds to PD-L1 of tumor cells, inducing immune escape from the tumor. MCL-1, an anti-apoptotic member of the BCL-2 family, has a high oncogenic potential. The relationship of these markers with escape from the tumor. MCL-1, an anti-apoptotic member of the BCL-2 family, has a high oncogenic potential. The relationship of these markers with escape from the tumor.

**Methods**

120 patients with DTC after total thyroidectomy and radioiodine therapy followed for a minimum of 2 years after complete treatment were included. Demographic features, tumors histopathological characteristics, initial risk classification of persistence/recurrence, factors associated with outcome, initial response to therapy, persistence or disease-free at the end of follow-up were evaluated. These factors were associated with outcome, initial response to therapy, persistence or disease-free at the end of follow-up.

**Results**

Among the patients, 100 (83.33%) were women and 20 men, age at diagnosis 46.64 ± 16.73 years; 37 (30.8%) patients were at high risk, 45 (37.5%) of intermediate risk and 38 (31.7%) of low risk of disease recurrence/persistence. At the end of follow-up, 65 (57.5%) were disease-free and 48 (42.5%) had persistent disease. The largest tumor diameter was 2.99 ± 1.79 cm; 103 (85.8%) patients had papillary thyroid carcinoma (PTC) and 17 (14.2%) had follicular thyroid carcinoma (CTF), with a follow-up time of 124.86 ± 65.36 months. BRAF V600E mutation was detected in 49 (59.8%) patients and absent in 33 (40.2%). Strong/moderate expression of PD-L1 was associated with cell variant (PTC: P = 0.0327), weak/present MCL-1 was associated with presence of the BRAF V600E mutation (P = 0.0468); and weak expression of MCL-1 was associated with multifocality (P = 0.0290). No patients with CFT presented weak MCL-1 expression, and all tumors with weak expression were PTC (P = 0.0409).

**Conclusions**

PD-L1, marker of ontogeny of proliferation and progress of tumors was associated with more aggressive PTC variant. The anti-apoptotic marker MCL-1 was associated with CDT carrying the BRAFV600E mutation. Additionally, lower anti-apoptotic marker expression was related to multifocal and papillary thyroid cancer. Additional studies are needed to confirm the possible role of these markers in the tumorigenesis and evolution of DTC.

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**PS2-08-76**

**Double mutation of the TERT promoter in extremely aggressive papillary thyroid carcinoma**

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**Objectives**

BRAFV600E mutation is present in 50% of aggressive papillary thyroid carcinoma (PTC). TERT promoter (pTERT) mutations (C228T, C250T) are related to cancer growth and reduced overall- and disease-free survival in differentiated thyroid carcinomas(DTC). We report a patient with an extremely aggressive PTC presenting in the primary lesion two pTERT mutations (C228T and C250T), and absence of BRAFV600E.

**Case Report**

Female, 39-year-old, euthyroid patient referred a 10-year multinodular goiter, developed compressive symptoms during last year. Cytology of largest nodule was not suggestive of malignancy. Total thyroidectomy was performed due to compression. Histopathology revealed multifocal FTC follicular variant with areas of classic form within the hyperplastic nodules (5.3 cm in right lobe; 3.5 cm in left lobe; two 0.9 cm foci in isthmus) (pT3N0M0). Patient received adjuvant radioiodine ablation therapy(RIT); 150mCi 131I; Tg = 0.029ng/dL, anti-TgAb undetectable, TSH = 73mUI/mL. Two years later, a whole-body 131I scintigraphy(WBS) demonstrated diffuse iodine-avid pulmonary metastases; Tg = 1,100ng/dL, negative TgAb. After five years, 18FDG PET/CT images revealed hypermetabolism in cervical lymph node metastases bilaterally and in pulmonary nodules; Tg = 2,991ng/dL, TgAb undetectable. After seven years, patient presented pathologic fractures (humerus, right tibia), soft tissues infiltration. 18FDG-PET/CT revealed widespread lungs metastases, cervical lymph node metastases, left breast, gluteus maximus, mediastinal, axillary, and inguinal lymph nodes. Hypermetabolic metastatic lytic bone lesions were noted in skull, mandible, clavicle, ribs, humerus, femur, pelvis, T2 vertebra. Patient received three adjuvant RIT (1223mCi), without response. Palliative radiotherapy was performed in skull, humerus, left leg with partial reduction. There was lung metastases reduction with

**Endocrine Abstracts (2022) Vol 84**
synthesis, and progression of the other. Patient progressed with bronchial obstruction from lung metastases and died from respiratory failure eight years after the initial diagnosis. Molecular analysis of primary tumor tissue revealed absence of BRAF V600E mutation, evaluated by qPCR in COBAS Z 480 System (Roche) and presence of both pTERT C228T and C250T mutation, detected by pyrosequencing and validated by droplet digital PCR.

Conclusions
The pTERT mutations C228T and C250T have been described as mutually exclusive, indicating that one mutation is enough for telomerase activation and exert its action on thyroid tumorigenesis. However, in this case report we observed the presence of both pTERT mutations.

DOI: 10.1530/endoabs.84.PS2-08-76

Thyroid Hormone ACTION

**PS2-09-77**
Correlation between plasmatic long pentraxin PTX3 and nodular thyroid disease: a preliminary report
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Introduction
The long pentraxin-3 (PTX3) is a key component of humoral innate immunity that is expressed in various cell types during stress and tissue injury. PTX3 also acts like an oncogene regulator controlling tumor-promoting inflammation and it is implicated in tissue repair and autoimmunity. Autoimmune disease, tissue remodelling and oncogenesis often coexist in the thyroid. PTX3 role in thyroid disease is still unknown. Aim of the study is to evaluate if plasmatic levels of PTX3 in patients submitted to thyroidectomy for benign or malignant nodular disease are higher than normal.

Materials and methods
After informed consent, patients over 18 years old with nodular disease of the thyroid who were eligible for thyroid surgery were enrolled in this study. All patients underwent total or hemithyroidectomy at Humanitas Mater Domini Clinical Institute in Castellanza (VA). A blood sample was taken on the day of surgery and another one was taken 45 days after surgery to evaluate plasmatic PTX3 level. Blood samples were centrifuged and PTX3 levels were evaluated with ELISA test. In this preliminary report, we evaluated the data of the first 53 consecutive patients enrolled in the study.

Results
We found that preoperative plasmatic PTX3 levels were significantly higher than normal in patients with thyroid disease (P < 0.05). Plasmatic PTX3 mean value was 4.54 ng/ml (range 1.06 – 8.63 ng/ml), when normal value is considered 2 ng/ml with 1 ng/ml of standard deviation. At 45 days follow-up PTX3 mean value was reduced to 3.40 ng/ml (range 0.89 – 9.21 ng/ml); this reduction was statistically significant (P < 0.05).

Conclusions
For the first time, at the best of our knowledge, we observed a correlation between elevated PTX3 plasmatic levels and nodular disease of the thyroid. We hope to identify if plasmatic PTX3 could be used as a marker for nodular thyroid disease.

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**PS2-09-79**
Ecotropic expression of human TRα and TRβ mutants disentangle the isofrom-specific regulation of gene expression during zebrafish development
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Thyroid hormone receptors (TRs) modulate various physiological functions in many organs. The conservation of TRα and TRβ isoforms during evolution of vertebrates suggests different roles for these TRs in thyroid hormone-dependent regulation of gene expression. TRα and TRβ are widely distributed and overexpressed in several tissues, functions that is mainly attributed to their variable tissue expression patterns and intrinsic properties of specific TR isoforms have not been extensively investigated. Here, we want to verify whether the two TRs can be interchangeable in their tissue actions by comparing the phenotypical alterations observed in zebrafish embryos ubiquitously expressing human TRα (hTRα) mRNAs, injected in zygotes at 1-2 cells stage at a concentration of 50 pg/embryo. We previously showed that zebrafish TRs (zTRs) can efficiently interact with their human homologues and the microinjection of wild-type hTRs does not affect the normal embryonic development. Conversely, the dominant-negative hTRα1-E403X or hTRβ2-E464X mRNAs results in distinct phenotypes despite their ubiquitous expression in zebrafish tissues. Embryos injected with hTRα1-E403X present aberrant angiogenesis, reduced heart looping and bradycardia, whereas only the embryos expressing hTRβ2-E464X show the typical RTHβ biochemical signature (high T4/T3 with unopposed tshba levels) confirming a dominant-negative effect on the pituitary negative feedback. Then, we generated mutant chimeras by switching the α1 and β2 functional domains: N-terminus A/B domain (A/B), DNA binding domain (DBD), hinge region (HR) and ligand binding domain (LBD). Multi-step PCR was used to generate wild-type and mutant chimeric fragments where the hTRα1 domain has been replaced with that of hTRβ2, and vice versa. Using tshba expression as marker of TRβ2-dependent activity, we attempted to discriminate which domain dictates the specific function. Several experimental replicates indicate the chimeric E403X mutant containing the A/B of hTRβ2 linked to DBD-HR-LBD of hTRα1 as functionally similar to the hTRβ2-E464X on tshba expression, suggesting that the A/B domain of TRβ2 is both required and sufficient to mediate this specific transcriptional effect, and that the variable structural properties of TRs represent another relevant factor dictating the isofrom-specific actions in vivo.

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PS2-09-80
Deiodinase type 1 (Dio1) regulation in non-alcoholic fatty liver disease (NAFLD)
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Background and Aim
Altered hepatic thyroid hormone (TH) signalling is associated with the onset and progression of liver diseases. Local hepatic hypothyroidism is related to a higher incidence of developing non-alcoholic fatty liver disease (NASH) in humans and animal models. Thyroid hormone treatment proved to be a promising therapy, slowing the progression of NAFLD to non-alcoholic steatohepatitis (NASH), a more advanced stage of the disease characterized by inflammation and occasional fibrosis. Hepatic thyroid hormone activity is regulated by TH transporters, deiodinases, and receptors. Among these, deiodinase type 1 (Dio1) is a major player, it converts the prohormone thyroxine (T4) to the bioactive form T3 within the hepatocytes. Unfortunately, the precise regulation of Dio1 in liver diseases remains incompletely understood.

Methods
We studied Dio1 expression in different hepatic disease models, including male C57BL/6 mice fed with high-fat diet (HFD) for 18 weeks and treated with metformin for the last four weeks of treatment, male C57BL/6 mice fed with choline-deficient HFD for 4 and 8 weeks at thermoneutrality, and finally, male C57BL/6 mice treated with carbon tetrachloride to induce liver failure. Results
Dio1 expression is rapidly induced by HFD and remained elevated throughout the treatment without alterations by metformin treatment. Notably, none of the other conditions resulted in an induction of Dio1, despite a similar degree of liver lipid deposition.

Conclusion
Our results show that Dio1 is rapidly induced by HFD, an effect that seems to be independent of insulin sensitivity, as it was not reversed by metformin treatment. This effect was not visible in other animal models with a similar degree of hepatic lipid deposition, suggesting that other factors such as liver inflammation and fibrosis may prevent the HFD induced Dio1 induction. We suggest Dio1 increases as part of a protective response in NAFL and early NASH.

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PS2-09-81
An experimental framework for probing molecular mechanisms of local thyroid hormone action during cortical neurogenesis in human cerebral organoids
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Background and Aim
Recently, human cerebral organoids (hCOs) emerged as powerful three-dimensional in vitro models recapituating key aspects of early human cerebral cortex development. Improved protocols for hCO generation from induced pluripotent stem cells (hiPSC) paved the way for new disease modeling approaches and enabled molecular analyses of perturbations from manipulation of signaling pathways or gene function. These prospects prompted us to adopt this technology as a model system to delineate the regulatory logic of local TH action during early human brain development and to model the consequences of impaired TH function for cortical neurogenesis. Here, we report results from our efforts to develop experimental strategies for targeted perturbation of TH signaling in hCOs and highlight critical quality measures to prevent experimental artifacts. Titration of graded amounts of exogenous TH to culture media is commonly regarded as the simplest means for manipulating TH signaling. Yet, we found that the variable amounts of TH present in culture media and commercial supplements (i.e. B27) can confound experimental outcomes and that rigorous analytical verification of TH levels is required to ensure reproducible endpoint measurements. Patient-derived hiPSC lines carrying genetic variants conferring reduced functionality of specific proteins gained great popularity for disease modeling. However, differences in the inherent propensity of individual hiPSC lines to generate cortical cerebral tissue in vitro can result in enormous variation and hamper robust phenotypic comparisons. We therefore developed CRISPR/Cas9-based strategies for generation of isogenic wildtype and mutant hiPSC lines to minimize this source of variation. In developing hCOs, progenitor and neuronal cell type positions themselves in three-dimensional in vivo-like laminar structures along with lineage specification. We validated a panel of canonical cell type and layer markers to distinguish germinal zones and a cortical plate-like zone and define the timing of the sequential appearance of deep and upper layer neurons consistent with the in vivo inside-out manner of cortical layer emergence. Due to the complexity of the tissue, we apply single cell transcriptome techniques to comprehensively capture the temporal and cell type-specific expression of TH transporters, receptors and deiodinases in developing hCOs and use single molecule fluorescent in situ hybridization to register cell type-specific expression patterns in the spatial context of the laminar cortical organization. Currently, we present a strategy combining various measurements and quality measures to faithfully exploit the enormous potential of hCOs for studies on TH action in a human model system.

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PS2-09-82
Novel central actions of thyroid hormone in the control of body temperature
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The ability of thyroid hormones to regulate body temperature is well established. While the active hormone T3 can act peripherally to induce thermogenesis in fat and muscle, it also acts centrally in the brain to increase body temperature through the sympathetic nervous system. Most remarkably, recent studies show that T3 treatment in mice causes an elevated body temperature even at 10°C, far below
thermoneutrality, suggesting that the T3 effect constitutes pyrexia rather than hyperthermia. Therefore, mice with induced hyperthermiaism seem to have an altered temperature set point in the brain; however, the precise neuroanatomical substrate has remained unknown. The goal of this research project is to identify the brain region where T3 acts to regulate the body temperature setpoint. Using PET/CT scans of mice treated with T3, several candidate regions have been identified. Among these, the Zona Incerta (ZI), has been associated with the control of body temperature presumably. To test whether this region constitutes the missing link between the central T3 effect and pyrexia, we studied the ZI using well-established mouse models. Preliminary data show no difference in cell number of dopaminergic neurons in the ZI when comparing offspring of wild-type mice to those of mice with a mutation in thyroid hormone receptor α1, indicating no developmental effect of thyroid hormones on ZI dopaminergic neurons. However, further studies will be needed to illuminate the acute actions of T3 in this enigmatic brain region.

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PS2-09-83

FAM83B is involved in thyroid cancer cell differentiation and migration

Valentina Cicorelli1, Elisa Stellaia Grassi1, Gabriele Pogliaghi1, Verina FAS83B in TC cell differentiation and migration. Its expression is reduced in more differentiated tumors and the decrease in its expression and its nuclear re-localization could favour distant migration, suggesting that FAM83B should be considered a possible diagnostic and prognostic biomarker.

Background

Resistance to thyroid hormone (TH) beta (RTHβ), caused by mutations in T3Rb, is characterized by elevated serum (f)T4 accompanied by non-suppressed TSH concentrations. Disease features arise from variable resistance to TH action in tissues expressing Thyroid Hormone Receptor (TR) β (hypothyalamic, pituitary, liver) and from thyrotoxic effects in tissues expressing TRα (heart, bone, brain). In symptomatic patients, treatment mainly involves beta blockade to ameliorate tachycardia. In a subgroup of patients, the T3-analogue TRIAC has been employed to alleviate thyrotoxic symptoms. TRIAC preferentially activates TRβ rather than TRα, and has been proven to suppress TSH, thereby lower circulating TH concentrations. Despite its clinical use for decades, the exact mechanism by which TRIAC works in RTHβ, is as yet unclear. Here, by linking clinical observations with molecular studies, we investigated whether TRIAC exerts its effects through activation of mutant TRβ or by stimulating residual wild-type TRβ.

