41st Annual Meeting of the European Thyroid Association

Abstracts

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Guest Editors
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OF A ‘FIRST-IN-HUMAN’ STUDY

Antigen-specific immune modulation using TSH receptor peptides (ATX-GD-59) for Graves’ hyperthyroidism: Results of a first-in-human study

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Graves’ hyperthyroidism is characterized by an immune response against the extracellular domain of the TSH receptor (TSHR). Two immunodominant TSHR peptides (ATX-GD-59) that ameliorated both the humoral and cell-mediated immune response against TSHR in a murine HLA-DR3 transgenic model induced by TSHR A-subunit inoculation have now been clinically evaluated.

In this study, 11 females and 1 male with mild untreated Graves’ hyperthyroidism were treated for 20 weeks once each fortnight with 5 intradermal injections of ATX-GD-59 in a gradually escalating dose to a maximum of 800 μg followed by 5 further injections of 800 μg. Inclusion criteria included FT4 <35 pmol/l, FT3 <15 pmol/l, detectable TSHR antibodies and presence of an HLA-DR3, -DR4 or DR15 allele. Two subjects did not complete the 10 injections (lost to follow up after 1 and 6 injections) and a further subject completed the study, but did not receive the full dose of ATX-GD-59.

In the 9 subjects receiving the full treatment regimen, mean pre-treatment FT4 was 25.1 pmol/l with a range 15.6–32.1 (upper limit of normal 22.7); mean FT3 was 9.5 pmol/l, range 6.2–13.1 (ULN 6.5) and mean TRAb concentration was 6.55 IU/l (ULN 1.75). Following 10 doses of ATX-GD-59, six of the 9 subjects (67%) had a complete or partial response, with 4 having both FT3 and FT4 within reference range (mean 5.1 pmol/l and 15.8 pmol/l, respectively; full response). Two subjects improved their free thyroid hormone concentrations during the treatment period but still had FT3 above reference range following the 10 doses (partial response). No subjects had to be rescued with carbimazole during the 20 weeks of dosing, but 3 subjects had higher FT3 or FT4 concentrations at the end of the treatment than at baseline. There were significant falls in TRAb (mean reduction 29%, range 14–64%) in the subjects who responded during the study, which were significantly correlated with changes in free thyroid hormones. Moreover, 5/6 subjects who had a decrease in free thyroid hormones also showed falls in the level of TSHR stimulating antibodies by bioassay (mean reduction 30%, range 16–62%). Of the data presented, 6 of 9 subjects (67%) could be considered to show a signal of the efficacy of ATX-GD-59. Other than mild injection site tenderness, redness and swelling, there were no consistent adverse events reported.

There have been no new treatments for Graves’ hyperthyroidism in 60 years. This study shows a first signal for the efficacy of ATX-GD-59 in patients with untreated Graves’ hyperthyroidism.
USE OF NANOSTRING TECHNOLOGY TO DEFINE THE IMMUNE PROFILE OF THYROID CARCINOMA

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Objectives: The understanding of the mechanisms underlying thyroid cancer immune escape can lead to the identification of new molecular targets and/or efficacy biomarkers possibly translatable to other cancer models. For this purpose, we performed immune expression profiling in thyroid cancers to obtain a comprehensive view on immune mechanisms activated in the microenvironment of the tumors during cancer progression.

Methods: The study was conducted retrospectively in 25 papillary thyroid carcinomas (PTC), 14 poorly differentiated thyroid carcinomas (PDTc), 13 anaplastic thyroid carcinomas (ATC) and 7 normal thyroid tissue samples (NT). DNA and RNA were purified from FFPE tissues. An extensive genotyping was carried out by NGS on DNA samples. Conversely, gene expression profiling was obtained on the RNA samples using the Nanostring platform and its nCounter PanCancer Immune Profiling Panel.

Results: Unsupervised hierarchical clustering of the normalized expression data indicated a very strong separation according to the histotype descriptors. Conversely, no association could be detected with the genetic descriptors (WT, BRAFV600E, RAS mutation, TERT mutation, RET/PTC rearrangements, BRAF+TERT, RAS+TERT). Gene expression comparison of ATC, PTC and PDTc vs NT showed high number of up- and down-regulated genes in the cancer samples. In detail, adhesion, B-Cell functions, chemokines, cytokines, interleukins, leukocyte functions, macrophage functions, NK cell functions, T-cell functions, TRL, TNF superfamily gene sets were significantly modulated (ATC > PTC >> PDTc). Interestingly, using the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, ATC, and to a lower extent PTC, showed a significant enrichment of up-regulated genes in the cell adhesion (including PD-L1, PD-L2, LAG-3, TIGIT and their receptors) and cytokine-cytokine receptor pathways. Evaluation of immune cell abundance showed a strong association between the detected immune expression profiles and the density of tumor-infiltrating leukocytes (TIL). Moreover, ATC showed the highest macrophage infiltration. Conversely, ATC showed the lowest T-cell and B-cell infiltration. Finally, ATC and PDTc showed the highest levels of exhausted CD8+ T-cells.