Methods

We collected clinical and biochemical data from 17 RTHβ patients treated with TRIAC in 3 centres. A proof-of-concept study was done with two TRβ mutants (G432del and R438fsx445). G432del and R438fsx445 were studied in the TRβ2 pituitary isoform background. Transcriptional activity was measured using two TRE-luciferase reporters (DR C G432del and R438fsx445). G432del and R438fsx445 were studied in the TRβ2 pituitary isoform background. Transcriptional activity was measured using two TRE-luciferase reporters (DR C G432del and R438fsx445). G432del and R438fsx445 were studied in the TRβ2 pituitary isoform background. Transcriptional activity was measured using two TRE-luciferase reporters (DR C G432del and R438fsx445). G432del and R438fsx445 were studied in the TRβ2 pituitary isoform background. Transcriptional activity was measured using two TRE-luciferase reporters (DR C G432del and R438fsx445). G432del and R438fsx445 were studied in the TRβ2 pituitary isoform background. 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level. Here, we sought to assess the release of T1AM and TA1 in a mouse model of ischemia-induced EC synaptic dysfunction. EC brain slices were obtained from 3-4 months old C57BL/6 male mice (n = 5), using a vibratome (Leica VT1200S). All steps were performed in ice-cold oxygenated artificial cerebrospinal fluid (aCSF). Slices were perfused at 2–3 ml/min rate with oxygenated aCSF at 33 ± 1 °C. Field excitatory postsynaptic potentials were evoked by a concentric bipolar stimulating electrode in the layer II of the EC. After 10 min of stable baseline recordings, slices were perfused with deoxygenated glucose-free aCSF to obtain a transient oxygen-glucose deprivation (OGD). After 10 min of OGD slices were reperfused with aCSF for 50 min. Effluent aCSF was collected over 10 min intervals during the whole duration of experiments, and assayed by tandem mass spectrometry coupled with liquid chromatography (LC-MS/MS). In additional experiments electrical stimulation was omitted and/or amine oxidase inhibitors were included in aCSF. T1AM release was not observed in any experiment, however a significant release of its metabolite TA1 was detected during OGD (0.41 ± 0.04 ng/ml) and during the first 10 min of reperfusion with aCSF (0.24 ± 0.04 ng/ml), but not at the baseline. Notably, no TA1 release was observed if EC were subjected to OGD in the absence of electrical stimulation. Moreover, preliminary experiments showed that semicarbazide, an amine oxidase inhibitor, was able to block TA1 release. We conclude that in functional, but not in electrically silent, EC-stimulated ischemia elicits TA1 release. TA1 might be produced by oxidative deamination of an endogenous precursor, possibly T1AM. To our knowledge, this is the first report of TA1 production and release in a pathophysiological relevant condition. DOI: 10.1530/endoabs.84.PS2-09-85

PS2-09-86

Quantification of CDSL as circulating marker of peripheral thyroid hormone action

Sabrina Asaad1, Thilo Chillon2, Waldemar Minich3, Peter Kühnen4, Bernhard Volker2, G. Brabant, and J. Mittag. 2020. CD5L Constitutes a Novel Biomarker for hormone action in different and challenging clinical constellations. Supported by the DFG-funded Pro 2000, DFG VO 2031/2-1. The quantification of TSH from a serum or plasma sample constitutes the cornerstone of assessing the thyroid axis in the clinical routine. In addition, T4 and/or T3 levels may be determined to diagnose pathological conditions. However, these data do not necessarily reflect the local action of thyroid hormone in the target tissues and are sensitive to distortion, as best known from pregnancy when chorionic gonadotropin disturbs the regular feedback control. Recently, we identified CDSL as a liver-derived thyroid hormone-responsive biomarker in mice and men, and observed a positive correlation to circulating thyroid hormone in human subjects. [1] In order to enable large-scale clinical analyses, we decided to develop a reliable and robust CDSL-specific sandwich ELISA. To this end, CDSL was recombinantly expressed in HEK293 cells, purified to homogeneity and used to develop monoclonal antibodies. Specificity of the antibodies was tested by commercial CD5L preparations, and a pair of monoclonals was selected for sandwich assay development that allowed sensitive and robust CDSL quantification. Performance parameters were determined by measuring standard curves four times in double determination; one log level of concentration differences was spanned by an automated assay design, and two log levels were spanned by an automated format. Each with a coefficient of variation below 10% and a relative error below 20%. Stability of CDSL in serum samples was verified by repeated freeze-thaw cycles, and linear dilution experiments indicated reproducible detection over a range of 100- to 32,000-fold with a coefficient of variation below 6%. Given this positive achievement, we are confident to next turn to clinical samples and test whether CDSL assessment may indeed provide the clinically needed additional information on peripheral thyroid hormone action in different and challenging clinical constellations. Supported by the DFG-funded CRC/TR296, LoCoTact.


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PS2-10-88

Neoadjuvant effects of apatinib in progressive, metastatic differentiated thyroid cancer (DTC)

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Purpose

Recently, apatinib, an orally anti-angiogenic tyrosine kinase inhibitor (TKI) is reported to be useful for treatment of progressive RAIR-DIC. The aim of this study was to evaluate the effect of apatinib and the combination therapy with radioactive iodine (RAI) in patients with progressive metastatic DTC.

Methods

Five patients (all female mean age 62 ± 8 years, ranged from 51 to 69 years) with progressive distant metastatic DTC (dmDTC) after total thyroidectomy (TTE) and neck lymph node dissection were treated with apatinib at a dose 500 mg per day after 18 F-Fluorodeoxyglucose (18F-FDG) PET/CT. The effects of apatinib on DTC were evaluated by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) and metabolic activity using serum thyroglobulin (Tg) and 18F-FDG PET/CT.

Results

Positive 18F-FDG PET/CT results were found in all patients before apatinib therapy. The immunohistochemical analysis of primary tumour tissues showed significant decrease in tumour size and maximum standardized uptake value

Endocrine Abstracts (2022) Vol 84
(SUV\text{max}) after 4 ± 1 month’s treatment with apatinib. Further significant reduction of tumour size and SUV\text{max} were observed in three patients after combination therapy with apatinib and RAI. Only one patient with both FTC and papillary thyroid cancer (PTC) demonstrated progressive disease (PD) after treatment with apatinib alone, however, a decrease in tumour size and SUV\text{max} as well as serum Tg levels was achieved after the combination with RAI therapy and apatinib.

Conclusions
Apatinib had significant neoadjuvant antitumour effects on progressive distant metastatic DTC. Moreover, beneficial complementary effects were shown when apatinib combined with RAI therapy.

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**PS2-10-89**

Follicular thyroid neoplasm with papillary-like nuclear features (NIFT-P) showed peculiar ultrasonographic features compared to follicular carcinoma of papillary thyroid carcinoma (FV-PTC), follicular carcinoma (FTC) and follicular adenoma (FA)

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Background
Up to 2016, NIFT-P was considered a non-invasive encapsulated follicular variant of papillary thyroid carcinoma (FV-PTC) and was reclassified and downgraded to a pre-malignant lesion. However, if these nodules have peculiar ultrasonographic features able to pre-operatively suggest their histology is still a matter of discussion. We evaluated a large series of NIFT-P, FV-PTC, FTC, and FA to characterize their ultrasonographic features.

Methods
We reviewed pre-operative digital ultrasound images and reports of NIFT-P (n = 116), FV-PTC (n = 170), FTC (n = 76), and FA (n = 90) evaluated at the Endocrine Unit of the University Hospital of Pisa, and surgically treated at the Endocrine Surgery Unit of the same hospital. For each nodule we evaluated the following ultrasonographic features: size, composition, echogenicity, shape, margins, and calcifications.

Results
In table 1, the differences in ultrasonographic appearance among the four considered histologies, were highlighted.

**Conclusion**

While FV-PTC and FTC showed significantly more frequent ultrasonographic features suggestive for malignancy; most NIFT-P showed ultrasonographic features suggestive for benignity, similar to FA.

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**PS2-10-90**

**ABSTRACT WITHDRAWN**

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**PS2-10-91**

Comparison of the clinicopathological features and oncologic outcomes of the classic papillary thyroid carcinoma with tall cell features and tall cell variant

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Background
The tall cell variant (TCV) of papillary thyroid carcinoma (PTC) (TCVPTC) is the most common aggressive variant of PTC. Classic PTC with tall cell features (TCF) is defined as PTC with noticeable tall cells but the percentage of these cells is lower than that required for the diagnosis of TCVPTC. We aimed to investigate the potential differences between TCVPTC and classic PTC with TCF with respect to clinicopathological characteristics and long-term oncologic outcomes.

Methods
We retrospectively assessed 509 patients with TCVPCT or classic PTC with TCF who underwent thyroid surgery between January 2013 and December 2018 at the Seoul St. Mary’s Hospital (Seoul, Korea). Clinicopathological characteristics and long-term oncologic outcomes between TCVPTC and classic PTC with TCF were compared in terms of disease-free survival. The mean follow-up duration was 70.7 ± 21.7 months.

**Endocrine Abstracts (2022) Vol 84**
Results
The mean tumor size was significantly larger in the TCVPTC group. There was no significant difference between the TCVPTC and classic PTC with TCF groups with respect to disease-free survival. Tumor size >2 cm (odds ratio, 1.922; \( P = 0.019 \)), bilaterality (OR, 1.668; \( P = 0.030 \)), extrathyroidal extension (ETE) (OR, 2.352; \( P = 0.002 \)), and lateral LN metastasis (OR, 1.700; \( P = 0.045 \)) were significantly associated with TCVPTC compared with classic PTC with TCF.

Conclusions
TCVPTC and classic PTC with TCF have similar clinicopathological characteristics and long-term oncologic outcomes. Therefore, we suggest a potential re-classification of classic PTC with TCF from low-risk to intermediate-risk category in the American Thyroid Association (ATA) risk stratification system.

Keywords: Tall cell features, Papillary thyroid carcinoma, Disease-free survival

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PS2-10-92
Incidence of non-diagnostic and undetermined cytologies in ultrasound-guided fine needle aspiration biopsy specimens of thyroid nodules – a single-center cohort
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Objectives
Ultrasound-guided fine needle aspiration biopsy (FNAB) is a commonly performed diagnostic procedure for evaluation of thyroid nodules. The Bethesda System for Reporting Thyroid Cytology comprises six categories. Bethesda categories I and III present a challenge for deciding on further diagnostic and therapeutic procedures. Category I includes non-diagnostic or unsatisfactory results that may be due to both aspiration of cystic material from simple cysts or aspiration of too few thyroid cells to render a diagnosis. Category III includes atypia of undetermined significance or follicular lesions of undetermined significance. In the literature, the rate of Bethesda I ranges from 6.1% to 26.8%, while the rate of Bethesda III ranges from 3.7% to 27.4%. In these studies, 164 to 1399 specimens were included. The aim of our study was to evaluate the incidence of categories I and III in ultrasound-guided FNABs of thyroid nodules in the tertiary medical center with a very large number of thyroid patients.

Methods
Our retrospective study included 2167 specimens provided by ultrasound-guided FNAB. The selection of nodules for the FNAB was based on clinical findings, laboratory tests, thyroid scintigraphy with 99mTc-pertechnetate and ultrasound malignancy risk stratification according to the European Thyroid Association Guidelines. Simple cysts were excluded from the study. FNABs were performed by seven thyroid specialists from January 2019 to April 2021. For the procedure, 21-gauge and, rarely, 23-gauge needles were used. All ultrasound-guided FNABs were performed by an on-site cytologist, who used the aspirated material to immediately perform an air-dried smear. All cytology reports were performed by the same very experienced cytologist using the Bethesda System for Reporting Thyroid Cytology.

Results
Among the 2167 samples, there were 168 (7.7%) non-diagnostic or unsatisfactory (Bethesda I), 1750 (80.8%) benign (Bethesda II), 37 (1.7%) atypias of undetermined significance or follicular lesions of undetermined significance (Bethesda III), 119 (5.5%) follicular neoplasms or suspicious for a follicular neoplasm (Bethesda IV), 25 (1.2%) suspicious for malignancy (Bethesda V) and 68 (3.1%) malignant (Bethesda VI).

Conclusions
To the best of our knowledge, this study includes the largest number of ultrasound-guided FNAB specimens of thyroid nodules. When compared with the literature data, the incidence of Bethesda I and Bethesda III categories in our center is in the lower part of the reported range or lower, respectively. Most likely, this is due to the high frequency of FNABs in our center and the experienced cytologist who performs smears on site immediately after FNAB.

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PS2-10-93
Elastography in the assessment of cold solid thyroid nodules
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Introduction
The prevalence of thyroid nodules detected by ultrasound (US) is up to 50% in general population and approximately 5—10% of them is malignant. Diagnostic assessment includes laboratory tests thyroid US and thyroid scintigraphy, where suspicious nodules are characteristically cold when using99mTc-pertechnetate as a tracer. A useful tool for US-based risk stratification of thyroid nodules is Thyroid Imaging Reporting and Data System (TIRADS). Recently, a complementary role of elastography was shown. Our aim was to evaluate a diagnostic value of elastography using carotid artery pulsation in the assessment of cold solid thyroid nodules.

Methods
In 39 patients 31 females and 8 males (mean age 51.6±18.9 years), we evaluated solitary or dominant solid thyroid nodule that was cold on scintigraphy with99mTc-pertechnetate. In every patient, thyrotropin (TSH) was measured, thyroid and nodule volume were calculated using standard formula and TIRADS score was estimated on the basis of US characteristics. Elastography using carotid artery pulsation was performed and elasticity contrast index (ECI) of thyroid nodule and paranodular tissue was assessed. In every nodule, fine needle biopsy was performed and cytology was reported using Bethesda classification system. Patient and nodule characteristics were compared according to cytology result.

Results
Mean TSH level was 1.73±1.13 mIU/l. Mean thyroid volume was 29.6±18.9 ml and mean nodule volume was 13.4±14.9 ml. Males had significantly larger nodule volume than females (28.4±22.7 vs 9.6±19.3 ml, \( P = 0.05 \)). Mean ECI of thyroid nodules was significantly higher compared with mean ECI of paranodular tissue (1.81±0.84 vs 1.09±0.54, \( P < 0.001 \)). Suspicious Bethesda category (4 or 6) was confirmed in 20.5% (8/39) of patients. Compared with unsuspicious nodules, nodules with suspicious Bethesda category were confirmed in significantly younger patients (38.6±18.8 vs 54.2±14.6 years, \( P = 0.011 \)), their proportion was significantly higher in males than in females (\( P = 0.02 \)) and their TIRADS score was significantly higher (\( P < 0.001 \)). Patients with suspicious or unsuspicious cytology did not differ with respect to mean ECI of thyroid nodule (2.2±1.3 and 1.7±0.6, \( P = 0.33 \)), nodule volume (\( P = 0.71 \)) or TSH concentration (\( P = 0.87 \)).

Conclusion
Our results show a significantly higher ECI in cold solid thyroid nodules than in surrounding thyroid tissue. However, elastography with ECI evaluation does not seem to contribute significantly to the assessment of malignant potential of those nodules. Data based on larger number of nodules is needed to further evaluate the value of elastography.

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PS2-10-94
Follow-up and incidence of malignancy in eu-tirads 3 nodules with indication of fine needle aspiration cytology, a single-center descriptive study
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Endocrine Abstracts (2022) Vol 84
thoracic nodules that underwent surgery between 2012 and 2020. The genetic alterations were examined by polymerase chain reaction (PCR), followed by DNA sequencing. The association of the genetic alterations with clinicopathologic features was evaluated.

Results/Discussion
Our series of 231 patients included 80.1% females (mean age 53.7; SD = 15.9) and 19.9% males (mean age 57.8; SD = 6.9); cytology was non-diagnostic in 4.3%, benign in 18.2%, indeterminate in 36.8% and malignant in 40.7%; histology result presented 17.3% benign and 82.7% malignant nodules. In histology, the eighty-five indeterminate nodules correspond to 17.6% benign and 82.4% malignant lesions. Mutation frequencies in cytology and histology specimens were, respectively, TERTp: 4.3% v 8.2%; BRAF: 20.8% v 22.5%; HRAS: 4.3% v 5.2%; NRAS: 5.2% v 7.8%; KRAS: 1.7% v 1.7%. In indeterminate nodules, mutation frequencies in benign and malignant histology were: TERTp: 2.4% v 8.2%; BRAF: 2.4% v 9.4%; HRAS: 3.5% v 4.7%; KRAS: 2.4% v 3.5%. A good cyt-histologic agreement was obtained for molecular alterations (96.2%, k = 0.657), suggesting that US-FNAC can contribute to anticipate the molecular profile of the tumor. Indeterminate nodules showed more TERTp and BRAF mutations in malignant histology. Several statistically significant associations between the clinicopathological and molecular features of the tumors were found: TERTp, BRAF and TERTp + BRAF mutations were associated with aggressiveness, extra thyroidal invasion, and lymph node metastases. On the contrary, RAS mutations were associated with a better patient outcome.

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PS2-10-96
Prospective, observational study on radioiodine treatment in DTC patients with intermediate RISK or micro lymph node metastases
Agnieszka Blewaska1, Aleksandra Ledwon1, Ewa Paliczka-Cieslik1, Aleksandra Sygula1, Małgorzata Haras-Gil1, Aleksandra Kropinska1, Agnieszka Czarniecka1 & Daria Handzikiewicz-Junak2
1National Research Institute of Oncology, Poland; 2National Research Institute of Oncology, National Research Institute of Oncology, Gliwice, Poland

There are much controversy adjuvant radioiodine treatment (131-I-th) in intermediate/low risk patients with lymph node micrometastases. The first results of ESTIMABL2 trial showed no radioiodine benefit in low risk DTC, however intermediate patients were not included in this study.

Aim
Observational study was to evaluate effects of 131-I-th in intermediate/low risk patients with lymph node micrometastases. The first results of ESTIMABL2 trial showed no radioiodine benefit in low risk DTC, however intermediate patients were not included in this study.

Patients
There were 342 women (85%), the median age at diagnosis was 52. Most patients, 298 (91%), were diagnosed with papillary cancer; 117 (29%) had extrathyroid extension, 133 (33%) vascular invasion and 249 (61.6%) lymph node metastases. Median 131-I activity was 100 mCi and all patients were treated after rTSH stimulation. Median time from first operation to 131-I-th was 5 months. Media time of follow-up after treatment 14 months.

Results
In posttherapy scintigraphy only in 9 patients there was suspicion uptake in lymph nodes. In none of these patients persistent disease was confirmed. During first follow-up 318 (79%) had excellence response and 1 structural recurrence. Thereafter 5 (1.2%) of patients recurred.

Conclusion
Our results show that in a selected group of patients with low/intermediate risk, there are excellent treatment results. The question whether 131-I-th may be omitted in this group of patients should be confirmed in a prospective randomized trial.

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PS2-10-95
Contribution of cyto-histological genetic profile to a precocious diagnosis in thyroid neoplasm
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1Centro Hospitalar Universita´ rio de Lisboa Central, Nova Medical School, Maria, Faculdade Medicina de Lisboa, Endocrinology, Lisboa, Portugal; 2Metabolism Research Group, Pathology, Porto, Portugal; 3Hospital Curry Cabral, Endocrinology, Lisboa, Portugal; 4Ipatiunup/3, Porto, Portugal; 5Gabinete de Estatica Do Centro de Investigacao Do Centro Hospitalar Universitario de Lisboa Central, Nova Medical School, Estatistica, Lisboa, Portugal; 6Ipatiunup/3 - Instituto de Investigação e Inovação Em Saúde Da Universidade Do Porto, Cancer Signaling and Metabolism Research Group, Pathology, Porto, Portugal; 7Hospital de Santa Maria, Faculdade Medicina de Lisboa, Endocrinology, Lisboa, Portugal; 8Medical Faculty University of Porto, Ipatunup, Cancer Signaling and Metabolism Group, Porto, Portugal

Aim
The aim of this study was to compare the cyto-histologic genetic profile (TERTp, BRAF and RAS (NRAS, HRAS and KRAS)), by using a paired series of cytology and histology samples, to establish whether the molecular profile defined by US-FNAC is reliable to further characterize indeterminate nodules.