Conclusions: ATC, PTC and PDTc showed each a peculiar and specific pattern of interaction with the immune system compared to normal tissue; in regard, PDTc appear to have only a modest deregulation of immune-related pathways; several genes that resulted deregulated have already been described or even tested as therapeutic targets, thus representing easily targetable molecules; the most affected signaling pathways were the cytokine/ cytokine receptor interactions and the cell adhesion molecules pathways, thus confirming the importance of these cell processes in tumor progression.

LOCAL CONTROL OF THYROID HORMONE AVAILABILITY DETERMINES CELL FATE DECISIONS IN THE ADULT NEURAL STEM NICHE

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Adult neurogenesis occurs throughout life in specific regions of the brain and is tightly regulated by intrinsic and extrinsic factors. Thyroid hormones (THs) are well known to control neural stem cell (NSC) homeostasis in the mammalian neurogenic niches. Thus, a major question arising is how NSC fate, to either a neuronal or an oligodendrogial progenitor, is modified by TH availability.

We hypothesized that in the murine adult SVZ (Subventricular Zone), neuron-glial lineage fate decisions involve a tight regulation of TH availability. To this aim, we (i) characterized THs expression in the adult mouse SVZ, (ii) determined whether modulation of TH availability affects NSC differentiation (iii) evaluated how a strong reduction in TH availability impacts adult neurogenesis in the mouse SVZ.

First, we analysed THs expression using immunohistochemistry and RT-qPCR performed on NSCs and their progeny isolated by flow cytometry. We showed that THs, deiodinases and TH receptors are differentially expressed in NSC/progenitors cells and neuroblasts: MCT8 and OATP1C1 are highly expressed in NSCs and neuronal progenitors (NPCs), but not in oligodendrocyte progenitors (OPCs). In contrast, OPCs, but not NPCs, express high levels of the T3-inactivating deiodinase, D3, thus protecting OPCs from the neutralizing effects of T3.

Next, we addressed the effects of modulations of TH availability on cell fate. To this end, we treated neurosphere cultures with T3, or thyroid receptor antagonist N3. The addition of T3 increases NPC-gene expression at the expense of OPCs. Conversely, N3 reduced NPCs number counteraacting the neutralizing effects of T3.

Finally, we analysed the phenotype of the Mct8/Oatp1c1 double KO mice (DKO), where brain uptake of THs is strongly reduced, thus affecting deiodinase activities and TH target gene expression. In the adult DKO SVZ, we observed a dramatic reduction in the numbers of NSCs and NPCs, while OPCs number was unaffected.

Taken together, these data show that TH signalling is required for NSC commitment toward NPCs and hence a neuronal phenotype in the adult mouse SVZ. In NPCs, high intracellular TH availability is favoured by the expression of THTs and effects of TH by the presence of Trα1. In contrast, in OPCs, D3 expression reduces T3 availability thereby promoting glial determination. The absence of THTs induces a strong reduction of SVZ-derived NSCs and NPCs. Our work could have numerous applications in stem cell research for neurodegenerative diseases, by providing a better understanding of the mechanisms underlying TH availability in the control of glia-neuron cell-fate choice.
profile between RET positive samples and samples with no detectable somatic RAS and RET mutations were also significant and 422 probes demonstrated distinct methylation status. No significant changes were found during the comparison of methylation profile between samples with mutation in codons 634 and 918 of the RET gene. Regarding MTC clinical outcome significant differences in tumor methylation pattern were noticed between the group of patients, who achieved complete remission and those with persistent biochemical or structural disease. We were able to distinguish more than 3000 differentiating methylation sites. However, no differences in MTC methylome were observed comparing samples from patients with and without recurrent disease.

**Conclusions:** Significant differences in MTC methylome were noticed between the samples carrying RET and RAS mutations and with reference to the clinical outcome of the disease. The obtained results suggest that MTC methylation status may be considered as a prognostic factor of MTC outcome. This research was supported by NCBiR [MILESTONE]: STRATEGMED2/267398/4/NCBR/2015.

**OP-01-06**

**THYROID HORMONE ANALOG THERAPY IN PATIENTS WITH MCT8 DEFICIENCY: THE TRIAC TRIAL**

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**Introduction:** Mutations in the thyroid hormone (TH) transporter MCT8 result in MCT8 deficiency, which is characterized by severe intellectual and motor disability and high serum T3 concentrations inducing thyrotoxicity in peripheral tissues. At present, no effective treatment is available, although preclinical studies suggest that the T3 analog Triac is a promising candidate to 1) normalize serum T3 concentrations in patients with MCT8 deficiency. Both clinical outcomes (BW, BMI and HR) and biochemical markers representing thyroid state in different tissues improved on Triac treatment. Future studies should aim to evaluate the effect of Triac on the neurocognitive phenotype once treatment is installed early after birth.