Methods
The series in this study was composed by a cytology and corresponding formalin-fixed paraffin-embedded (FFPE) tissue from 231 consecutive patients with thyroid nodules that underwent surgery between 2012 and 2020. The genetic alterations were examined by polymerase chain reaction (PCR), followed by DNA sequencing. The association of the genetic alterations with clinicopathologic features was evaluated.

Results/Discussion
Our series of 231 patients included 80.1% females (mean age 53.7; SD = 15.9) and 19.9% males (mean age 57.8; SD = 6.9); cytology was non-diagnostic in 4.3%, benign in 18.2%, indeterminate in 36.8% and malignant in 40.7%; histology result presented 17.3% benign and 82.7% malignant nodules. In histology, the eighty-five indeterminate nodules correspond to 17.6% benign and 82.4% malignant lesions. Mutation frequencies in cytology and histology specimens were, respectively, TERTp: 4.3% v 8.2%; BRAF: 20.8% v 22.5%; HRAS: 4.3% v 5.2%; NRAS: 5.2% v 7.8%; KRAS: 1.7% v 1.7%. In indeterminate nodules, mutation frequencies in benign and malignant histology were: TERTp: 2.4% v 8.2%; BRAF: 2.4% v 9.4%; HRAS: 3.5% v 4.7%; KRAS: 2.4% v 3.5%. A good cyt-histologic agreement was obtained for molecular alterations (96.2%, k = 0.657), suggesting that US-FNAC can contribute to anticipate the molecular profile of the tumor. Indeterminate nodules showed more TERTp and BRAF mutations in malignant histology. Several statistically significant associations between the clinicopathological and molecular features of the tumors were found: TERTp, BRAF and TERTp + BRAF mutations were associated with aggressiveness, extra thyroidal invasion, and lymph node metastases. On the contrary, RAS mutations were associated with a better patient outcome.

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PS2-10-96
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Agnieszka Blewaska1, Aleksandra Ledwon1, Ewa Paliczka-Cieslik1, Aleksandra Sygula1, Małgorzata Haras-Gil1, Aleksandra Kropinska1, Agnieszka Czarniecka1 & Daria Handzikiewicz-Junak2
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Conclusion
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Monday, September 12th, 2022
Poster Session 3 Case Reports
PS3-11-97
Van wyk-grumbach syndrome: an unusual presentation of long-standing primary hypothyroidism mimicking ovarian tumor
Kar Wejaphikul, Prapai Dejkhamron & Kevalee Unachak

Endocrine Abstracts (2022) Vol 84
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Introduction
Children with long-standing primary hypothyroidism usually have growth retardation, neurodevelopmental impairment, and delayed puberty. However, paradoxical precocious puberty, namely Van Wyk-Grumbach syndrome (VWGS), has been described. The postulated mechanism is high levels of TSH stimulate gonadal FSH receptors, resulting in ovarian over-stimulation and precocious puberty. Since the enlarged ovarian cyst is commonly found in VWGS, gonadotropin-independent precocious puberty (GIPP) was first misdiagnosed with ovarian tumors. Case report
A 9-year and 10-month-old girl presented with slow-progressive abdominal distention, heavy vaginal bleeding, and pelvic pain for a month. Her thelarche and menarche occurred at the age of nine years with regular periods and cycle length of 4 weeks, suggesting precocious puberty. Physical examination showed breast Tanner stage IV with no pubic or axillary hair. A midline cystic mass was palpated at the lower abdomen. A pelvic ultrasound found a pubertal-size uterus with endometrial thickness and large bilateral ovarian cysts (8.5x4.2x7 cm and 8.1x4.7x8 cm in right and left ovary, respectively) with multiple internal septations. The bilateral ovarian tumors were initially suspected. However, no tumor markers were elevated, except slightly increased LDH (266 IU/l (135-214)). In addition, the patient was disproportionately short (height at -4.5SDS with upper/lower ratio of 1.39:1 and weight of +2.0 SDS) and had a history of hypothyroidism, including mild pallor, puffy eyelids, flat nasal bridge, dry skin, gross motor and speech delays, and muscular pseudohypertrophy. Her skeletal age was markedly delayed (5 years). Severe primary hypothyroidism was diagnosed by high TSH and low FT4 (TSH 621 uIU/ml (0.60-4.84), FT4 0.15 ng/dl (0.97-1.67), TPOAB 6.9 IU/ml (<40), TGA 37.6 IU/ml (<125), thyroglobulin level 1.1 mg/ml (5-40)). Baseline LH was below 0.1, FSH 6.62 IU/l, and estradiol 6.22 pg/ml, indicating GIPP. Thyroid scan revealed an ectopic lingual thyroid. VWGS was diagnosed based on the concurrence of severe primary hypothyroidism, GIPP, and delayed bone age. After levothyroxine replacement, she had no further episode of vaginal bleeding, and bilateral ovarian cysts were gradually resolved. Conclusion
VWGS is an unusual presentation of long-standing primary hypothyroidism. The combination of precocious puberty, short stature, and delayed skeletal maturation is a clue for diagnosis. Ovarian cysts progressively regress with LT4 replacement. Physicians need to be aware of this condition to avoid unnecessary surgery due to suspected ovarian tumors.

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PS3-11-98
Complicated treatment with lenvatinib for hurthle cell carcinoma
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Introduction
The tyrosine kinase inhibitor (TKI) lenvatinib, used in radioiodine-refractory differentiated thyroid cancer, is usually well-tolerated. However, severe side effects can occur. We describe a life-threatening complication under lenvatinib, followed by a challenging treatment with levothyroxine (LT4). Case Report
A 62-year-old man was diagnosed with a bone-metastasized Hurthle cell thyroid carcinoma (pT3N0M1). He underwent a total thyroidectomy, external neck radiation and radioiodine after LT4 withdrawal (55 MBq stimulation TSH 104.7 mU/l, stimulated thyroglobulin 2.7 µg/l, thyroglobulin antibodies <10 U/l). A 113I scintigraphy showed radioiodine-refractory disease. His medical history included a sleeve gastrectomy with conversion to gastric bypass and repeat sleeve gastrojejunostomy intervention, evolutions and creation of a new adenoblastomy. He required LT4 250µg/day (weight 85 kg) to obtain a low normal TSH (table). Ten months after starting lenvatinib resulting in stable disease, he presented with an ischemic stomach pouch with perforation and fistulisation. An urgent laparotomy was performed and lenvatinib was stopped. Afterwards, he developed diarrhoea, for which cholestyramine 8g/day was started. Two months later, overt hypothyroidism was diagnosed (table, time 0 and the LT4 dose was doubled. An oral challenge with 1000µg LT4 showed an adequate increase of FT4, excluding deterioration of mucosal gastrointestinal malabsorption. After stopping cholestyramine, his thyroid hormone levels returned to baseline under LT4 250µg/day. Conclusions
Treatment with lenvatinib can result in gastrointestinal perforation and fistulisation, which is attributed to the anti-angiogenic effect. Caution is needed, especially in patients with a history of complex abdominal surgery. The need for high doses of LT4 should be reminiscent of either reduced gastrointestinal absorption or availability, such as interaction with cholestyramine. Cholestyramine, an anionic exchange resin used in the treatment of bile acid diarrhoea, binds LT4 in the intestine thereby reducing its absorption. The passage of LT4 through the enterobacterial circulation further contributes to this interaction. This interference can be minimized by providing at least four hours between ingestion of the two agents.

Table. Evolution of thyroid function tests and treatments.

<table>
<thead>
<tr>
<th>Timeline</th>
<th>TSH (mU/l)</th>
<th>FT4 (pmol/l)</th>
<th>LT4 dose (µg)</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5m</td>
<td>0.49</td>
<td>23.7</td>
<td>250</td>
<td>12m post laparotomy for ischemic stomach pouch with stop lenvatinib</td>
</tr>
<tr>
<td>-2m</td>
<td>83.3</td>
<td>8.9</td>
<td>250</td>
<td>start cholestyramine 8g/day on LT4 250µg/day</td>
</tr>
<tr>
<td>0</td>
<td>8.1</td>
<td>4.7</td>
<td>500</td>
<td>PO LT4 1000 µg</td>
</tr>
<tr>
<td>+1d</td>
<td>0</td>
<td>8.1</td>
<td>250</td>
<td>PO LT4 1000 µg</td>
</tr>
<tr>
<td>+2d</td>
<td>0</td>
<td>8.1</td>
<td>250</td>
<td>PO LT4 1000 µg</td>
</tr>
<tr>
<td>0min</td>
<td>11.2</td>
<td>28.3</td>
<td>500</td>
<td>PO LT4 1000 µg</td>
</tr>
<tr>
<td>+1hr</td>
<td>27.1</td>
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<td>32.2</td>
<td>28.3</td>
<td>500</td>
<td>PO LT4 1000 µg</td>
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<td>1.39</td>
<td>20.5</td>
<td>250</td>
<td>PO LT4 1000 µg</td>
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</table>

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PS3-11-99
The clinical outcome of covid-19 infection in a patient with the history of multinodular goiter: case report
Sona Nersisyan1, Eveline Aghajanova2, Alvard Hovhannisyan3 & Vijay Asayan1
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Introduction
The thyroid gland and COVID-19 infection with its associated inflammatory-immune responses are known to be engaged in complex interplay. Until now, the evidence on the outcome of COVID-19 in patients with a history of thyroid cancer remains scarce, and most of the recommendations given are based on common sense. Case report
A 71-year-old man was admitted to Mikaelyan University hospital with general weakness shortness of breath, hiccups and tumor-like mass on the anterior part of the neck. The patient had a history of tumor-like mass for 20 years. The patient presented with weakness and fatigue that became severe two days before hospitalization. Examination revealed Ps = 77mmHg, BP = 125/70 mmHg, T = 36.5°C, SpO2 84 % (O2), BMI = 19/kg/m². On the anterior surface of the neck, from the middle line to the left there was a tumor-like mass with mobile, smooth, elastic surface of about 7*8 cm, according to the results of the ultrasound scan, there were evidence of many metastases in the liver and the right kidney. Thyroid ultrasound showed significant diffuse changes and foci of cystic degeneration. There was a pronounced blood circulation in color Doppler mode. Parajugular lymph nodes up to 1.8 cm in size were visualized. The Chest X-ray revealed bilateral pneumonia and lung metastasis. Therefore, nasal swabs were collected for the COVID-19 PCR test, and the result was positive. Lab results: CRP-107.71 mg/l, LDH 266 IU/l, TSH 10.9-17.2/mU/l, FT4 11.6-21.9 pmol/l.

Endocrine Abstracts (2022) Vol 84
metastases. This patient underwent treatment for COVID-19, that included infusion therapy, dexamethasone 12 mg with dose decrease to 4 mg, ceftriaxone, heparin 10000U daily, aspirin, famotidine, oxygen. Finally, he was discharged in good general health condition after eight days. The patient was recommended to perform fine needle aspiration biopsies of thyroid nodules and total thyroidectomy afterwards.

Conclusion
As there are few cases of combination of thyroid tumor and COVID-19 reported worldwide, our clinical case can contribute the management of such patients. In our clinical case, a step-by-step management of the patient led the favorable outcome of COVID-19.

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**PS3-11-100**

**Differentiation of parathyroid gland from a lymph node in clinical practice**

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Introduction
How to differentiate lymphadenitis from parathyroid gland?

Case report
The patient, a 45-year-old woman, applied to “Muratsan” Polyclinic complaining of asthenia, dry skin, easy fatigability, muscle and bone pain, palpitations. Anamnesis was gained and an examination was carried out. According to the patient’s indication in the anamnesis, total thyroidectomy was done a year before, followed by radioiodine therapy with regard to papillary carcinoma of the thyroid gland. A normal menstrual period.

The following examinations have been carried out:

**PS3-11-101**

**Carpal Tunnel Syndrome in Subclinical Hypothyreosis**

Shushanik Kostandyan1, Armine Khroyan2, Elena Aghajanova3, Artashes Tadevosyan4 & Lilit Kambulyan5

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Introduction
Is treatment with Levothyroxine indicated for subclinical hypothyreosis concomitant with Carpal Tunnel Syndrome?

Case Report
The patient, a 35-year-old woman, applied to “Muratsan” Polyclinic in Armenia with complaints of weakness, fatigue, dry skin, pain in hands, swelling, numbness, all these intensified at night. The above mentioned complaints appeared approx a year ago.

The following findings have been determined:

Conclusions
In case of Subclinical Hypothyreosis and Carpal Tunnel Syndrome it is recommended to prescribe Levothyroxine for 3 months, thereafter the patient’s condition should be assessed. If the clinical symptoms subside or disappear on the background of the treatment, continue treatment with Levothyroxine, if not then stop the treatment.

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>The result after 3 months</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>5.42 uIU/mL</td>
<td>0.43 uIU/mL</td>
<td>0.27-4.2 uIU/mL</td>
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<td>FT4</td>
<td>1.28 ng/dL</td>
<td>1.68 ng/dL</td>
<td>0.93-1.7 ng/dL</td>
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<tr>
<td>Vitamin D</td>
<td>23.43 ng/ml</td>
<td>34.3 ng/ml</td>
<td>30-70 ng/ml</td>
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<td>PTH</td>
<td>96.06 pg/ml</td>
<td>103 pg/ml</td>
<td>15-65 pg/ml</td>
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<td>Ca</td>
<td>1.26 mmol/l</td>
<td>1.21 mmol/l</td>
<td>1.2-1.32 mmol/l</td>
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<tr>
<td>P</td>
<td>1.3 mmol/l</td>
<td>1.21 mmol/l</td>
<td>0.84-1.45 mmol/l</td>
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<td>Neck ultrasound</td>
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<td>of the parathyroid</td>
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<td>Densitometry</td>
<td>Osteoporosis:</td>
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<td></td>
<td>T score = 2.7</td>
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</table>

*The examinations have been carried out on the background of 100 mg of levothyroxine. Levothyroxine 150 mg 1x1. vitamin D 5000IU for 3 months, CaD3 1000 mg 1x1 for 3 months were prescribed followed by the same results of the laboratory tests. Due to the high PTH level, the secondary hyperparathyroidism was denied and the patient was directed to scintigraphy. Adenoma of the parathyroid gland was confirmed and surgical treatment was advised.

PS3-11-99

**Doi: 10.1530/Endoabs.84.PS3-11-99**

Endocrine Abstracts (2022) Vol 84
PS3-11-102

Do not rush to overdiagnose when a newly formed node is detected
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28 years old woman has presented to the Armenian-American Wellness Center complaining of muscular weakness, fatigue, palpitation, dysphagia, dry skin and hair fall. The patient was visited by the endocrinologist and referred to the following tests: ultrasound of the thyroid gland, blood test for TSH, FT4 and anti-TPO.

Results
Diffusely enlarged thyroid gland with diffuse heterogeneous echotexture and the presence of hypoechogenic micronodules. In the left lobe a large nodule 7x8 mm is detected, hypoechogenic with uneven outline and prominent hypervascularisation.

(TIRADS-4a)

Test
Results
Test after 3 months
Normal range
TSH
5.87 uU/ml
1.2 uU/ml
0.27-4.2 uU/ml
FT4
0.83 ng/dl
1.3 ng/dl
0.93-1.7 ng/dl
Anti-TPO
208.21 IU/ml
< 34 IU/ml

Diagnosis
Autoimmune thyroiditis, hypothyroidism. The presence of T-4 a is a direct indication for FNA but conservative treatment has been taken as a start with Levothyroxine 50 mcg/day. The next follow up was in 3 months.

Ultrasound of the thyroid gland - in the left lobe 4x5 mm. TIRADS-S-2 Conclusion: In case the node of the thyroid gland is based on hypothyroidism and has rather no indications for FNA but conservative treatment has been taken as a start with Levothyroxine 50 mcg/day.

2022 Endocrine Abstracts

PS3-11-103

Suspicious thyroid nodule in de Quervain's thyroiditis
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2Elias Hospital, Endocrinology, Bucharest, Romania; 3Elias Hospital, Endocrinologie, Bucharest, Romania; 4Carol Davila University of Medicine and Pharmacy, Elias Hospital, Endocrinology, Bucharest, Romania

Introduction
De Quervain’s thyroiditis, also known as subacute granulomatous thyroiditis, is a self-limiting inflammatory disorder of the thyroid gland. It is presumed to be caused by a viral infection and many patients have a history of an upper respiratory infection 2-8 weeks prior to the onset of thyroiditis. It is the most common cause for neck pain or discomfort, and it usually has a predictable course of thyroid function evolution. On ultrasonography the thyroid gland might be slightly enlarged or normal with a diffuse or focal hypoechogenic appearance.

Ay(m)
We report the case of a 50-year-old female patient referred for the work-up of a TIRADS 5 thyroid nodule with satellite enlarged lymph nodes.

Materials and methods
Anamnesis revealed a progressive onset low anterior neck pain after an upper respiratory infection. On physical examination the thyroid gland was enlarged and tender. Laboratory assessment showed subclinical hyperthyroidism with suppressed TSH (0.05 uU/ml) and normal levels of FT4 and TT3. Anti-thyroid peroxidase antibodies, anti-thyroglobulin and anti-TSH receptor antibodies were negative. Our patient associated high levels of inflammatory markers: erythrocyte sedimentation rate level was 57 mm/h and C-reactive protein was 24.9 mg/dl. Neck ultrasound identified multiple thyroid nodules with a left dominant nodule of 2.75/1.5/1.5 cm with a high index of sonographic suspicion for thyroid cancer and multiple left lymph nodes.

Results
Thus, the diagnosis of subacute granulomatous thyroiditis was established and treatment with oral corticosteroids was initiated. Thyroid ultrasound-guided fine needle aspiration cytology was performed and the result showed follicular cells without nuclear atypia and several multinucleated giant cells. One month after treatment onset, follow-up ultrasound examination showed complete resolution and disappearance of the thyroid nodules. The patient became hypothyroid and replacement treatment with Levothyroxine was initiated.

Conclusion
De Quervain’s thyroiditis can sometimes show on ultrasound the presence of ill-defined hypoechogenic thyroid lesions that may be interpreted as thyroid nodules. Thus, it is important to properly identify these transient lesions to improve the treatment and follow-up of these patients and de Quervain’s thyroiditis should be included in the differential diagnosis of thyroid nodules.

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PS3-11-104

Parathyroid adenoma apoplexy mimicking a thyroid bleeding cyst, a seemingly innocent condition may harbor a threatening one
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Introduction
Primary hyperparathyroidism most commonly presents with hypercalcemia. Rarely, parathyroid apoplexy or haemorrhagic, mimicking a thyroid bleeding cyst is the first presentation of a parathyroid adenoma.1,2,3 Case Report
A 55-year-old woman presented to the ENT department with a sudden onset painful goiter. Ultrasound revealed a sharply defined hypoechogenic nodule in the right thyroid lobe measuring 2.4 x 17.8 x 18.2 mm. The patient was referred to the endocrinology department for fine-needle aspiration (FNA). Repeat ultrasound showed a partially cystic nodule located posterior to rather than in the right thyroid lobe, suggesting parathyroid adenoma bleeding rather than thyroid nodule bleeding. FNA was deferred. Lab testing confirmed hypercalcemia and hyperparathyroidism. 99mTc-Pertechnetate/SestaMIBI one month after initial presentation showed no uptake in the nodule, which was interpreted as a cold thyroid nodule. F-18 fluorocholine-PET/CT two months after presentation showed uptake in the nodule, suggestive of a parathyroid adenoma. The patient was referred for parathyreoidecaytomy along with right thyroid lobectomy in case of thyroid adhesion. At surgery, the right inferior parathyroid was strongly fused with the thyroid. A right hemithyroidectomy and resection of the parathyroid adenoma was performed. Pathology showed a parathyroid adenoma, approximately 17 mm in diameter, with an eccentrically located cystic structure (5 mm in diameter), filled with red blood cells and surrounded by a thickened fibrous capsule. The cyst wall contained numerous macrophages with iron pigment deposition.

Conclusion
Diagnostic workup includes dedicated ultrasonography to raise the suspicion of a parathyroid adenoma haemorrhage and to discern it from thyroid nodules. A negative 99mTc-Pertechnetate/SestaMIBI scan has been reported as presence of parathyroid adenoma haemorrhage. A negative 99mTc-Pertechnetate/SestaMIBI uptake may contribute to the assessment of SestaMIBI uptake. To our knowledge, this is the first parathyroid adenoma apoplexy case in which F-Choline-PET/CT has been performed. In conclusion, cervical pain/hypercalcemia along with hypercalcemia point to the diagnosis of parathyroid apoplexy, mimicking a thyroid bleeding cyst. Expeditious work-up with ultrasound and if available F-Choline-PET/CT allows for timely surgery, minimizing the risk of recurrent and more severe bleeding. Hence, a two-step process with a localized parathyroid adenoma haemorrhage preceding massive life threatening haemorrhage has been reported.4

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PS3-11-105

Pseudomalabsorption of levothyroxine
Nata Megvelashvili1 & nino zavarsvili
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Pseudomalabsorption of Levothyroxine Hypothyroidism due to non-compliance with levothyroxine therapy (pseudomalabsorption) is rare. The diagnosis is considered in patients with persistent refractory hypothyroidism despite treatment high doses of levothyroxine. Intestinal malabsorption, drug and dietary interference with levothyroxine absorption and nephrotic syndrome should be
Graves’ disease 2 and Orbitopathy
PS3-12-106

Alterations in the gut microbiota are associated with the humoral immune response in Graves’ disease
Yalei Liu
People’s Hospital of Zhengzhou University, Department of Endocrinology, Zhengzhou, China

Background
Graves’ disease (GD) is characterized by lymphocytic infiltration and autoimmune activation. The gut microbiota plays a pivotal role in immune regulation. The underlying mechanism of the gut microbiota in GD autoimmunity remains elusive. The present study aimed to investigate the role of the gut microbiota in the humoral immunity of GD.

Methods
A total of 45 healthy controls (HCs) and 68 GD patients [52 without treatment (U_GD) and 16 with treatment (T_GD)] were enrolled in the study. B-cell subset distribution and CD32b expression on B cells were analyzed by flow cytometry. Cytokines were measured by enzyme-linked immunosorbent assays. The gut microbial composition was analyzed by 16S rRNA gene sequencing.

Results
In the discovery cohort, we observed aberrant B-cell subset distribution, decreased CD32b expression and elevated proinflammatory cytokines in U_GD patients compared with HCs. The diversity and structure of the microbial community in U_GD patients were different from those of HCs, and some alterations in gut microbiota were significantly correlated with changes in humoral immunity. Moreover, we identified a fecal microbiome index that could be used to distinguish U_GD patients from HCs in the validation cohort, whereas the structure of the microbial community and B-cell activation-related cytokines in T_GD patients were similar to those of HCs.

Conclusions
The interaction between the microbiota and humoral immunity is involved in the development of GD, and antithyroid drug therapy could relieve the disease by rebuilding homeostasis of gut microbiota.

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PS3-12-107

Macrophase-orbit fibroblasts interaction in context of hypoxic signaling for inflammatory processes during graves’ orbitopathy
Gina-Eva Görtz1, Anja Eckstein2, Christoph Jesenek3, Mareike Horstmann3, Svenja Philipp5, Kirsten Bruderek6, Michael Oeverhaus1, Anne Dase3, Nikolaos Bechrakis5, Svenja Philipp5, Kirsten Bruderek6, Michael Oeverhaus7, Anke Daser6, Nicolaus Bünemann1, Uta Berchner-Pfannschmidt10
1University Hospital Essen, Molecular Ophthalmology, Essen, Germany; 2University of Duisburg-Essen, Molecular Ophthalmology, Essen, Germany; 3University Hospital Essen, Department of Ophthalmology, Essen, Germany; 4Department of Ophthalmology, Molecular Ophthalmology Group, University of Duisburg-Essen, Essen, Germany; 5Klinik für Augenheilkunde, Essen, Germany; 6Klinik für Augenheilkunde, Universitätsklinikum Essen, Department of Ophthalmology, Molecular Ophthalmology Group, University of Duisburg-Essen, Essen, Germany; 7Klinik für Hals-, Nasen-, Ohrenheilkunde, University Hospital Essen, Department of Otorhinolaryngology, Essen, Germany; 8Klinik für Augenheilkunde, Universitätsklinikum Essen, Department of Ophthalmology, University Hospital Essen, Essen, Germany; 9University Hospital Essen, University of Duisburg-Essen, Molecular Ophthalmology, Department of Ophthalmology, University of Duisburg-Essen, Essen, Germany; 10Molekularer Ophthalmologie, Department of Ophthalmology, University Hospital Essen, Essen, Germany

Introduction
The inflammatory eye disease Graves’ orbitopathy (GO) is the main complication of Graves’ disease in patients. In previous studies we have shown that hypoxia and HIF-1 dependent pathways could play an important role in the pathogenic process of GO. Hypoxia is known to attract inflammatory cells and therefore maintains inflammation and recruitment of immune cells like macrophages (MQ). However, few is known about the specific contribution of MQ to the progression of orbitopathy. Therefore, we investigated the role and interaction of MQ and orbital fibroblasts (OF) in context of inflammation and hypoxia.

Methods & Results
We analyzed the expression levels of hypoxic marker HIF-1α, MQ marker CD68, proinflammatory cytokine TNFα and recruitment proteins CCL2, CCL5 and CCL20 in fat biopsies of control and GO patients by real-time PCR. We found that HIF-1α, CD68, TNFα, CCL2, CCL5 and CCL20 mRNA expression was increased in the fat tissue of GO patients. Next, we analyzed the cytokine profile of supernatants from fat biopsies with a multiplex ELISA. We could show an enhanced secretion of TNFα, CCL2 and CCL20 only under hypoxia while CCL5 was induced on protein level under normoxia as well as under hypoxia in GO tissue. An immunofluorescence stain of CD68 and TNFα was used to demonstrate the source of TNFα in the orbital tissue. The Immunofluorescence indicated that TNFα secretion occurs in conjunction with CD68 positive MQ. To further investigate the inflammatory interaction of MQ and OF, we stimulated OF with TNFα or co-cultured them with M1-MQ from a THP-1 cell line under normoxic and hypoxic conditions. We found that OF expressed hypoxic marker HIF-1α, hypoxia target gene VEGF and immune marker ICAM-1 as well as chemokines CCL2, CCL5 and CCL20 most pronounced upon TNFα stimulation and hypoxia. M1-MQ enhanced the induction of HIF-1α and CCL2 in OF in addition to hypoxia alone, whereas proinflammatory inhibitors Etanercept and dexamethasone reduced this effect. Furthermore, we found that OF-macrophage co-culture enhanced adipogenic differentiation and adiponectin secretion under hypoxia. PX-478, a HIF-1α inhibitor, reduced the adipogenic differentiation of OF significantly.

Conclusion
In summary, our results show that hypoxia and macrophage-OF interactions have a cumulative effect. The findings indicate that the inflammatory milieu and hypoxic signaling in the orbit are characterized by TNFα positive macrophages, which interact with OF which results in constant inflammation and tissue remodeling. A combination of anti-inflammatory treatment and HIF-1α reduction could be an effective treatment option for GO.

DOI: 10.1530/endoabs.84.PS3-12-107
Methods
We retrospectively reviewed patients with solitary toxic adenoma or toxic nodular goiter who were negative for TSHRAb and received I-131 between January 2013 and December 2018. Prior to treatment, antibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) were measured, and the uptake of iodine-123 (I-123) at 20 hours or technetium-99m-pertechnetate (Tc-99m) was determined. Patients were treated with median activity of 747 MBq I-131 (range 478–1140 MBq) and followed-up for 12 months. We monitored for de novo occurrence of GD measuring thyroid function and TSHRAb concentration. Patients' characteristics influencing the occurrence of I-131-induced GD were analysed; p-value of <0.05 was considered statistically significant.

Results
A total of 1551 patients (277 males, 1274 females) with an average age of 68.6±14.0 years (range 14-95 years) were included. Prior to I-131 therapy, TPOAb and/or TgAb concentration was raised in 14.5% (225/1551) of patients. The median I-123 uptake, measured in 64.7% (1004/1551) patients, was 29.0%, and the median Tc-99m uptake, measured in 35.5% (547/1551) patients, was 0.82%. An increase in TSHRAb concentration was observed in 4.4% (68/1551) patients at 4.1±3.3 months following I-131 application; of those, 63.2% (43/68) presented with overt hyperthyroidism. Patients with de novo occurrence of GD were significantly younger (63.1±14.3 vs 68.7±13.8 years, P < 0.01) and more likely to be positive for TPOAb and/or TgAb before I-131 application than those with negative TSHRAb (47.1% vs 13.0%, P < 0.001). Furthermore, they had significantly higher median concentrations of TPOAb (41.6 KU/l vs 30.3 KU/l, P < 0.001) and TgAb (15.0 KU/l vs 15.0 KU/l, P < 0.001). Additionally, their median uptake of I-123 before treatment was significantly higher (32.5% vs 29.0%, P < 0.05), but their Tc-99m uptake did not differ (0.89% vs 0.82%, P = 0.72). There was no significant difference in applied activity of I-131 (median, 741 vs 747 MBq, P = 0.09), or gender (P = 0.47).

Conclusions
We show that I-131-induced GD occurs in 4.4% of patients treated for thyroid autonomy. Younger patients and those with increased TPOAb and/or TgAb levels prior to I-131 therapy are at a higher risk of developing GD post-treatment. We therefore recommend monitoring these patients closely following I-131 application.

DOI: 10.1530/endoabs.84.PS3-12-109

PS3-12-109
Blocking the TSH receptor with human monoclonal autoantibody K1-70TM in patients with Graves’ disease – results from a phase 1 clinical trial
Jadwiga Furmaniak1, Jane Sanders1, Paul Sanders2, Yang Li2 & Bernard Rees Smith1
1Av7 Limited, Rsr Limited; 2Rsr Limited

Objectives
TSH receptor (TSHR) autoantibodies (TRAB) which mimic the actions of TSH and are responsible for hyperthyroidism in Graves’ disease (GD) which is often associated with Graves’ orbitopathy (GO). K1-70 is a TSHR specific human monoclonal autoantibody which binds to the TSHR with high affinity and prevents stimulation of the TSHR by TSH and TRAb. Safety, tolerability, pharmacokinetic, pharmacodynamic and immunogenic effects of K1-70 in patients with GD were assessed in a phase 1 clinical trial.

Methods
K1-70TM was administered to 18 GD patients stable on anti-thyroid drugs in 6 cohorts of 3 subjects each. The subjects were randomly assigned to receive placebo or higher doses of K1-70 (25 mg and 150 mg intravenous (iv) routes in 6 cohorts of 3 subjects each. The subjects were followed up for 100 days post dosing.

Results
K1-70TM was well tolerated in all subjects at all doses with no reported deaths or Serious Adverse Events. The reported Adverse Events were mild or moderate and none were directly related to K1-70TM. No significant immunogenic responses were observed in any of the subjects. The iv administration resulted in improved systemic exposure compared to im administration indicating this was the correct dosage route for future stages of drug development. The half-life of K1-70TM given iv was about 500 hours. Subjects receiving higher doses of K1-70 (25 mg and above) demonstrated expected pharmacodynamic effects with T3, T4 and TSH progressing into hypothyroid ranges. At 28 days post dose 11/18 (61%) of patients were in a hypothyroid state while for higher dose cohorts 99% (100%) progressed to the hypothyroid state on or before day 28. This corresponded to clinically observed and patient reported improvements in symptoms of both GD and GO. Patients reported improvements in tremor, sleep, mental focus, toilet urgency, aches, pains and general wellbeing. Clinically significant reductions in exophthalmos measurements (>2 mm) were observed in subjects receiving higher doses of K1-70TM. In addition, patients reported improvements in photosensitivity, gritty eyes sensation, conjunctival redness and gaze-evoked pain.

Conclusions
Our phase 1 trial demonstrated that K1-70TM was safe and well tolerated in all subjects. Systemic exposure following iv administration was as expected and the risk-benefit profile for K1-70 was favourable for later phases of development. The pharmacokinetic/pharmacodynamic relationship exceeded the expectations of the phase 1 trial design and the beneficial effects of K1-70 on patients’ eye signs support suggestions of a key role for TRAb stimulation of orbital TSHRs in GO.

DOI: 10.1530/endoabs.84.PS3-12-109

PS3-12-110
Linear mixed model analysis of quality of life scores in patients with thyroid eye disease treated with teprotumumab from three 24-week clinical trials
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1Johannes Gutenberg University (Jgu) Medical Center, Department of Medicine I, Mainz, Germany; 2Horizon Therapeutics, Deerfield, Il, United States

Objectives
Teprotumumab, an IGF1-receptor antagonist, has been shown in three clinical trials to markedly improve the clinical course of Thyroid Eye Disease (TED) or Graves’ Orbitopathy (GO) with significant improvements noted in inflammation, proptosis, and diplopia. Furthermore, compared to placebo moderate-to-large improvements were noted in the total, appearance (AP), and visual function (VF) scores as measured by EUGOGO quality of life (GO-QOL) scores after 24 weeks of therapy. Based on these findings, we undertook an analysis to determine the major outcomes associated with these substantial changes in QOL.

Methods
A total of 120 patients with moderate-to-severe TED who were treated with teprotumumab from the phase 2, phase 3 (OPTIC, and OPTIC-X controlled studies were examined with observation points on study day 1, week 6, 12, and 24. Linear mixed-effects models were employed to measure the impact of Demographics, Time on treatment, Proptosis (mm), Diplopia (Gorman Grade), presence/absence of Gaze Evoked Orbital Pain, and Spontaneous Orbital Pain on Total, AP, and VF GO-QOL scores, via hierarchical addition. Random effects accounted for within-patient response variability.

Results
Mean age was 52 (SD 12) years and females represented 73% of the population examined. Total, AP and VF GO-QOL scores improved 27%, 33%, and 23% respectively from baseline to Week-24. Patients with proptosis improved Total, AP and VF GO-QOL by 44%, 37%, and 49% respectively. The final model indicated that within-patient variability accounted for 80% of Total GO-QOL Score variance. Improvements in Diplopia and Gaze Evoked Orbital Pain were significantly related to higher (improved) Total, AP, and VF scores (P < 0.001) for all. Improvements in Spontaneous Orbital Pain were associated with higher Total and VF scores (P < 0.001). Increasing age (P < 0.001) and male sex (P = 0.02) had a significant positive correlation with the AP Score. All scores were positively associated with time on study (P < 0.001). Gaze Evoked Orbital Pain and Proposis were found to interact significantly, such that an improvement in proptosis correlated to a greater improvement in the AP score in patients without Gaze Evoked Orbital Pain as compared with those that had Gaze Evoked Orbital Pain (P < 0.001).

Conclusions
These novel data indicate that improvement in Diplopia and orbital pain, particularly Gaze Evoked Orbital Pain are strong contributors to GO-QOL improvement in TED patients receiving teprotumumab. Gaze Evoked Orbital Pain may impact patients’ perception of AP improvements through its interaction with proptosis reduction.