**Results:** Currently, all patients (age: 1–66 yr) have been enrolled of which 35 completed 1 year of follow-up. Triac treatment effectively reduced serum TSH concentrations (mean ± SD: 2.9 ± 1.6 to 1.0 ± 1.0 mU/L, p < 0.001), resulting in a strong reduction of T3 concentrations (5.2 ± 1.4 to 1.8 ± 0.8 nmol/L, p < 0.001), when comparing baseline and end-study measurements in these 35 patients. Importantly, the age-specific SD scores for BW (–3.1 ± 1.9 to –2.7 ± 1.8, p < 0.05) and BMI (–2.8 ± 2.6 to –2.2 ± 2.6, p < 0.05) significantly increased, whereas basal HR (102 ± 13 to 93 ± 8 bpm, p < 0.01) significantly decreased. Moreover, serum markers that reflect tissue thyroid state improved such as SHBG (222 ± 88 to 186 ± 76 nmol/L, p < 0.005) and Creatinine (31.5 ± 10.3 to 36.1 ± 13.0 μmol/L, p < 0.005). The youngest patients had some improvement in neuropsychological markers. No (severe) adverse reactions to Triac occurred.

**Conclusions:** This interim analysis indicates that Triac treatment effectively normalizes serum T3 concentrations in patients with MCT8 deficiency. Both clinical outcomes (BW, BMI and HR) and biochemical markers representing thyroid state in different tissues improved on Triac treatment. Future studies should aim to evaluate the effect of Triac on the neurocognitive phenotype once treatment is installed early after birth.

**Table 1. (for Abstract OP-02-07)**

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**Oral Presentations**

**OP-02-07**

**PREGNANCY WEEK SPECIFIC REFERENCE RANGES FOR TSH AND FREE T4 DURING EARLY PREGNANCY IN A COHORT OF 10,438 ANTI-TPO AND ANTI-TG NEGATIVE DANISH PREGNANT WOMEN**

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**Objectives:** Physiological changes in maternal thyroid function during pregnancy necessitate the use of pregnancy specific reference ranges. Much emphasis has been on the use of trimester specific intervals, but more evidence is needed to clarify the week specific changes in TSH and free T4 (fT4).

**Sunday, 16th September 2018**

**Oral Session 2: Pregnancy, and Inherited Thyroid Disease**
Methods: We consecutively collected sera from all pregnant women in the North Denmark Region who had a blood sample drawn in early pregnancy as part of the screening program for chromosomal abnormalities, 2011–2015. TSH, fT4, TPO- and Tg-antibodies were measured in sera from 14,323 pregnant women on an ADVIA Centaur (Siemens Healthcare Diagnostics) immunoassay. Pregnancy week specific reference ranges were established (2.5–97.5 percentiles) after exclusion of multiple pregnancies, women who were positive for TPO- and/or Tg-antibodies, had thyroid disease, other autoimmune diseases, or used thyroid interfering medication (n = 3,885). Box-Cox transformation and Tukey’s fences were used for detection and exclusion of outliers.

Results: Altogether 10,438 pregnant women were included, and 92% terminated with live birth. Reference ranges for TSH were dynamic, especially the lower limit, which showed a gradual decrease during the first trimester (Table) that continued in the beginning of second trimester (week 13), and then started to rise again (week 14 (n = 149): 0.06–2.9 μIU/l, week 15–20 (n = 142): 0.30–2.9 μIU/l). Comparison of MDI and PDI scores between offspring of different iodine nutrition groups during pregnancy. The use of a uniform TSH reference range in the first trimester of pregnancy may be too simple.

Conclusions: Establishment of pregnancy week specific reference ranges in a large cohort of anti-TPO and anti-Tg negative Danish pregnant women corroborates the dynamics of TSH in early pregnancy. The use of a uniform TSH reference range in the first trimester of pregnancy may be too simple.

OP-02-08
EFFECTS OF IODINE NUTRITION OF PREGNANT WOMEN ON OBSTETRIC COMPLICATION DURING PREGNANCY AND INTELLECTUAL DEVELOPMENT OF OFFSPRING
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Objectives: The present study aimed at exploring the effects of iodine nutrition of pregnant women on obstetric complication and intellectual development of offspring in a prospective cohort of pregnant women in China.

Methods: 700 pregnant women at 4 to 12 weeks of gestation were registered in three iodine adequate cities of China. Subjects who had thyroid dysfunction and miscarriage were excluded. Finally, 471 mother and children pair participated in the present study. The mothers were followed at first, second and third trimester and children were followed at one year of age. Serum TSH, FT4, TPOAb, TgAb, urinary iodine concentrations and creatinine were measured in the pregnancy. The Bayley Scale of Infant Development (BSID II), which including Mental Development Index (MDI) and Psychomotor Development Index (PDI), was used for children evaluation. Median urinary iodine (μg/L) for assessing iodine intake in pregnant women were as follows: mild to moderate iodine deficiency, below 99 μg/L; marginal iodine deficiency 100–149 μg/L; adequate, 150–249 μg/L; more than adequate group (8.8%) was significantly higher than iodine adequate group (7.4%) (p = 0.005), but negative results for MDI in every group comparison. During the third trimester of pregnancy, the prevalence of gestational hypertension in iodine more than adequate group was 5.3%, significantly higher than 0% in iodine adequate group (p = 0.017). The prevalence of gestational diabetes in mild to moderate iodine deficiency group (16.5%) was much higher than that of iodine adequate group (4.7%) (p = 0.008). The prevalence of preterm labour in iodine more than adequate group (8.8%) was significantly higher than iodine adequate group (0.9%) (p = 0.011). There was no significant difference between the iodine nutrition groups in every trimester about low birth weight infants, macrosomia and breech presentation.