DOI: 10.1530/endoabs.84.PS3-12-110

PS3-12-111
Circulating marginal zone b cells and IGA serum levels as potential biomarkers of clinical activity of Graves’ orbitopathy
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1Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia; 2Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia; 3Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia; 4Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia; 5Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia; 6Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia; 7Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia

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Endocrine Abstracts (2022) Vol 84
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Objectives
The Clinical Activity Score (CAS) is used to measure and classify Graves orbitopathy activity (GO). However, CAS is partly subjective, and the evaluation of its components is binary. As CAS is known to be correlated with TSH receptor antibodies (TRAb), we wanted to evaluate other immunological parameters in the peripheral blood as markers of GO activity.

Methods
The study included 32 patients (19 females, 13 males). CAS was evaluated by a single experienced physician. Patients were not treated for GO, except by local measures. All patients were euthyroid on therapy. We measured TRAb, immunoglobulins, and B lymphocyte subpopulations. Multicolour flow cytometric analysis of B cell subsets was performed using the backbone of six monoclonal antibodies (anti-CD38 - CD27, CD221 - CD19, IgM, -IgG). This approach provided phenotypic characterization of naive B cells, circulating marginal zone B cells (MZB), CD21high B cells, class-switched B cells, transitional B cells and plasmablasts in peripheral blood. Ordinal regression was used for data analysis with CAS as a dependent variable.

Results
In the multivariate analysis, there was a positive association between CAS (1-4) and TRAb but a negative association between CAS and MZB and IgA.

Conclusions
Although this is just preliminary data from a small study, it seems that the activity of GO may be modulated by or associated with changes of some less often considered components of the immune system. While TRAb drives the inflammatory response and positively correlates with CAS, we found that IgA and the presence of MZB are associated with the less active form of GO. The role of MZB in autimmunity is still unclear. However, it has been demonstrated that these cells may have a dual role in autoimmune pathophysiological processes. MZB may promote autoimmune by rapid production of low-affinity antibodies with self-reactivity to clear pathogens and apoptotic cell debris. On the contrary, this subset promote autoimmunity by rapid production of low-affinity antibodies with self-reactivity to clear pathogens and apoptotic cell debris. MZB in autoimmunity is still unclear. However, it has been demonstrated that these cells may have a dual role in autoimmune pathophysiological processes. MZB may promote autoimmune by rapid production of low-affinity antibodies with self-reactivity to clear pathogens and apoptotic cell debris. MZB and the presence of MZB are associated with the less active form of GO. The role of MZB in autimmunity is still unclear. However, it has been demonstrated that these cells may have a dual role in autoimmune pathophysiological processes. MZB may promote autoimmune by rapid production of low-affinity antibodies with self-reactivity to clear pathogens and apoptotic cell debris. On the contrary, this subset promote autoimmunity by rapid production of low-affinity antibodies with self-reactivity to clear pathogens and apoptotic cell debris.

Aim of the study was to evaluate the temporal trend of the clinical presentation of GO in the last decade on the population of our area.

Methods
We selected 221 consecutive patients observed from January 2005 to December 2006 and from January 2005 to December 2016. 21 patients were excluded because underwent to surgical orbit decompression, 40 patients because were previously treated by oral or parental corticosteroids and/or radiotherapy and 49 patients because longer GO duration. Finally we studied 111 patients with Graves’ Disease, diagnosed with GO according to EUGOGO criteria within 12 months from the Graves’ Disease diagnosis. We compared 55 consecutive patients, 11 males (F) and 44 females (M) come to our observation from January 2005 to December 2006 [group 1 (G1)], with 56 patients, 15 males, and 41 females, referred to us from January 2015 to 2016 [group 2 (G2)]

Results
We assumed that iodine and selenium intake were similar between the groups; sex, age, smoke, thyroid function, LDL cholesterol, diabetes, impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), come from GD diagnosed to start of therapy (TGDD) and GO different grade of severity were tested by univariate analysis investigating only TGDD reduced in G2 vs G1, P = 0.057. We built multivariate logistic regression model considering the effect of age, TGDD, Hertel measurements, CAS, eyes motility improvement and GO severity (considering moderate to severe and severe GO as a same group) at presentation respect the two different temporal range considered in the study. GO severity was.
Pregnancy & Iodine
PS3-13-114
The troubled discourse of hypothyroidism in pregnancy: sentiment analysis of the literature from 2011 to 2021
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Introduction/Aim
The diagnosis and management of hypothyroidism in pregnancy is a domain of shifting paradigms, with changes in guidelines, which may have led clinicians to confusion or angst (Endocrine Today; October 2019). Since sentiment analysis (SA) of medical texts can be implemented (Artificial Intelligence in Medicine 2015; 64: 17-27) we sought to use SA regarding this clinical issue.

Materials/Methods
We collected the English language abstracts of review articles in PubMed from 2011 to November 2021, using the Medical Subject Headings (MeSH) terms ”hypothyroidism”, “pregnancy” and “human” and performed SA with an online artificial intelligence tool (courtesy of Prof. Daniel Soper, California State University, Fullerton, CA, USA; https://www.danielsoper.com/sentimentanalysis/default.aspx). The results were evaluated by year with the Kruskal-Wallis and Chi square tests.

Results
From 2011 to 2015 a slight trend from negative to positive sentiment (P = 0.08) was noted in the literature studied, while from 2018 wide and significant (P = 0.04) sentiment fluctuations were noted by year.

Discussion
Regarding hypothyroidism and pregnancy uncertainties remain vis-à-vis screening and management bearing in mind the need to optimize perinatal outcomes. Researchers continue to debate the very definition of subclinical hypothyroidism, which can differ between nonpregnant or pregnant states. This situation is reflected in the sentiment of the published literature, especially in review articles, usually by experts in the field worldwide, which try to provide a critical evaluation of the data that is available from existing studies.

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PS3-13-115
Higher thyroid FT3-to-FT4 ratio is associated with gestational diabetes mellitus and adverse pregnancy outcomes
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Objective
The Danish population was previously iodine deficient with regional differences, and a mandatory iodine fortification of salt was introduced more than 20 years ago. Despite iodine fortification and frequent use of iodine-containing supplements, the iodine status in Danish pregnant women was insufficient when evaluated in 2012 (median urinary iodine concentration (UIC): 101 µg/l). From July 1, 2019 the authorities implemented a mandatory increase from 13 to 20 ppm in the level of iodine added to salt in Denmark. The aim of the present study was to evaluate iodine status in Danish pregnant women after such increase in iodine fortification.

Materials/Methods
This case-control study was a sub-analysis of the BEDIP-N study, in which 199 GDM women were matched for age and body mass index with 398 controls. Thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), and thyroid peroxidase (TPO) antibodies were measured at 6-14 weeks and 26-28 weeks pregnancy. TSH and fT4 were also measured in early postpartum in GDM women.

Results
TSH and TPO were not associated with the risk to develop GDM. The fT3-to-fT4 ratio at 26-28 weeks was positively associated with GDM risk with an adjusted odds ratio (aOR) for smoking, education, parity, ethnicity, gestational weight gain and (family) history of diabetes or GDM of 2.12 (95% CI 1.07, 4.23) comparing the highest with the lowest tertile. Higher fT3 levels and FT3-to-fT4 ratio were associated with a less favorable metabolic profile with higher BMI and more insulin resistance in pregnancy and postpartum. Women in the upper fT3 tertile and upper FT3-to-FT4 ratio had a higher rate of preeclampsia [respectively 4.6% (10 vs. 1.0% (2), P = 0.040, and 4.4% (9) vs. 0.5% (1), P = 0.020], gestational hypertension [8.3% (18) vs. 3.1% (6), P = 0.034 and 8.9% (18) vs. 2.0% (4), P = 0.003], and caesarean sections [29.4% (63) vs. 16.1% (31), P = 0.002 and 32.2% (65) vs. 12.7% (25), P < 0.001].

Conclusions
Higher FT3-to-fT4 ratio late in pregnancy was associated with GDM, adverse pregnancy outcomes, and an adverse metabolic profile in early postpartum.

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PS3-13-116
Iodine status in danish pregnant women after an increase in iodine fortification: a regional study
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Objectives
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Materials/Methods
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Results
From 2011 to 2015 a slight trend from negative to positive sentiment (P = 0.08) was noted in the literature studied, while from 2018 wide and significant (P = 0.04) sentiment fluctuations were noted by year.

Discussion
Regarding hypothyroidism and pregnancy uncertainties remain vis-à-vis screening and management bearing in mind the need to optimize perinatal outcomes. Researchers continue to debate the very definition of subclinical hypothyroidism, which can differ between nonpregnant or pregnant states. This situation is reflected in the sentiment of the published literature, especially in review articles, usually by experts in the field worldwide, which try to provide a critical evaluation of the data that is available from existing studies.

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Endocrine Abstracts (2022) Vol 84
Method
We performed a cross-sectional study in the North Denmark Region which is within the geographical part of Denmark with previously most severe iodine deficiency. From September 8 until October 12, 2021, pregnant women referred for routine obstetric ultrasound in the Department of Obstetrics, Aalborg University Hospital, were included. All women delivered a spot urine sample and filled out a questionnaire. UIC was determined after alkaline ashing by the ceric-arsenite method, and measurement of urinary creatinine concentration (Cobas 8000, Roche Diagnostics) was performed for calculation of urinary iodine/creatinine ratio and estimated 24-hours urinary iodine excretion. Results were reported as medians with 95% confidence intervals.

Results
Altogether 147 pregnant women were included in the study (median gestational week 20), and 130 women (88%) reported current use of iodine-containing supplements (Table). The overall median UIC was 77 μg/l (Table). When stratified by intake of iodine-containing supplements, median UIC as well as the creatinine-adjusted measures of urinary iodine status were higher in iodine-containing supplement users compared with nonusers (Table).

Conclusion
Despite a recent and considerable increase in mandatory iodine fortification in Denmark, iodine status in pregnant women within the North Denmark Region was insufficient and median UIC was even lower than previously found. Results call for detailed assessment of underlying factors and continued attention to ensure adequate iodine status during pregnancy in Denmark.

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PS3-13-117

Iodine status during pregnancy in the veneto region: impact on maternal and newborn thyroid function and analysis of the nutritional and socio-economic determinants

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Objectives
The aim was to evaluate the iodine nutritional status in pregnant women residing in Veneto region and its associations with diet, iodine supplements and social status (nationality and education).

Methods
292 consecutive pregnant women at the third trimester of pregnancy were enrolled (≥18 years old, and resident in Veneto). Exclusion criteria were a personal history of thyroid disease and the refusal of the informed consent. Every woman provided an early-morning spot urine sample (to assess iodine to creatinine concentration ratio, UI/Creat) and a blood sample (to measure TSH, FT4, FT3 and Thyroglobulin (Tg)) and were administered a questionnaire regarding diet habits, and the use of iodine supplements. The new-borns' TSH levels were obtained from the congenital hypothyroidism screening program, together with their data at birth.

Results
Use of iodized salt was spread to 72.5% of women. Median UI/Creat was 112.37 μg/g (IQR: 60.95-185.93 μg/g). Only 36.9% of women had a UI/Creat ≥ 150 μg/g and the frequency was higher among Italian than foreign women (P = 0.01). UI/Creat was higher among higher educated women (P = 0.01). The frequency of women with a UI/Creat ≥ 150 μg/g was higher among regular cow’s milk consumers (P = 0.046) and among iodine supplement users (P = 0.0001) than among their counterparts, but no association was found with iodized salt use. Only the combined use of the iodine supplement plus cow’s milk guaranteed an adequate iodine intake (UI/Creat ≥ 150 μg/g) (P < 0.01). At the multivariate analysis, only regular cow’s milk and iodine supplement were independent predictors of an adequate iodine status. There was no association between maternal thyroid function and UI/Creat levels. Median Tg values were lower among the iodine-sufficient group than among iodine-deficient women 8.20 μg/l and 11.61 μg/l, respectively (P = 0.019). The weight at birth was lower in the offspring of women with UI/Creat < 50 μg/g and ≥ 250 μg/g than in the iodine-adequate or mildly deficient group (P = 0.02). The TSH at screening was higher among the offspring of women receiving an iodine supplement than among non-users (P = 0.04), but both in the normal range.

Conclusions
The iodine prophylaxis program should be implemented to reach a better iodized salt coverage and education among childbearing-aged women, especially the foreign and lower educated. In the meanwhile, both the iodine supplement and cow’s milk seem to be pivotal. Neonatal TSH levels resulted higher among the offspring of the women that took the iodine supplement than among non-users, suggesting a particular sensitivity to iodine in the fetal thyroid.

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PS3-13-118

Which is the best pre-conceptional TSH cut-off in women submitted to assisted reproductive technology?

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TSH is involved in the immunomodulation of early pregnancy stages. Thyroid function and fetal thyroid volume in pregnant women from iodine deficient regions have indicated 2.8 mU/l as the best TSH level below which women undergoing assisted reproductive technology (ART) need to be maintained, though this threshold is still controversial. Aims of the present study were to evaluate if pre-conceptional TSH is associated with an increased risk of miscarriage, to identify a TSH cut-off significantly associated with risk of miscarriage and to assess the impact of TSH levels on primary and surrogate outcomes. A series of 1484 infertile women (mean ± age 36.7 ± 4.1 years, mean ± SD BMI 22.7 ± 4) submitted to IVF in a single center from 2004 and 2014 was retrospectively studied. The majority of patients (60.8%) submitted to ART cycles had a primary infertility, while the remaining cases had a secondary infertility. Primary outcomes were biochemical pregnancy, clinical pregnancy, miscarriage and delivery. Surrogate outcomes were the number of oocytes, the number of embryos and the transfer of embryos. Embryo transfer was performed in 86% of cycles. A biochemical pregnancy was recorded in 369/1274 (29%) patients and 146 of them (39.5%) experienced a pregnancy loss. Moreover, among these 146 women, 52 (36%) were clinically pregnant and had a miscarriage in the first trimester, while in 94 patients (64%) a biochemical pregnancy without clinical evolution was documented. No significant differences in mean TSH levels were observed between women with different times of miscarriage. ROC curve analysis showed that a TSH of 3 mU/l is significantly associated with miscarriage (P = 0.001), while a TSH of 2.5 mU/l is associated with a higher chance to have a biochemical pregnancy. These two TSH thresholds (2.3 or 3 mU/l) were also studied in relation to surrogate outcomes: we observed a weak association between TSH ≤ 2.3 mU/l with the number of retrieved oocytes (P = 0.04) while no significant correlation was found with the number of either embryos obtained or transferred (P = NS). In conclusion, lower pre-conceptional TSH levels appears to favor the biochemical pregnancy and to reduce the risk of early pregnancy loss in women undergoing ART. TSH screening prior to IVF procedures and L-T4 treatment are strongly recommended in order to optimize TSH levels before ovarian stimulation.

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Endocrine Abstracts (2022) Vol 84
The aim of the study was to assess the impact of iodine supplementation (IS) on iodine intake, thyroid function and thyroid volume (Tvol) in pregnant women (PW) from iodine sufficient region of Zagreb, the capital of Croatia. The secondary aim was to assess the impact of nodular or diffuse thyroid ultrason (US) pattern on serum thyroglobulin (Tg) measurement.

Subjects and Methods
The study enrolled 91 PW taking IS (onIS) and 100 PW without IS (offIS) during pregnancy. Spot urine samples for urinary iodine concentration (UIC), blood samples for serum TSH, FT4 and Tg measurement and US was performed in PW in each trimester of pregnancy. Thyroid volume (Tvol) was measured with assessment of thyroid parenchima and nodules by US. UIC was measured by Seal 2000 XPi Siemens and Tg by ECLIA (Roche COBAS e411). All PW were euthyroid with negative Tg and TPO antibodies. SSFS (26.0, SSFS Inc., Chicago, IL, SAD) was used for statistical analysis.

Results
Overall median UIC, TSH, FT4, Tg and Tvol in PW onIS vs offIS were: 174 vs 158 ng/mL, 1.9 vs 1.8 μIU/l, 13.2 vs 12.1 pmol/L (P < 0.05), 11.0 vs 13.6 ng/mL (P < 0.01) and 12.3 vs 13.7 mL (P < 0.05). Trimester (1st, 2nd, 3rd) specific median UIC, TSH, FT4, Tg and Tvol in PW onIS vs offIS were: 173*, 177, 178 vs 155*, 163, 166 ng/mL, 1.8, 2.1*, 2.1 vs 1.7, 1.7*, 1.9 μIU/L, 12.6*, 13.3*, 12.9 vs 11.2*, 12.0*, 12.6 pmol/L, 10.2, 11.0*, 11.1* vs 13.5, 14.5*, 14.5* mg/L, 11.0*, 12.0*, 13.0* vs 12.5*, 14.0*, 14.0* mL (P < 0.05). Nodules < 1 cm were recorded in 15 (17%) PW onIS and 24 (24%) PW offIS, and diffuse US pattern in 12 (13%) PW onIS and 17 (17%) PW offIS. Median Tg in PW offIS with diffuse and nodular US pattern vs normal US was 13.4* and 12.5 vs 10.6* mg/L (P < 0.05). Median Tg in PW offIS with diffuse and nodular US pattern vs normal US was 15.7* and 15.0 and 13.2* μg/L (P < 0.05).

Conclusion
Pregnant women in the city of Zagreb, Croatia, have sufficient iodine intake regardless of IS. Iodine supplementation in pregnancy increases UIC and FT4 and decreases Tg and Tvol. Thyroglobulin is a valuable biomarker for assessment of iodine nutritional status. Nodular and diffuse thyroid US pattern increases Tg values with significant difference for diffuse pattern. DOI: 10.1530/endoabs.84.PS3-13-119

PS3-13-121
Thyroid homeostasis in iodine deficient healthy pregnant women from 10 villages of Bihar, India
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Background
Pregnancy is a physiological state characterised by enhanced thyroid hormone production resulting in increased demand for iodine. Iodine deficiency during pregnancy, is therefore, considered to be a risk factor for adequate growth and development in offspring. However our understanding of thyroid hormone homeostasis in iodine deficient environment is limited.

Objectives
1) To assess the current iodine status in pregnant women from an endemic zone 2) To assess the impact of iodine deficiency on homeostatic adjustments of thyroid hormones, pregnancy outcome and health of pregnant women.

Method
Epidemiological observational survey included pregnant women (18–48 year) from 10 villages of the Bihar State in India (2014-2018) in association with Government Hospital and Government Primary Health Centers. Total 900 healthy pregnant women fulfilling inclusion criteria were enrolled. A questionnaire survey was conducted for demographic socioeconomic and other parameters. Salt samples from relevant households were obtained for the measurement of iodine using State Govt UNICEF kits. Body weight, height and BMI were recorded. Blood and urine samples were procured from subsets of population for the assessment of UIC and thyroid hormones (TSH, FT4) respectively. UIC was measured spectrophotometrically. TSH & FT4 were measured in DBS using ELISA and Chemiluminescence methods. IEC approval & informed consent were obtained.

Results
Dietary iodine intake was less than 15ppm in 50% of pregnant women. UIC median values indicated iodine deficiency viz., 73, 82, 84 in 1st, 2nd, 3rd trimester with 88%, 96% and 94% subjects iodine deficient, respectively. Evidently dietary iodine intake need not necessarily reflect UIC status of a population. TSH values ranged as 1.3-5.1, 1.47-5.79, 2.32 -6.5 in 1st, 2nd, 3rd trimester indicating an increasing trend reflected in the quartile distributions. FT4 pmol/L ranged from 7.02-18.44, 7.19-19, 4.59-16.9 indicating a decline in 3rd tri. While FT4 values were comparable, TSH consistently was higher than the prescribed international guideline cut-offs. However, no individual showed overt symptoms of hypothyroidism. Pregnancy outcome (still birth, miscarriages) and BMI values were comparable with Indian/world normal figures.

Conclusion
TSH values were above the international standard cut off levels and may represent an attempt to restore equilibrium ensuring adequate thyroxine supply in these iodine deficient women. According to population outliers the TSH values were apparently normal (within 2.5-97.5 percentile). Financial assistance from Apeejay Education Society, and, facilities from Swami Rama Himalayan University,
Preconception TSH levels and early gestation maternal thyroid function in a large cohort of women with Hashimoto’s thyroiditis (HT) diagnosed preconceptionally.

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Several lines of evidence indicate an increased risk of adverse gestational outcomes in women with Hashimoto’s thyroiditis (HT) already as of TSH levels at early pregnancy >2.5 mU/l, and definitely greater for TSH concentration >4 mU/l. The latest guidelines recommend preconception TSH levels (pre-C-TSH) in HT women be maintained below 2.5 mU/l, this threshold being expected to prevent hypothyroidism occurrence at early gestation.

Objectives
To prospectively evaluate: i) whether maintaining pre-C-TSH values <2.5 mU/l in HT women was effective in preventing the occurrence of early gestation thyroid insufficiency, defined by TSH >2.5 mU/l (diagnostic criterion 1) or >4.0 mU/l (diagnostic criterion 2) at early gestation; ii) the cut-off values of TSH that would best preconceptionally identify euthyroidism at early gestation in HT women, by means of Receiver-Operating Characteristic (ROC) curves.

Methods
Two-hundred and sixty women preconceptionally diagnosed with HT and pre-C-TSH <2.5 mU/l, whose thyroid function was prospectively monitored from preconception up to pregnancy term.

Results
Of the 260 women, 122 (46.9%) were on LT4 therapy (Hypo-HT group) and 138 (53.1%) were confirmedly euthyroid without LT4 (Eu-HT group) prior to conception. At 1st trimester, 37/122 (30.3%) Hypo-HT women had TSH >2.5 mU/l, with almost 2/3 of these women (24/37, 64.9%) displaying TSH values >4.0 mU/l. Analogously, at 1st trimester evaluation TSH was >2.5 mU/l in 42/138 (30.4%) EU-HT women, but >4.0 mU/l in 14/138 (10.1%) only. The optimal pre-conception TSH cut-offs found were 1.24 mU/l and 1.73 mU/l for the diagnostic criteria 1 in Hypo-HT and Eu-HT women, respectively, and 1.74 mU/l and 2.07 mU/l for the diagnostic criteria 2 in Hypo-HT and Eu-HT women, respectively. Applying the above cut-offs, the relative risk reduction (RRR) of early gestational thyroid insufficiency was 82.7% and 94.0% for the diagnostic criteria 1 in Hypo-HT and Eu-HT women, respectively, and 82.5% and 97.9% for the diagnostic criteria 2 in Hypo-HT and Eu-HT women, respectively.

Conclusions
In our series, about one third of HT women whose pre-C TSH were in the range recommended by current guidelines (<2.5 mU/l) required to increase or to start LT4 therapy once pregnant because of TSH levels exceeding the advisable TSH threshold at early pregnancy. In contrast, a more than halved rate of HT women showed mild expansion in all dimensions: 14.4x13.2x15.7 m. We re-assessed the following US features: non-oval shape, irregular margin, microcalcifications, marked hypoechogenicity and resulted in a EU-TIRADS 5 score. The repeated FNAC showed again a benign lymphocytic thyroiditis. Despite of the benign cytology result, thyroid lobectomy with adjunctive central lymph node dissection was recommended because of the growing tendency and high EU-TIRADS score. The histological diagnosis was WLPTC and lymphocytic thyroiditis of the nodule (pT1bN0Mx). The additional contralateral lobectomy resulted only lymphocytic thyroiditis without malignancy. Further genetic analysis is ongoing to decide on the need for the adjuvant radioidine treatment.

Conclusion
In clinical practice, evaluation of thyroid nodules based on EU-TIRADS criteria can rarely overrule the FNAC results with an impact on surgical decision-making. In some cases, the growing tendency and the very suspicious US signs of malignancy (e.g. microcalcification) of a nodule results in a higher risk for malignancy, than that based on the FNAC results. Furthermore, in the case of WLPTC, when both the benign lymphocytic thyroiditis and malignant tumour can be seen in one nodule, the FNAC can be misleading when the aspiration is taken from the benign part of the lesion.

Endocrine Abstracts (2022) Vol 84

Thyroid Cancer CLINICAL 2

A case of warthin-like papillary thyroid cancer. surgical decision based on eu-tirads criteria

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Introduction
The Warthin-like variant of papillary thyroid cancer (WLPTC) is a rare subtype of papillary thyroid carcinoma (PTC) resembling Warthin tumours of the salivary glands, and more commonly associated with Hashimoto’s thyroiditis than other types of PTCs. The WLPTC is characterized by papillae lined by large oncocytic cells with cores having dense lymphoplasmacytic infiltrate. The prognosis of WLPTC is the same or less aggressive than that of classical PTC, but in some cases it is associated with poor outcome. The preoperative fine needle aspiration cytology (FNAC) is the most reliable technical approach for surgical decision, but it shows sometimes false negative result. The EU-TIRADS criteria (European Thyroid Association for ultrasound (US) assessment of thyroid nodules and stratification) can significantly increase diagnostic accuracy with a direct impact on treatment decisions.

Case
A 45-year-old male patient presented at outpatient clinic with Hashimoto thyroiditis for hormone replacement therapy. The first thyroid US showed an 8.1x7.6x10.4 mm irregular, hypoechogenic nodule in the right lobe. A FNAC was taken from this target lesion, which resulted in a diagnosis of lymphocytic thyroiditis without suspicious malignant cells. Two years later the target nodule showed mild expansion in all dimensions: 14.4x13.2x15.7 mm. We re-assessed the following US features: non-oval shape, irregular margin, microcalcifications, marked hypoechogenicity and resulted in a EU-TIRADS 5 score. The repeated FNAC showed again a benign lymphocytic thyroiditis. Despite of the benign cytology result, thyroid lobectomy with adjunctive central lymph node dissection was recommended because of the growing tendency and high EU-TIRADS score. The histological diagnosis was WLPTC and lymphocytic thyroiditis of the nodule (pT1bN0Mx). The additional contralateral lobectomy resulted only lymphocytic thyroiditis without malignancy. Further genetic analysis is ongoing to decide on the need for the adjuvant radioidine treatment.

Conclusion
In clinical practice, evaluation of thyroid nodules based on EU-TIRADS criteria can rarely overrule the FNAC results with an impact on surgical decision-making. In some cases, the growing tendency and the very suspicious US signs of malignancy (e.g. microcalcification) of a nodule results in a higher risk for malignancy, than that based on the FNAC results. Furthermore, in the case of WLPTC, when both the benign lymphocytic thyroiditis and malignant tumour can be seen in one nodule, the FNAC can be misleading when the aspiration is taken from the benign part of the lesion.

Endocrine Abstracts (2022) Vol 84

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PS3-14-124

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Background
Medullary thyroid cancer (MTC) is a rare malignancy with a variable and sometimes unpredictable disease course. To predict the course of disease more accurately at diagnosis, we introduce dynamic risk stratification by analyzing factors related to “stage migration” within the first 5 years after diagnosis.

Methods
All patients diagnosed at the University Medical Center of Groningen between 1999 and 2015 were retrospectively studied. Patients were staged according to the 8th edition of the TNM classification and variables were collected. Stage migration was defined as i) an upgrade of the N and/or M stage, i.e., the development of i) a lymph node metastasis in a previously unaffacted cervical compartment or ii) distant metastases in an initially M0 stage patient or 2) death due to MTC progression, within 5 years after diagnosis. Clinical and pathological variables were then evaluated in univariate Cox regressions to find prognostic factors.

Results
Of the 75 included patients, 41 were male and 47 had sporadic MTC. The median age at diagnosis was 49 (IQR 32 – 58) years. A total of 29 (39%), 7 (9%), 9 (12%) and 30 (40%) of the patients were classified with stage I, II, III and IV, respectively. Sporadic MTC patients had a higher stage at diagnosis than hereditary patients (P < 0.001). Five years after diagnosis, 61 (81%) patients were still alive. Eleven patients died due to MTC progression and 3 died from other causes. Twenty-one out of 75 included patients developed stage migration in 5 years after diagnosis, after a median time of 17.0 (IQR 11.5 – 30.5) months. Stage migration was a result of an upgrade of the N and/or M stage in 8 patients and a result of M and/or M stage followed by death in 3 patients. Stage migration occurred in 1 (14%), 6 (67%) and 14 (47%) of stage II, III and IV patient(s), respectively. In univariate Cox regressions, sporadic MTC, pulpal lymph node(s) at diagnosis, a
higher TNM stage, angioinvasion, a positive resection margin, and extrathyroidal growth significantly increased the risk of stage migration.

Conclusion

MTC is a dynamic disease where disease progression is always lurking. This stage migration model could improve the clinician’s prediction of disease progression and thereby help to design a better patient-tailored follow-up strategy after initial treatment. To verify this method, further collaborative studies with larger datasets need to be performed.

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Background

Lymph node metastases at histology (pN1) are usual findings in differentiated thyroid cancer (DTC) patients. Their detection has an impact on the extent of surgery, the further treatments after surgery, and on the clinical outcome.

Material and methods

We evaluated data of 1332 consecutive DTC patients who performed the first 131I treatment between January 2010 and September 2012. According to their pN status, they were divided into 2 groups: Nx/N0 and N1. The latter was subdivided in central compartment (N1a) and lateral-cervical compartment (N1b) metastases.

Clinical outcome, according to 2015 ATA was defined as: post-operative and post-131I (median time from surgery: 6 months), first evaluation after 131I (median time from 131I: 8 months) and last evaluation (median time from 131I: 83 months).

Results

1064 (79.9%) patients were in the Nx/N0 and 268 (20.1%) in the N1 group. N1 patients were more frequently males (35.8 vs 27.3%, P < 0.01) and younger (median age 40 vs 47, P = 0.01). Several histologic features were significantly more frequent (P < 0.01) in the N1 group: multifocality (63.4 vs 46.8%, mETE (67.9 vs 24.6%), vascular invasion (28 vs 8.9%) and intermediate ATA-risk (94.8 vs 36.5%). Structural incomplete response (SIR) rate was higher in N1 group throughout the follow-up (P < 0.01), although these patients experienced higher 131I activities over time and more neck re-intervention. Also, N1b (n = 142, 53%) patients, compared to N1a (n = 126, 47%), had more frequently mETE (74.6 vs 59.5%, P < 0.01) and vascular invasion (33.1 vs 22.2%, P < 0.05) and lower prevalence of histologic thyroiditis (21.1% vs 35.7, P < 0.01). Nevertheless, N1b patients experienced higher 131I activities and more neck re-intervention during the follow-up. SIR rate was significantly higher in N1b at post-operative (16.2 vs 6.3%), post-131I (26.1 vs 8.7%) and at first evaluation after 131I (24.3 ± 9.6%). Conversely, at the last evaluation, significance was not reached (17.9 ± 10.4%, P = 0.09).

Conclusions

pN1 status is related to more aggressive histologic features in DTC patients. Although more treatments were performed during the follow-up, the N1 patients had a higher SIR rate at each time of the follow-up when compared with Nx/N0. Moreover, N1b patients, compared to N1a, experienced more frequent and aggressive treatments during the follow-up but still with a higher persistence of SIR.

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The prognostic role of chromosomal gains and loss in sporadic medullary thyroid carcinoma

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Objectives

Image-guided thermal-ablation (LTA; RFA) are well-established therapy options in selectedBTN. PMWT is a mini-invasive technique recently applied in thyroid disease; aim of this work is investigate its effectiveness as treatment in BTN.

Methods

From May 2021, 45 patients (30 F, 15 M, Aged 37-90, Mean 55.8) with BTN symptomatic/in growing, refusing/non eligible to surgery were enrolled. Inclusion criteria: nodule diameter ≥ 2 cm, mainly solid ≥ 20%, 2 FNA cytology pathologically confirmed as benign (TIR2 see ITCCS 2014). Baseline were performed ECG, anesthesiology and ENT consults, laboratory assessment (serum levels of fT3, fT4, TSH, TPOAb, TgAb, calcitonin, blood count, clotting indexes).

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Additionally 25/45 pts done Thyroid Scintiscan with 99mTc-Pertechnecate (19 cold 3 hot 0; 3 non focal findings). Ultrasound-guided PWMTA was carried out under local anesthesia through TATO antenna (18G x 8 cm/17G x 10 cm Terumo) delivering 10-15 W in 10-15 minutes, depends on the Volume of BTN. Physician effects an anamnestic evaluation, thyroid physical examination rating symptomatology with a Comprehensive Score (CS on a 10 visual-analog scale), assigned an Aesthetic Score (AS from 1-no palpable-visible nodule to 4 palpable-visible in all positions). US thyroid scan was performed to record Volume of BTN target (VnT) baseline and during follow-up scheduled at 1.3 months after procedure. Additionally volume reduction rate % (VRR) was calculated, and success rate fixed in a volume reduction ≥ 50%.

No peri-procedural major complications were observed. 1/45 has developed in 10 days after PWMT transient thyrotoxicosis and atrial fibrillation pharmaco-logically reverted. 10 patients still missing the follow-up; the data will be available and presented during the meeting. Clinically was registered CS mean score from 4.2 (baseline) to 3 and 1.7 (1 and 3 months respectively), AS from 3.2 (baseline) to 2 (1 and 3 months). Interestingly both scores were stable at 6 months follow-up. Baseline mean VnT was 17.29 mL (range 77-1.6 mL) and mean VnT post-procedure was 8.79 mL (range 32.9-0.31mL). The estimated mean VRR at 1.3 months was 52% (range 12-82%), 58% (range 45-91%), 66% (range 45-94%), respectively. If consider as a therapeutic goal a volume reduction of ≥ 50 % the success rate was approximately 82%. Neither a re-growth occurred in this short-term evaluation.

Conclusion
In BTN disease use of PWMT has shown effective nodule shrinking, well tolerated, safe and with low complication rate. Furthermore we registered a satisfactory clinical response. Our data need a validation in large series and long term follow-up.

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PS3-14-128
ProGRP as an additional screening marker in the diagnostic work up for medullary thyroid carcinoma
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Background
Medullary thyroid carcinoma (MTC) is a rare disease accounting for 1-3% of all thyroid carcinomas. Unfortunately, most patients present with metastasized disease: 70% with cervical lymph node metastasis and 5-10% with distant metastasis. Survival strongly correlates with stage of disease at diagnosis, illustrating the need for early diagnosis. Calcitonin is a well-established tumour marker for MTC, but its use in the screening phase is limited by a high rate of false positives. Among thyroid cancer types, progastrin-releasing peptide (proGRP), is illustrated the need for early diagnosis. Calcitonin is a well-established tumour marker for MTC, suggesting a potential role for proGRP as an additional screening marker for MTC. This was confirmed by the good correlation between proGRP and calcitonin in patients with a calcitonin above 100 pg/ml. Further research should determine whether proGRP can be employed as a screening tool to diagnose MTC.