Conclusion: Iodine deficiency and more than adequate during the third trimester of pregnancy might predict a greater risk for obstetric complication of pregnancy and intellectual development of offspring.

OP-02-09
SIMILARITIES AND DIFFERENCES OF DIETARY AND OTHER DETERMINANTS OF IODINE STATUS IN PREGNANT WOMEN FROM THREE EUROPEAN BIRTH COHORTS
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Objectives: Iodine is an integral component of the thyroid hormones which are important for optimal fetal and early postnatal neurodevelopment. Pregnant women have higher iodine requirements than the general population, putting them at greater risk of deficiency. Although worldwide, many pregnant women are still iodine deficient, data are lacking on factors associated with iodine status in pregnancy. Determining the main iodine food sources in pregnancy is essential so that information on how to achieve adequate iodine nutrition can be provided to pregnant women. This study aimed to explore the determinants of iodine status during early pregnancy in three European populations of differing iodine status.

Methods: Data on 6,566 pregnant women from three prospective population-based birth cohorts were used: 2,852 from ALSPAC (United Kingdom), 2,254 from Generation R (The Netherlands), and 1,460 from INMA (Spain). Urinary iodine-to-creatinine ratio (UI/Creat, μg/g) was measured in a spot-urine sample collected at ≤18 weeks’ gestation [median (25th-75th percentiles): 11.0 (8.0–15.0) weeks in ALSPAC, 13.1 (12.1–14.6) weeks in Generation R, and 13.0 (12.4–13.9) weeks in INMA] was used as a measure of individual iodine status. Iodine intake was estimated from food frequency questionnaires (FFQs) administered during pregnancy in each cohort. Multiple linear regression models were used with dietary variables (adjusted for daily energy intake) and maternal characteristics as predictors.

Results: Gestational week at urine sampling, maternal age, body mass index (BMI, kg/m²) and intake of milk and dairy products were significant predictors of UI/Creat in all three cohorts. Maternal age was significantly positively associated with UI/Creat across all cohorts [ALSPAC (Beta = 3.77, p < 0.0001); Generation R (Beta = 4.55, p = 0.001); INMA (Beta = 6.18, p = 0.002)]. Intake of fish and shellfish was significantly positively associated with UI/Creat in pregnant women in INMA (p = 0.029) and the UK (ALSPAC) (p = 0.017). Cohort-specific determinants were also identified, e.g. family adversity index, marital status, intake of fruit, and cakes and confectionary in ALSPAC; smoking, ethnicity, intake of cereals, eggs, added fats, and nuts and seeds in Generation R; and salt and meat intake in INMA.

Conclusions: Various maternal characteristics and dietary habits were associated with UI/Creat during pregnancy, some of which were population-specific. Public-health interventions focusing on improving the dietary iodine intake of pregnant women therefore need to be country-specific.
OP-02-10
CONTROLLED ANTENATAL THYROID SCREENING (CATS) II: LONG-TERM CARDIOMETABOLIC EFFECTS OF TREATING MATERNAL SUB-OPTIMAL THYROID FUNCTION
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Objectives: The Controlled Antenatal Thyroid Screening (CATS) study II is a follow-up of a randomized trial investigating the effects of levothyroxine treatment for suboptimal gestational thyroid function (SGTF). We have previously reported cognitive and behavioural outcomes. Here we present the effects of treatment on anthropometric and cardiometabolic outcomes.

Methods: 336 mothers were evaluated 7–10 years after pregnancy: 203 with normal gestational thyroid function (NGTF), 56 with untreated SGTF (SGTF untreated) and 77 SGTF who received levothyroxine (150 μg daily) during pregnancy (SGTF treated). 334 paired children were also evaluated. Subsets (a) provided blood (294 mothers, 83 children) for measurement of thyroid stimulating hormone (TSH), free-thyroxine (FT4), free-triiodothyronine (FT3), autoantibodies to thyroid peroxidase (TPOAb), lipids, insulin and adiponectin, and (b) underwent Vicorder® analysis (190 mothers, 195 children). BMI was calculated by 2.5–97.5th percentiles after excluding TPOAb and/or TgAb positive women. Reference ranges were calculated by cubic splines with three knots to assess non-linearity, to investigate the association of determinants with maternal serum concentrations of TSH, FT4, FT3, TT4 and TT3.

Results: The mean (±SD) age and BMI at evaluation was 41.2 ± 5.3 years, 27.3 ± 5.8 Kg/m² for mothers and 9.34 ± 0.9 years, 17.9 ± 3.0 Kg/m² for children. Untreated SGTF mothers had significantly higher BMI (29.0 ± 6.2 Kg/m²) compared with NGTF (26.9 ± 5.4 Kg/m²) and SGTF treated (27.2 ± 6.3 Kg/m²; p = 0.019). Multiple comparison analysis, including thyroid function, revealed that the increased BMI was mainly explained by higher TSH levels in untreated SGTF mothers (2.9 ± 1.6 μu/L) compared with SGTF treated (2.1 ± 1.9 μu/L) and NGTF (1.7 ± 0.9 μu/L; p = 0.001), since a high percentage of SGTF untreated women (64%) had never received levothyroxine treatment. Insulin (p = 0.20), lipid (cholesterol p = 0.57 triglycerides p = 0.20 HDL p = 0.12) and adiponectin (p = 0.96) levels were similar in the 3 groups; adiponectin levels correlated inversely with BMI, and hence were lowest in untreated SGTF women. There were no differences in systolic (p = 0.25) and diastolic (p = 0.36) blood pressure, aortic blood pressure (p = 0.11), aortic pulse wave velocity (p = 0.88), peripheral vascular resistance (p = 0.57) and pulse pressure (p = 0.51) between groups.

In children, there were no significant differences in TGAb level between groups (p = 0.06), adiponectin (p = 0.98), insulin (p = 0.15), lipids (cholesterol p = 0.43, triglycerides p = 0.13, HDL p = 0.10), systolic (p = 0.50) and diastolic (p = 0.49) blood pressure, heart rate (p = 0.29), aortic pulse wave velocity (p = 0.94), peripheral vascular resistance (p = 0.09) and pulse pressure (p = 0.39).

Conclusions: Thyroxine supplementation of women with SGTF during pregnancy did not benefit children’s BMI or other cardiometabolic parameters. However, screening for SGTF during pregnancy identified women that would benefit from levothyroxine replacement: absence of such treatment resulted in sustained long-term BMI increase.

OP-02-11
REFERENCE RANGES AND DETERMINANTS OF THYROID FUNCTION DURING PREGNANCY: THE SELMA STUDY
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Background and Objective: Establishing reference ranges as well as identifying and quantifying the determinants of thyroid function during pregnancy is important for proper clinical interpretation and optimizing research efforts. However, such data is sparse, specifically for (F)T3 measurements and most studies do not take into account thyroid antibodies or hCG. We aim to determine reference ranges and identify/quantify determinants of TSH, FT4, FT3, TT4 and TT3.

Methods: This study was embedded in the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study (SELMA), a population-based prospective cohort study of mother–child pairs recruited and followed from the 10th week of pregnancy. Serum samples were collected at enrollment and analyzed for different biomarkers. Reference ranges were calculated by 2.5–97.5th percentiles after excluding TPOAb and/or TGAb positive women. We used multivariable linear regression analyses, utilizing restricted cubic splines with three knots to assess non-linearity, to investigate the association of determinants with maternal serum concentrations of TSH, FT4, FT3, TT4 and TT3. All analyses were adjusted for maternal age, BMI, parity, ethnicity, education level, smoking status (based on questionnaire or serum cotinine), TPOAb, TGAb, hCG, child sex and gestational age.

Results: After exclusion of TPOAb positive women, reference range were: TSH: 0.11–3.48 mU/L, FT4: 11.6–19.4 pmol/L, FT3: 3.72–5.92 pg/mL, TT4: 82.4–166.2 pmol/L and TT3: 1.28–2.92 nmol/L. Additional exclusion of TGAb positive women did not change the reference ranges substantially.

Compared to non-smokers, women who were categorized as both active and passive smokers based on the questionnaire had a significantly lower TSH and higher FT3 and TT3. These findings were supported by serum cotinine which was also associated with lower TSH but a higher FT3 and TT3 concentrations. There was no association of serum cotinine or questionnaire-defined smoking status with FT4 or TT4. A lower BMI was associated with a lower TSH and TT4 while a higher BMI was associated with higher FT4, TT3 and TT4. A higher gestational age was associated with a lower FT4 and a lower FT3, but a higher TT4 and a higher TT3.

Conclusions: We show that the exclusion of TGAb positive women on top of excluding TPOAb positive women hardly affects clinical reference ranges. We identified various relevant clinical determinants of TSH, FT4, TT3 and TT4 which could reflect endocrine disrupting effects and/or effects on thyroid hormone transport or deiodination.
**THE FEATURES OF CYTOKINE AND STEROID ENDOMETRIUM EXPRESSION IN WOMEN WITH AUTOIMMUNE THYROID PATHOLOGY AND REPRODUCTIVE FAILURES**

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Autoimmune thyroid imbalance can be a reason of serious complications during pregnancy and can be combined with generalized autoimmune disorder, in particular, in endometrium. The pathology in regulation of immunocompetent cells activity (cytokines) and steroid receptivity in endometrium tissue can lead for failed implantation or disruption of embryo development with future consequences.

**Objective:** To evaluate immunohistochemical (IHC) endometrium expression of autoantibodies against cytokine receptors IL-1 alpha (IL-1α), IL-2 (CD 25), TNF-alpha (TNFsα), interferon-gamma (INFγ) and steroid receptors (ERα, ERβ, PR) in women with autoimmune thyroid diseases and spontaneous miscarriages.