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PS3-14-129
Hypocalcaemia secondary to lenvatinib induced-hypoparathyroidism: a case-report
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In the last decades, multi-tyrosine-kine inhibitors (mTKI) have emerged as an effective treatment for radioiodine refractory differentiated thyroid cancer. Due to their pleiotropic mechanism of action, these drugs may cause different side effects. Hypocalcaemia has been reported in up to 35% of patients treated with mTKI, but up to date little is known about its pathophysiology and relevance. We report the case of a 78 years old woman operated on for a papillary thyroid cancer infiltrating striated muscles, oesophagus, blood and lymphatic vessels. The extent of surgery was limited to hemithyroidectomy, because of tumour extension and infarction to contiguous structures. Radioactive-iodine treatment was not performed due to the remnant tissue dimension. The patient was therefore started on lenvatinib at the initial dose of 10 mg per day, in order to avoid istabilisation. During the first months of therapy, the largest diameter of the main neoplastic lesions in the neck significantly reduced. Serum Tg levels decreased from 370 μg/L to 49.6 μg/L. The patient experienced grade I-II proteinuria, anorexia, fatigue, diarrhoea, nausea, mucositis and hypertension, according to CTCAE. After four months, the patient accessed the E.R. for sudden dyspnoea, muscular cramps and limb spasms. Blood exams revealed a grade III hypocalcaemia (corrected serum calcium: 6.6 mg/dL), due to primary hypoparathyroïdism (serum PTH: 12.6 pg/mL; serum phosphorus: 4.7 mg/dL). The patient was treated with calcium infusions and oral vitamin D and magnesium supplementation. After discharge, the oral dose of carbonate calcium was of 6 g per day. Lenvatinib was discontinued for the duration of hospitalization and restarted three days after discharge, when serum calcium levels were proven to be stable (corrected serum calcium: 8.8 mg/dL). Calcium intake was titrated according to blood exams performed every 3-5 days. Two weeks after discharge, while taking calcium 3 g per day, the patient complained worsening of anorexia and stupor. Grade II hypercalcemia (serum calcium: 11.7 mg/dL) was demonstrated. She was treated with an intravenous infusion of physiological solution and calcium supplementation was interrupted. During the subsequent follow up, the patient remained and still is eucalcemic without calcium supplementation. Though hypocalcaemia has been described as potential side effect, this is the first report of a lenvatinib-induced primary hypoparathyroidism. This case is of particular interest since the patient was submitted to hemithyroidectomy and the hypoparathyroidism was thus definitely not-related to surgery. Further studies are needed to clarify pathogenesis and relevance of this life-threatening adverse event.

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PS3-14-130
The role of calcitonin wash-out in the diagnosis of small sporadic medullary thyroid cancer - case reports
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Introduction
Medullary thyroid cancer (MTC) is a rare thyroid malignancy whose prognosis is highly dependent on the early diagnosis as well as on the available treatment options. Serum calcitonin represents the most sensitive test for the detection of MTC thus its measurement is strongly recommended in patients with known genetic or hereditary conditions associated with high risk of medullary hyperplasia or cancer. However, its diagnostic utility and routine clinical application in all patients with thyroid nodules are highly controversial especially in nodules less than 1 cm.

Case Description
Case 1: A 49-year-old woman was referred for further evaluation after finding increased levels of serum calcitonin on routine laboratory tests. Medical history and physical examination were unremarkable, the elevated levels of serum calcitonin were confirmed – 136.3 pg/ml. Neck ultrasound scan showed a solid hypoechoic lesion in the dorsal part of the right lobe measuring 7.6/4 mm in size with type 3 vascularization, no suspicious lymph nodes were detected. FNAB and calcitonin wash-out measurement were performed. Cytological report fell in BETHESDA III category, but calcitonin levels from the wash-out were > 5000 pg/ml, suggesting the lesion was medullary cancer. The patient was referred for surgery, histology and immunohistochemistry analysis confirmed the diagnosis of a micromedullary cancer.

Case 2: The second patient is a 49-year-old woman in whom slightly elevated levels of calcitonin were found on occasion. She did not have any significant medical conditions, family history or medication intake. On neck ultrasound examination a 4.8/4 mm solid hypoechoic nodule in the ventral part of the right lobe was seen without any other abnormal neck findings. The cytological report from the FNAB was inconclusive but calcitonin wash-out measurement was >5000 pg/ml, suggesting the lesion was medullary cancer. The patient was referred for surgery, histology and immunohistochemistry analysis confirmed the diagnosis of a medullary micromedullary cancer.

Conclusions
MicromTC is generally defined as a medullary cancer ≤ 1 cm in the greatest dimension and represents a rare entity with increasing incidence over the past decade. Calcitonin wash-out measurement can be a useful tool in the comprehensive evaluation of micromedullary thyroid lesions. Early detection of micromedullary thyroid cancer significantly reduces the risk for local and distant metastasis and increases the rate of disease-free survival of the patients with this potentially lethal neuroendocrine malignancy.

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PS3-14-131
Somatic BRAF V600E mutation in a patient with medullary thyroid carcinoma
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Introduction
Medullary thyroid carcinoma (MTC) is a calcitonin-producing tumor that predominantly occurs in a sporadic form (75%) and less commonly in an inherited form. Nowadays activating germline mutations of the RET proto-oncogene in hereditary syndromes of MEN2, somatic RET mutations are detectable in about 50% of sporadic MTC. Further, also RAS mutations have been discovered in 30% of RET-negative tumor tissues. Other genetic alterations, chromosomal rearrangements or point mutations in minor genes, are very rare.

Case Report
We report a case of a 38-year-old woman with a nodule in the left lobe, cytologically suspected of MTC. Serum calcitonin was elevated at 217 pmol/l. The patient underwent total thyroidectomy and histopathological examination revealed a 1.3 cm MTC with positive immunohistochemical staining for calcitonin and chromogranin. Molecular genetic analysis detected neither germline RET mutation, nor RET/RAF somatic mutations in examined fresh frozen tumor tissue. A comprehensive NGS panel targeted especially fusion genes, but also other genetic changes, was used for subsequent analysis. Surprisingly, a common V600E BRAF mutation, typical for papillary thyroid carcinoma (PTC), was found. The mutation was confirmed by allele-specific real-time PCR performed from material isolated from both fresh frozen and FFPE tumor tissue. The histological examination demonstrated morphologic features of MTC, no signs of mixed tumor and no evidence of PTC.

Conclusions
Only two other cases of BRAF V600E in MTC patients have been reported. In all these studies, the results of molecular genetic analysis were verified by an alternate method, and the tumors were histologically confirmed as pure medullary thyroid carcinomas, without concurrent PTC. The study was supported by projects of the MHR CR AVZ N221-01-00448 and MHCRRV (00023561).

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PS3-14-132
Efficacy and safety of lenvatinib in a cohort of well-differentiated advanced thyroid carcinoma
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Introduction
Treatment of differentiated thyroid carcinoma (DTC) remains a challenge in the setting of locally advanced or metastatic disease refractory to radiodine (RAI) therapy. SELECT trial demonstrated that Lenvatinib improved progression free survival (PFS) comparing to placebo.

Objective
Our aim is to report the efficacy and safety of lenvatinib in our population with aggressive DTC.

Methods
We retrospectively reviewed the clinical records of 25 patients with advanced well-DTC who started treatment with lenvatinib in our center between January 2016 and January 2022. Patients with poorly differentiated or anaplastic thyroid carcinomas were excluded. Response evaluation was made according to the RECIST version 1.1 criteria. PFS and median overall survival (OS), best overall response (BOR), disease-control rate (DCR), response rate (RR) and clinical benefit rate (CBR) were also evaluated as efficacy measures. Additionally, the change of the sum of target lesion’s greatest diameters from baseline to nadir and tumor volume doubling times (TVDT) before and after therapy were also calculated.

Results
A total of 25 patients with well-DTC treated with lenvatinib were analyzed. Mean age at the initiation of treatment was 67.6±1.8 and 64% of patients were female. Twenty-four (96%) had metastasis (M1): 91.7% in the lung; 62.5% in bone and 62.5% of patients had M1 in ≥ 2 locations. Median duration of treatment with lenvatinib was 8 months.

Conclusions
Lenvatinib is effective and well tolerated in our population with advanced well-DTC. DTC with high risk of progression and treatment failure benefit most from lenvatinib treatment in the adjuvant or palliative setting.

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Endocrine Abstracts (2022) Vol 84
lenvatinib was 9.1 months and mean daily dose was 16.7 mg. The BOR was complete response in 1 patient (4%), partial response in 10 (40%), stable disease in 9 (36%) and progressive disease in 2 patients (12%). Response was not evaluable in 3 patients. RR was 44%; DCR 80% and CBR 68%. Median PFS was 25.6% (95% confidence interval (CI): 5.5-60.4) and OS was 29.6% (95% CI 25.3-34.1). The mean change of the sum of target lesion’s greatest diameters from baseline to nadir was -32.7% (± 6.9). Median TVD T pre-lenvatinib was 10 months and median TVDT post-lenvatinib was 3.5 months. Our data showed that lenvatinib results in prolongation of TVDT in 86.7% of patients. AE were reported in 96% of patients, resulting in interruption and dose reduction in 68% and 52% respectively. The most frequent AE was hypertension in 85%. One patient had a grade 5 AE (rectum-vaginal fistulae with sepsis) and she had history of previous pelvic irradiation.

Discussion

Our results are in line with other real-life data and show that the clinical benefit can be obtained with lower doses. In addition, in our series lenvatinib showed an increased benefit in rapidly progressive disease. AE were frequent and serious AE related with wound healing may be potentiated by previous radiotherapy.

Conclusions

Children with a thyroid nodule or DTC require expert care in an experienced center. The present guideline provides guidance for healthcare professionals to make well-considered decisions together with patients and parents regarding diagnostics, treatment and follow-up of pediatric thyroid nodules and DTC.

PS3-15-134

Patient-reported outcomes (PROs) from patients with RET-mutant medullary thyroid cancer (MTC) and ret fusion-positive TC treated with pralsetinib in the arrow trial

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Objectives

RET alterations are targetable oncogenic drivers in TC. Patients with TC, especially those with MTC treated with the multikinase inhibitors cabozantinib and/or vandetanib (C/V), often experience significant treatment-related side effects. Pralsetinib, a selective RET tyrosine kinase inhibitor, showed efficacy in patients with RET-altered TC from the phase 1/2 ARROW trial (NCT03037385). We present the impact of pralsetinib on PROs in patients with RET-mutant MTC and RET fusion-positive TC, including quality of life (QoL) and disease-related symptoms.

Methods

PROs (exploratory endpoint since protocol v4.1) were evaluated in adults with RET-altered, non-resectable advanced TC from ARROW (pralsetinib 400 mg QD) who completed the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ-C30) before treatment initiation (baseline). Patients then completed the QLC-C30 every 4 weeks until treatment discontinuation. Score changes >10 points from baseline were considered clinically meaningful. Data cut-off: 18 October 2021.

Results

Of 100 efficacy-evaluable patients with RET-mutant MTC enrolled from protocol v4.1, 98 (98%) completed a baseline PRO assessment. They reported moderate baseline Global Health Status (GHS)/QoL (mean score: 67/100) and high baseline functioning scores (mean scores: 82/100) than those who had received prior C/V, and their PROs remained stable in patients with RET-altered TC from the phase 1/2 ARROW trial (NCT03037385). In the prior C/V RET-mutant MTC subcohort (n = 39), baseline mean GHS/QoL score was 59/100 and functioning scores were >68/100. Clinically meaningful increases in mean scores from baseline were observed throughout Weeks 8-32 for GHS/QoL, Weeks 24-32 for physical functioning and Weeks 12-44 for role functioning. At Week 44, disease-related symptoms including diarrhoea (mean score change from baseline: -20.6), fatigue (-14.8), appetite loss (-12.7) and insomnia (-12.7) were improved. Patients with treatment-naive RET-mutant MTC (n = 54) had higher baseline GHS/QoL (mean score: 71/100) and functioning scores (mean scores: >82/100) than those who had received prior C/V, and their PROs remained stable following pralsetinib treatment. In patients with RET fusion-positive TC enrolled from protocol v4.1 (n = 24), baseline PRO questionnaire completion rate was 100%. At baseline, these patients had moderate GHS/QoL (mean score: 59/100), and moderate-to-high functioning scores (mean scores: >70/100); episodic clinically meaningful improvements were seen for GHS/QoL and role functioning, and symptom burden remained low throughout.

Conclusions

Following pralsetinib treatment, patients with RET-altered TC, especially those with RET-mutant MTC treated with prior C/V, reported improved or stable GHS/QoL and functioning scores, and a reduced symptom burden from baseline.

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Thyroid Cancer Diagnosis & Treatment

PS3-15-133

European thyroid association guideline on the management of pediatric thyroid nodules and thyroid carcinoma

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Objectives

At present no European recommendations for the management of pediatric thyroid nodules and differentiated thyroid carcinoma (DTC) exist. Differences in clinical, molecular, and pathological characteristics between pediatric and adult DTC emphasize the need for specific recommendations for the pediatric population.

Methods and results

An expert panel was instituted by the executive committee of the European Thyroid Association (ETA) including an international community of experts from a variety of disciplines including pediatric and adult endocrinology, pathology, endocrine surgery, nuclear medicine, clinical genetics, and oncology. The American Thyroid Association (ATA) pediatric guideline 2015 was used as framework for the present guideline. Areas of discordance were identified, clinical questions were formulated and literature searches were performed. The expert panel members discussed the evidence and formulated recommendations based upon the latest evidence and expert opinion.

Endocrine Abstracts (2022) Vol 84
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Clinical relevance of lower titer thyroglobulin (TG) autoantibodies in patients with differentiated thyroid carcinoma

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Objectives
Thyroglobulin (Tg) is an established tumor marker for differentiated thyroid carcinoma (DTC) patients. However, Tg immunosassays can be subject to assay-to-assay (TgAb) interference resulting in incorrect Tg values. Tg measurement with liquid chromatography-tandem mass spectrometry (LC-MS/MS) could be promising in patients with TgAbs. In this study, we compared a Tg immunoradiometric assay (Tg-IRMA) and a Tg-LC-MS/MS analytically in the presence of TgAbs. Furthermore, we evaluated the clinical concordance between both assays in DTC patients with lower TgAbs titers (<10 U/ml) TgAbs during 131I ablation therapy.

Methods
118 DTC patients diagnosed between 2006 and 2014 in a University Medical Center were followed up with the Tg-IRMA (Thermo Fischer Scientific) and ARCHITECT Anti-Tg (Abbott Laboratories) assays. TgAbs ≥ 10 U/ml were defined as potentially interfering. We re-analyzed their samples with a sensitive Tg-LC-MS/MS method (Labcorp, North Carolina, USA, limit of quantification of 0.02 ng/ml). Passing-Bablok regression analysis was performed on samples obtained during 131I ablation therapy and follow-up.

Results
In 304 samples with lower titer TgAbs titers, good agreement was found between both Tg assays (slope of 1.09 (95% CI 1.05 - 1.16)). Fifty-five samples with potentially interfering TgAbs showed higher Tg-LC-MS/MS values than Tg-IRMA (slope of 1.45 (95% CI 1.12 - 1.80)). For patients (n = 91) with lower TgAbs titers at the time of 131I ablation therapy, the clinical concordance of both Tg assays was 91.2%.

Conclusions
In DTC patients with lower titer TgAbs, Tg-IRMA is a reliable and useful tumor marker. In DTC patients with potentially interfering TgAbs, Tg-IRMA values are decreased due to TgAb interference.

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PS3-15-136
The role of core needle biopsy in the diagnosis of primary thyroid lymphoma and anaplastic thyroid carcinoma: a systematic review and meta-analysis

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Objective
Anaplastic thyroid carcinoma (ATC) and primary thyroid lymphoma (PTL) are two highly aggressive malignancies of the thyroid, both leading to a rapidly enlarging neck mass. Fine-needle aspiration cytology (FNAC) is generally performed as the primary examination for diagnosis in thyroid pathology but shows low sensitivity in diagnosing ATC or PTL. Non-diagnostic FNACs are usually followed by core-needle biopsy (CNB) or diagnostic surgery. As sensitivities of up to 100% have been described, we investigate whether executing CNB primarily is more desirable than FNAC in the diagnosis of ATC and PTL. We want to determine the diagnostic value of CNB by combining all published data on the reliability of CNB in diagnosing ATC and PTL in a systematic review and meta-analysis.

Methods
A search was performed on June 23rd, 2021 on PubMed, Embase, Web of Science and Cochran. Population of interest were patients who underwent CNB due to clinical or ultrasonographical suspicious features of ATC or PTL or patients with final diagnosis of ATC or PTL after CNB or after surgery following CNB.

Results
A total of 166 patients were included of which 136 patients were diagnosed as PTL and 14 patients as ATC after CNB. CNB proves to be superior to FNAC with a sensitivity and PPV of respectively 93.8% and 100% for PTL and 82.4% and 100% for ATC. Furthermore, rate of diagnostic surgery after CNB was only 6.2% for PTL and 17.6% for ATC.

Conclusions
We conclude that CNB could be a more appropriate intervention for diagnosis of ATC and PTL than FNAC.

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PS3-15-137
Tendency of progression of antithyroglobulin antibody as a predictor of prognosis in patients with papillary thyroid carcinoma

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Objectives
The clinical significance of antithyroglobulin antibody (TgAb) levels verified concomitantly with undetectable thyroglobulin (Tg) during the follow-up of patients with differentiated thyroid carcinoma remains under debate. The present study aimed to evaluate the presence and prognostic predictive value of TgAb during the follow-up of patients with differentiated thyroid carcinoma.

Methods
A retrospective cohort study was performed by reviewing the medical records of patients being followed up in a tertiary service, from 2000 to 2020. Measurement of Tg was performed by chemiluminescence (Cobas 601, Roche) and of TgAb by electrochemiluminescence (Liaison, Diasorin). Results
Data from 868 patients diagnosed with papillary thyroid carcinoma were evaluated, including 62 patients (7.1%) who had detectable TgAb during follow-up, either preoperatively or postoperatively. Most are female (85%), white (81%), non-smokers (77%), mean age of 43.18 years, mean follow-up time of 94 months. There was no relationship between preoperative TgAb levels and worse prognostic characteristics at follow-up. A higher percentage of time with detectable TgAb after thyroidectomy was showed as a predictive factor to non-excellent response to therapy (P = 0.001, OR 1.089; CL95% 1.045-1.135), and also, it was observed in carcinomas with angiolymphatic invasion (P = 0.002), extrathyroidal invasion (P = 0.015), lymph node metastases (P = 0.008) and distant metastases (P = 0.009), as well as in T3 and T4 tumors (P = 0.008). Patients with incomplete structural response had a higher percentage of time with detectable TgAb compared to patients with excellent response one year after thyroidectomy (P < 0.001) and current response (last assessment during follow-up) (P < 0.001). The majority of patients with detectable TgAb had antibody negative throughout the follow-up period (59%); 24.1% remained stable, 9.6% showed a trend to decrease and 6.4% to increase, and in this last group, 100% of the patients presented incomplete structural response.