**Materials and Methods:** 84 women, considering pregnancy, divided into 4 groups: I- women with reproductive losses and primary hypothyroidism, n = 21, II- TPOAb² positive women with a history of reproductive losses, n = 21, III- women with reproductive failures without autoimmune thyroid disease, n = 21, IV- healthy women of the control group, n = 21.

IHC endometrium study was performed using mouse/monoclonal antibodies. The IHC reactions (IL-2 receptor, IL-1α, TNFsα, INF-γ) were assessed by a quantitative score method for immunointensity, for steroid receptors (ERβ, ERα, PR)- AllRed Score evaluation method. Evaluation for reliability of the differences was used Spearman’s nonparametric rank correlation method. Statistically significant differences were considered for p < 0.05.

**Results:** In the research was found the expression decrease of ERα in stroma and glandular compartment in I and II groups compared with III (p < 0.001 and p = 0.002, respectively) and IV group (p < 0.001); in the I group was shown lower rate of ERβ expression vs III and IV (p = 0.04). The results of PR expression indicated their decrease in the I group in relation to the remaining cohorts (PR stroma: p < 0.001, PR of the gland: p = 0.03). In comparative analysis in all 4 groups was negative expression of IL-1 alpha and IL-2/CD 25 (p > 0.05). Significant differences in the expression level of INFγ and TNFα were observed in glands in the group with hypothyroidism and TPOAb² positive women (p = 0.06 and p = 0.001 respectively) than in control group.

**Conclusions:** Women with autoimmune thyroid pathology have a decrease expression of ERα, ERβ and PR in endometrium tissues, that indicates that this group of women are at risk of miscarriage and determines the expediency of pregancy survey.

Expression of INFγ is helpful to assess the risk of a possible complication of pregnancy in women with autoimmune thyroid disease, but further research is required.

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**REVISITING THE DIAGNOSIS OF CONGENITAL HYPOTHYROIDISM: HIGH INCIDENCE OF THYROID DYSFUNCTION ASSOCIATED WITH MUTATIONS IN DUOX2 AND DUOXA2 IN INFANTS UNDETECTED BY CURRENT UK NATIONAL NEWBORN SCREENING CUT POINTS**

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**Objective:** We aimed to investigate whether preconceptional TSH level above 2.5 mIU/L predicts delivery rates in euthyroid healthy women undergoing first IVF.

**Methods:** In a retrospective study 623 women with first referral for fertility treatment at Aarhus University Hospital, Denmark, between January 1st 2012 until March 31th 2014 were included. Exclusion criteria were chromosomal abnormalities, comorbidity, prior levothyroxine (LT4) treatment, and lack of TSH measurement. TSH and anti-thyroidperoxidase-antibodies (TPOab) were measured as part of infertility work-up. Impact on success of first IVF cycle was assessed using multiple logistic regression adjusted for BMI, smoking, age, fertility status, and initiation of LT4.

**Results:** Overall live birth rate was 27.0% (n = 168), 30.3% (73) of women conceived miscarried, 80.8% (59) of these occurred before week 8 of gestation. 18.3% (114) had TSH above 2.5 mIU/L. Baseline demographics according to grouping of TSH showed no differences in age, BMI, history of smoking, fertility status or infertility diagnosis. However, women with TSH above 2.5 mIU/L had lower change of clinical pregnancy (21.1% vs 31.0%, p = 0.035) and delivery (18.4% vs 28.9%, p = 0.023), despite comparable chance of conception (22.2% vs 39.9%, p = 0.19). These associations were confirmed in the adjusted analysis with odds ratio (OR) for clinical pregnancy 0.49 (95% CI: 0.27–0.90, p = 0.022) and OR for delivery 0.54 (95% CI: 0.29–1.00, p = 0.049), comparing TSH above vs below 2.5 mIU/L. In crude analysis odds for any pregnancy loss was significantly higher among women with TSH above 2.5 mIU/L, but not in the adjusted analysis.

TPOab was only measured in a subcohort. In subanalysis adding TPOab to the model, the adverse impact of TSH on success of IVF remained regarding clinical pregnancy. In line with this finding, odds for early pregnancy loss was higher in women with TSH above 2.5 mIU/L (OR 3.43 (95% CI:1.03–11.40, p = 0.04)).

**Conclusion:** Our data, though retrospective, suggests worse IVF outcomes with preconceptional TSH above 2.5 mIU/L. This adverse effect occurs in very early pregnancy. Potentially challenging the recommendation on optimal TSH level to initiate treatment, these findings need replication.
in mutation negative cases. Frequency and associated biochemical characteristics of DUOX2 and DUOX2A mutations were evaluated and novel DUOX2A mutations were characterized in vitro.

Results: 26 cases (50%) harbour likely pathogenic mutations in either DUOX2 (n = 20, 38%) or DUOX2A (n = 6, 12%). We detected novel pathogenic mutations in DUOX2 (n = 3) and DUOX2A (n = 7); two recurrent pathogenic DUOX2 mutations (p.Q570L, p.F666S/+29) occurred frequently in individuals of specific ethnicities in population databases (MAF ≥0.01). Confirmatory venous hormone levels in mutation-positive cases demonstrated moderate CH (mean fT4 9.6, range 3.9–15.8 pmol/L) despite bTSH <10 mU/L in 46%.

Conclusion: Recommended TSH screening cut offs fail to detect individuals with true dyshormonogenesis who develop at least moderate CH, despite borderline bTSH concentrations. Targeted sequencing of DUOX2 and DUOX2A in such cases will have a high diagnostic yield, facilitating prompt diagnosis in familial cases.

Oral Session 3: Targets of Thyroid Hormone Action

OP-03-15
EXOGENOUS HYPERTHYROIDISM INDUCES OSTEOCYTIC OSTEOLYSIS IN MALE MICE
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Objective: Osteocytic osteolysis, a process where osteocytes remodel their periacicular matrix, has been demonstrated during lactation. Our previous studies show that hyperthyroidism in mice results in a rapid bone turnover and a larger percentage of low mineralized bone. Here, we tested the hypothesis that hyperthyroidism may contribute to low bone mineralization through osteocytic osteolysis.

Methods: Twelve-week-old C57BL/6 male mice were rendered hyperthyroid by adding L-thyroxine (T4) to drinking water (1.2 g/ml) for 4 weeks. Osteocyte lacunae were quantified using a silver precipitation stain, and osteocytic expression of the osteoclast marker tartrate-resistant acid phosphatase (TRAP) was investigated using a TRAP stain. Furthermore, the osteocyte-like cell line MLO-Y4 was exposed to 3,5,3’-triiodo-L-thyronine (T3) for 24–72 hours. At these conditions, T3 enhanced mRNA expression of the transcriptional co-activator known as TAZ (transcriptional co-activator with PDZ-binding motif) regulates the activity of several transcription factors including PAX8 and NKX2-1 and plays a central role in tissue-specific transcription. It has been shown that TAZ, together with PAX8 and NKX2-1 are co-expressed in the nucleus of thyroid cells and that TAZ interacts directly with genomic modulators mediated by non-genomic mechanisms via cell surface receptor integrin αvβ3. The deaminated T4 derivative tetrac is a specific inhibitor of thyroid hormone action at the integrin site. The aim of this study was to evaluate the effects of T3 and T4 versus tetrac on MSCs in the context of angiogenesis.

Treatment of primary human MSCs with T3 or T4 in the presence of hepatocellular carcinoma (HCC) cell-conditioned medium resulted in stimulation of expression of genes associated with angiogenesis as determined by qPCR. Additional treatment with tetrac reversed these effects. Primary human umbilical vein endothelial cells (HVECs) were seeded on Matrigel and tube formation was analysed microscopically. Compared to untreated HVECs, treatment with thyroid hormones and MSC-conditioned medium stimulated tube formation, while tetrac reduced tube formation. As the vascular endothelial growth factor (VEGF) is a critical angiogenesis mediator, we established a reporter gene system by placing the sodium iodide symporter (NIS) gene under control of the VEGF promoter. MSCs transfected with this construct (VEGF-NIS-MSCs) showed enhanced perchlorate-sensitive NIS-mediated iodide uptake activity in vitro after stimulation with HCC cell-conditioned medium in either T3 or T4. In vitro stimulation of HCC cell-conditioned medium with T3 was blocked by tetrac. T3 effects were additionally blocked by the PKA inhibitor LY294002 and the ERK1/2 pathway inhibitor RAF265, while T4 effects were only blocked upon RAF265 treatment, supporting integrin αvβ3-dependency. Effects of thyroid hormone on VEGF-driven NIS expression in MSCs in vivo were evaluated by iodide-124 PET in an orthotopic HCC xenograft mouse model. Tumoural radiiodide uptake demonstrated successful tumoural recruitment of VEGF-NIS-MSCs after systemic application followed by VEGF promoter-driven NIS expression. In hyperthyroid animals, a strongly enhanced radiiodide signal was detected in orthotopic HCC tumours compared to euthyroid and hypothyroid mice, while treatment with tetrac resulted in a markedly reduced signal. These data confirm the in vitro data suggesting significant thyroid hormone-mediated stimulation of VEGF in HCC tumours that was inhibited by tetrac.

Our data suggest that thyroid hormones T3 and T4 influence angiogenic signalling in MSCs in an integrin-dependent fashion, providing further evidence of the critical role of thyroid hormones in the regulation of angiogenesis and the anti-angiogenic activity of tetrac in the context of tumour stroma formation.

OP-03-16
NON-GENOMIC EFFECTS OF THYROID HORMONES ON MESENCHYMAL STEM CELLS IN TUMOUR ANGIOGENESIS
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Tumour stroma formation is associated with angiogenesis and requires interactions of various different cell types, including endothelial cells and mesenchymal stem cells (MSCs), which are actively recruited into growing tumour stroma. Thyroid hormones T3 and T4 act as non-classical proangiogenic modulators mediated by non-genomic mechanisms via cell surface receptor integrin αvβ3. The deaminated T4 derivative tetrac is a specific inhibitor of thyroid hormone action at the integrin site. The aim of this study was to evaluate the effects of T3 and T4 versus tetrac on MSCs in the context of angiogenesis.