Conclusions
This study showed that preoperatively detected TgAb are not associate to a worse prognosis in patients with differentiated thyroid carcinoma. We found that not only the appearance or increase of TgAb, but also the presence of stable TgAb levels were indicative of disease persistence or recurrence. In contrast, significant decline in TgAb was associated with disease-free status. In conclusion, when TgAb was detected during follow-up, temporal evaluation was important for defining the trend of TgAb and the relation with the progression of the disease.

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Endocrine Abstracts (2022) Vol 84
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**Routine molecular analysis of fine-needle aspiration biopsies of thyroid nodules**

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**Objectives**

Molecular testing of fine-needle aspiration biopsy (FNAB) samples is increasingly used mainly for indeterminate categories of the Bethesda System for Reporting Thyroid Cytopathology. Our aim was to introduce a routine molecular analysis of the main genetic causes of thyroid cancer.

**Methods**

In total, 1358 FNAB samples of thyroid nodules were analyzed. Testing procedures mainly in samples evaluated as Bethesda categories III and above were gradually established. First, DNA for the most common mutation V600E in the BRAF gene using allele specific Real Time PCR (LC480, Roche) is analyzed. BRAF-positive samples are screened for TERT mutations using direct sequencing (CEQ 8000, Beckman Coulter). BRAF-negative samples are analyzed by next generation sequencing (MiSeq, Illumina) using the Thyro-ID panel (dbGaP examining other 12 genes. The samples negative in the Thyro-ID panel are subjected to detection of 23 fusion genes including ALK, BRAF, GLIS3, NTRK1, NTRK3, PPARG, RET genes using Real Time PCR. Samples suspected of medullary thyroid carcinoma (MTC) for RET and RAS mutations are tested.

**Results**

BRAF mutations in 153 patients, RAS mutations in 87 patients, RET mutations in 4 patients, TERT mutations in 24 patients and fusion genes in 52 patients were detected. Genetic variants in other genes (TP53, PTEN, PIK3CA, KIT, TSHR) were detected in 25 patients. From our cohort, in 430 patients post-surgical histopathological evaluation has been known. Positive predictive values (PPV) of BRAF, TERT, KRAS, HRAS, NRAS mutations and fusion genes were 99.5%, 94.1%, 73%, 50%, 45.8% and 97.7%, respectively, if borderline tumors were not included in malignancy. PPV for BRAF, TERT and fusions were almost 100% except for a follicular adenoma with BRAF K601E mutation, one case of follicular tumor of uncertain malignant potential with TERT and NRAS mutations and one case of hyalinizing trabecular tumor (HTT) with PAX5/GLIS3 fusion that is pathognomonic for HTT.

**Conclusions**

We established molecular testing of thyroid nodules that significantly contributed to clinical management of patients in the Czech Republic. Mutations of BRAF, TERT and fusion genes are associated with almost 100% risk of malignancy or even worse prognosis, therefore according to ETA guidelines from 2017 and TERT germline mutation. Subjects harboring RET germline mutation without awareness of their condition are defined gene carriers (GC). Thyroid surgery timing is decided upon RET mutation and calcitonin levels (both basal, bCT, and stimulated, sCT). However, bCT and sCT thresholds for planning thyroid surgery have not been established yet. Methods were evaluated 189 GCs by clinical, biochemical (bCT and sCT) and neck US every 6-12 months. Thyroid surgery was planned in case of elevated bCT (i.e., higher than upper limit of normal range) and/or positive stimulation test, or subjects (or parents, if minor) willing. After surgery, all patients were submitted to biochemical analysis (bCT and, if necessary, sCT) and neck ultrasound.

**Results**

92/189 GCs were submitted to thyroid surgery after a median time of 6 months (IQR 2-13). MTC foci (73.3% < 1 cm, 15% between 1 and 2 cm, 11.7% > 2 cm) were present in 71 (77.2%) while CCH in 21 (22.8%) subjects. At last clinical evaluation after surgery (median follow-up 85.5, IQR 35.25-147 months), clinical remission was observed in 71 patients (88.6% of microMTC, 66.6% of MTC between 1 and 2 cm, 28.6% of MTC > 2 cm and 100% of CCH patients) while 18 presented disease persistence (11.4% of microMTC, 33.4% of MTC between 1 and 2 cm and 71.4% of MTC > 2 cm): 13 and 5 MTC patients presented biochemical and structural persistence, respectively. Both presurgical bCT (P < 0.001) and sCT (P = 0.009) were higher in not cured patients (median 218 and 1326 pg/ml, respectively) compared to cured ones (20 and 178 pg/ml, respectively). Interestingly, presurgical bCT lower than 28.25 pg/ml significantly identified CCH and MTC who will be cured, with a high specificity (93.3%) and good sensitivity (76.2%). Conversely, values of presurgical sCT higher than 12.60 pg/ml and of presurgical sCT higher than 134.0 pg/ml, correlated with the presence of MTC foci with high sensitivity (95.0% and 94.40%, respectively) and good specificity (75.0% and 61.40%, respectively). Conclusions in a large cohort of consecutive GCs who were submitted to thyroid surgery, presurgical bCT < 28.25 pg/ml identified, with high specificity and good

Endocrine Abstracts (2022) Vol 84
sensitivity, CCH or small MTC that will be cured with thyroidectomy. When presurgical bCT is > 12.6 pg/ml, some cases of MTC may be present but, if the bCT is still < 28.25 pg/ml, they also will be safely cured.

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**PS3-15-141**

**What do different echogenic micro-foci in papillary thyroid carcinoma nodules and metastatic lymph nodes represent in histopathology?**

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**Objective**

Ultrasonographic (US) echogenic micro-foci are frequently seen in papillary thyroid carcinoma (PTC). General belief is that microcalcifications represent psammoma bodies. But the subject is debatable and other sonographic intranodular echogenic figures can be seen in PTC. We aimed to examine the nonshadowing echogenic figures and their histopathological correlations in PTC.

**Methods**

We prospectively collected US video records of PTC cases with echogenic micro-foci or metastatic lymph nodes (MLN) and malignant nodules without echogenic foci between 2018 and 2021 in two centers. All video recordings were independently interpreted by three experienced sonographists. Non-shadowing echogenic micro-foci were classified as; microcalcification (punctate echogenic foci < 1 mm), linear (> 2 mm), comet-tail, coarse echogenic foci and unclassifiable. Histopathological evaluation was performed by two experienced pathologists. Data were evaluated by an investigator who is blind to these results.

**Results**

92 nodules and 12 metastatic lymph nodes out of 160 patients, agreed on the type of echogenic foci by at least two of three sonographers, was included in the statistics. While 72 of 92 malignant nodules had any kind of echogenic micro-foci (group 1), 22 did not (group 2). According to histopathological evaluation, number of psammoma bodies, coarse stromal calcifications and papillae are significantly higher in group 1 than in group 2 [(76% vs 5%, P < 0.001), (38.6% vs 4.5%, P = 0.002), (87% vs 50%, P = 0.001)]. Same parameters were significantly higher in nodules with microcalcifications than in nodules without echogenic foci [(85% vs 4.5%, P < 0.001), (29% vs 4.5%, P = 0.024), (85% vs 50%, P = 0.003)]. Coarse stromal calcifications and papillae are significantly higher in nodules with linear echogenic micro-foci than in nodules without echogenic foci [(57% vs 4.5%, P = 0.007), (100% vs 50%, P = 0.026)]. Most common histopathological findings in MLN with ecogenic foci were papillae (92%), psammoma (83%) and cystic areas (83%), respectively.

**Conclusions**

Punctate echogenic foci in PTC nodules indicate the presence of psammoma in pathology. Linear echogenic micro-foci are mostly associated with coarse stromal calcifications and papillae. Echogenic foci in metastatic lymph nodes may be associated with microcystic areas as well as psammoma and papillae.

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Author Index

Abisil, Julie OP-12-61
Accardi, Roberto PS3-14-127
Adkhamova, Madina PS1-02-10
Adler Cohen, Chagit PS2-06-51
Aghanahi, Benilda OP-01-06
Agate, Laura PS1-03-21
Agate, Laura OP-03-12
Agate, Laura PS2-07-62
Aghababyan, Aleksandr PS2-10-89
Aghajanova, Elena PS3-11-99,
PS3-11-100, PS3-11-101,
PS1-01-06, PS1-01-05
Aghajanova, Elena PS3-11-102
Agostini, Maura PS2-09-84,
OP-08-37, OP-01-04
Agretti, Patrizia PS1-02-14
Agretti, Patrizia PS1-02-15
Agretti, Patrizia PS1-02-16
Aliquo`, Federica PS2-06-56
Alibrandi, Angela PS3-13-122
Alexopoulou, Orsalia PS2-07-66
Alexis, Werion OP-05-22
Alcide Martin, Andrea PS1-04-30
Alevyzaki, Androniki
Alevizaki, Maria OP-09-43
Alessandro PS2-07-63,
PS2-09-81
Almeida, Lucía PS2-06-55
Allen, Lloyd OP-01-01
Almeida, Lúcia PS2-06-55
Alonso-Gordoa, Teresa PS3-15-134
Alvarsson, Michael PS3-13-120
Alves, Helena PS2-06-55
Alves, Marta PS2-10-95
Ambrosini, Carlo Enrico PS2-10-89
Anagnostis, Panagiotis
Aversa, Tommaso PS1-05-39
Azizi, Fereidoun OP-06-28
Baccini, Andrea PS2-09-78
Backes, Helko PS2-09-82
Bae, Ja Seong PS1-03-19, PS1-03-23
Bagaglini, Maria Flavia OP-05-25,
OP-11-53
Bagattini, Brunella PS1-02-16
Bagattini, Brunella PS1-02-15
Bahcecioglu, Begum PS3-15-141
Bajuj Studen, Katica PS2-10-92
Bajuj Studen, Katica PS2-10-93,
OP-07-06
Baker, Stuart OP-04-21
Bakker, Stephan JL OP-06-28
Balestri, Eugenia PS2-07-63
Barata, Teresa PS3-15-134
Barbá, Kurt PS1-01-07
Barbu, Carmen PS1-05-46
Barolo, Susi PS3-13-117
Barretto, Naina PS3-12-110
Barros, Rita OP-07-33
Basolo, Fulvio PS2-10-89
Basolo, Fulvio PS3-15-140
Basolo, Fulvio PS3-01-20
Basso, Daniela PS3-13-117
Bauer, Douglas C. OP-06-28
Bavor, Petr PS2-08-74, OP-07-35
Bazzanova, Lyudmila OP-03-14
Becchirakis, Nikolos PS3-12-107
Bedernjak Bajuj, Nataa PS2-10-92
Bedernjak Bajuj, Nataa PS2-10-93
Beirinckx, Annemie PS2-07-57
Beleslin, Biljana PS3-12-111
Belliere, Antonino PS3-12-113
Bendlova, Bela PS2-08-74
Bendlova, Bela PS3-15-138
Bendlova, Bela PS3-14-131
Bendlova, Bela OP-07-35
Benenati, Nicoletta PS1-02-13
Benhalima, Katrien PS3-13-115
Bennett, Martin OP-01-04
Bensoussen, Isabela OP-06-28
Bertagnolli, Uta PS3-12-107
Bertazzoni, Loris PS3-13-117
Bertini, Veronica PS3-14-126
Bertolomi, Andrea PS2-09-85
Bertolomi, Andrea OP-08-38
Bex, Marie PS3-11-98
Bianchi, Francesca PS1-03-20
Bijnens, Jacqueline PS3-11-104
Bilezkić, Banu PS3-15-141
Blazević, Ivan PS3-13-119
Bleivaska, Aleksandra PS2-10-96
Boaventura, Paula PS2-10-95
Bocca, Gianni OP-12-62
Bodor, Miklos PS2-07-64
Boelaert, Kristien OP-06-28
Boelen, Anita PS1-05-42
Boelen, Anita OP-04-17
Boets, Liesbeth PS2-06-47
Begelund Larsen, Camilla PS2-06-53,
PS1-05-43
Boni, Giulia PS2-10-89
Bonikowski, Anastasios OP-06-30
Bonnema, Steen Joop PS2-06-53
Bonnema, Steen Joop PS1-05-43
Borneheag, Carl-Gustaf OP-02-10
Bosak Butkovic, Marija PS3-13-119
Boschi, Antonella OP-05-22
Bosco, Daniela OP-12-63
Botrini, Chiara PS2-06-50
Bottaro, Valeria PS1-03-20
Bottazzi, Giovanna PS1-05-45
Bottacci, Valeria PS3-15-140
Bottacci, Valeria OP-10-46
Bötticher, Valeria PS2-06-53
Bresolin, Mehdi PS1-05-43
Bresolin, Mehdi PS2-06-53
Brancatella, Alessandro PS1-01-04
Brancatella, Alessandro PS1-02-14
Brandau, Sven PS3-12-107
Brauenboer, Bert PS1-01-07
Bresser, Audrey Amber Julie
PS1-04-35, OP-13-67,
PS2-09-81
Brilli, Lucia OP-09-44
Brilli, Lucia OP-01-05
Brittemmer,
Jan H. PS2-09-80
Brix, Thomas PS1-05-43
Brix, Thomas PS2-06-53
Laus, Ana Carolina PS2-08-75, PS2-08-76
Le Blay, Karine OP-04-19
Le Moli, Rosario PS3-12-113, PS3-03-25
Lebbink, Chantal PS3-15-133
Lebrun, Laetitia OP-12-59
Ledwon, Aleksandra PS2-10-96
Lee, Eun Jig PS2-08-69
Lee, Sohee PS3-01-19
Leeuwenburgh, Selmar OP-08-40
Lefever, Eveline PS3-11-98
Lefort, Anne PS1-04-33
Legius, Eric PS2-08-70
Leite, Valeriano OP-10-50
Leite, Valeriano OP-03-16, PS3-03-27, PS3-14-132
Lelio, Baldeschi OP-05-22
Lengél, Benoît OP-05-22
Leone, Roberto PS2-09-77
Lévay, Bernadett PS2-10-87
Li, Shaohua PS2-10-88
Li, Shuren PS2-10-88
Li, Yang PS3-12-109
Li Pomi, Alessandra PS1-05-39
Lin, Yansong PS2-10-88
Lindén Hirschberg, Angelica PS3-13-120
Lindh, Christian H. OP-02-10
Links, Thera PS3-15-133, PS3-15-135, OP-12-62
Links, Thera PS3-14-124
Little, Amy OP-05-26
Liu, Yulei PS3-12-106
Livadas, Sarantis OP-06-30
Loccuflor, Anne PS3-13-115
Lopez Alcántara, Nuria PS2-09-80
Lopez Martí, Anna PS1-04-36, PS3-04-31
Lorenz, Kerstin PS3-15-133
Lorusso, Loredana PS1-03-21
Losti, Raffaele PS3-14-127
Lupo, Mark OP-05-26
Luster, Markus PS3-15-133
Luton, Dominique OP-08-41
Luu N., Hung PS2-10-90
Lykkeboe, Simon OP-05-23
Lyons, Greta PS2-09-84, OP-08-37, OP-01-04
MacDonald, Stephen OP-08-37
Maciel, Joana PS3-14-132
Maenhaut, Carine PS1-04-33
Maenhaut, Carine OP-07-34
Maes, Toon PS2-07-59
Maes, Toon PS3-13-115
Maghakyan, Sona PS3-11-99
Maglionico, Maria Novella OP-05-24
Magnacca, Nunzia OP-13-65
Maia, Ana Luiza OP-01-06
Maia, Frederico PS2-08-75, PS2-08-76
Maier, Julia PS2-09-82
Main, Katharina M. OP-08-37
Maino, Fabio OP-09-44
Maino, Fabio PS1-03-26
Maino, Fabio OP-01-05
Maisi, Sara OP-11-54
Maiter, Dominique PS2-07-66
Malandrinis Pasqualino PS1-03-25
Malta Letro Kizys, Marina OP-01-06
Mammadova, Jamala OP-08-37
Mangino, Giorgio OP-11-53
Manni, Carlo PS3-14-127
Manso, Jacopo PS3-13-117
Mantovani, Giovanna OP-11-54
Many, Marie-Christine OP-05-22
Marc, de Bouronville OP-05-22
Marchand, Victor PS1-05-45
Marcocci, Claudio PS2-07-58
Marcocci, Claudio OP-05-24
Marcocci, Claudio OP-10-47
Marelli, Federica OP-08-37, OP-01-04, PS2-09-79
Marelli, Federica PS2-09-84
Margvelashvili, Natia PS3-11-105
Marin, Loris PS3-13-117
Marino, Michele PS2-07-58
Marino’, Michele OP-10-47
Marino’, Michele OP-05-24
Marique, Lancelot OP-05-22
Markova, Boyka PS1-04-29
Marks, Deborah OP-11-58
Martín, Carmen Sorina PS3-11-103
Martín, Sorina PS1-05-46
Martín, Mariano OP-11-58
Martirosian, Narine PS2-08-73
Massarelli, Erminia OP-03-14
Mastnikova, Karolina PS3-14-131
Mastnikova, Karolina PS3-15-138
Mastnikova, Karolina PS2-08-74, OP-07-35
Materazzi, Gabriele PS2-10-89
Materazzi, Gabriele PS3-15-140
MATHIEU, Céline OP-12-61
Mathieu, Chantal PS3-13-115
Matroni, Antonio PS1-03-20, PS2-10-89, PS3-14-125, OP-09-45, PS1-03-21, PS1-03-22
Matroni, Antonio OP-10-52
Matroni, Antonio PS3-15-140
Mattii, Letizia OP-08-38
Maul, Etienne PS1-05-45