Methods: Twelve-week-old C57BL/6 male mice were rendered hyperthyroid by adding L-thyroxine (T4) to drinking water (1.2 g/ml) for 4 weeks. Osteocyte lacunae were quantified using a silver precipitation stain, and osteocytic expression of the osteoclast marker tartrate-resistant acid phosphatase (TRAP) was investigated using a TRAP stain. Furthermore, the osteocyte-like cell line MLO-Y4 was exposed to 3,5,3’-triiodo-L-thyronine (T3) for 24–72 hours. At these conditions, T3 enhanced mRNA expression of the transcriptional co-activator known as TAZ (transcriptional co-activator with PDZ-binding motif) regulates the activity of several transcription factors including PAX8 and NKX2-1 and plays a central role in tissue-specific transcription. It has been shown that TAZ, together with PAX8 and NKX2-1 are co-expressed in the nucleus of thyroid cells and that TAZ interacts directly with genomic modulators mediated by non-genomic mechanisms via cell surface receptor integrin αvβ3. The deaminated T4 derivative tetrac is a specific inhibitor of thyroid hormone action at the integrin site. The aim of this study was to evaluate the effects of T3 and T4 versus tetrac on MSCs in the context of angiogenesis.

Results: 26 cases (50%) harbour likely pathogenic mutations in either DUOX2 (n = 20, 38%) or DUOX2A (n = 6, 12%). We detected novel pathogenic mutations in DUOX2 (n = 3) and DUOX2A (n = 7); two recurrent pathogenic DUOX2 mutations (p.Q570L, p.F666S/+29) occurred frequently in individuals of specific ethnicities in population databases (MAF ≥0.01). Confirmatory venous hormone levels in mutation-positive cases demonstrated moderate CH (mean fT4 9.6, range 3.9–15.8 pmol/L) despite bTSH <10 mU/L in 46%.

Conclusion: Recommended TSH screening cut offs fail to detect individuals with true dyshormonogenesis who develop at least moderate CH, despite borderline bTSH concentrations. Targeted sequencing of DUOX2 and DUOX2A in such cases will have a high diagnostic yield, facilitating prompt diagnosis in familial cases.

OP-03-17
EPIGENETIC CHANGES DURING HUMAN THYROID CELL DIFFERENTIATION
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The transcriptional co-activator known as TAZ (transcriptional co-activator with PDZ-binding motif) regulates the activity of several transcription factors including PAX8 and NKX2-1 and plays a central role in tissue-specific transcription. It has been shown that TAZ, together with PAX8 and NKX2-1 are co-expressed in the nucleus of thyroid cells and that TAZ interacts directly with both PAX8 and NKX2-1. This interaction leads to significant enhancement of the transcriptional activity of PAX8 and NKX2-1 on the thyroglobulin (TG) gene promoter hinting at a potential role for TAZ in the control of genes involved in thyroid differentiation. We previously reported that a small molecule called ethacridine, identified as a TAZ activator, was able to induce thyroid specific transcription in endodermal cells differentiated from human embryonic stem (hES) cells. Since epigenetic regulation of stem cell differentiation has been reported across an increasing number of cell types, we studied the epigenetic changes in methylation and acetylation in the promoter region

Oral Presentations

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of selected thyroid transcriptional factors and thyroid specific genes in hES cells treated with ethacridine. There was a low amount (~10%) of methylation found in the NKX2-1 promoter and no methylation in PAX8 and TAZ promoters using methylation-specific PCRs and sequencing. In contrast, the promoter activity of NKX2-1, PAX8 and TG was highly induced in ethacridine and Activin A treated hES cells as measured by acetyl-histone H4 immunoprecipitation (ChIP) assay (44 fold, 4 fold, and 6 fold respectively). These results indicated that acetyl-histone H4 is involved in the differentiation of thyroid follicular cells from hES cells. The epigenome may be a valuable resource for defining the genetic changes leading to thyroid development.

**OP-03-18**

**HYPOTHYROIDISM SEX-DEPENDENTLY REVERSES MURINE GALLSTONE FORMATION**

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**Objectives:** Hepatic cholesterol and lipid metabolism are influenced by thyroid hormones (TH). Epidemiological data show a correlation between low TH and cholelithiasis (Völzke et al., 2005). However, this only applies for men, whereas under euthyroidism women have a higher risk to develop gallstones (Hoogendam et al., 2006). This suggests a possible gender-specific association of hypothyroidism and gallstone formation. Using a gallstone susceptible mouse model, we asked whether TH and/or sex influences gallstone prevalence and whether changes in hepatic lipid and bile acid regulation are involved.

**Methods:** Female and male gallstone susceptible C57L/J mice received a lithogenic chow consisting of high cholesterol, high fat and cholate to induce gallstones either under euthyroid or hypothyroid (low-iodine chow, drinking water containing 0.02% methimazole and 0.5% perchlorate) state for four to eight weeks. Gallstone prevalence, liver and gallbladder histology were determined. Cholesterol and bile acid concentration in serum and liver tissue were investigated by ELISA and LC-MS. Hepatic expression of nuclear receptors, cholesterol and bile acid transporters were determined by qRT-PCR.

**Results:** Gallstone prevalence was higher in female than male mice under euthyroidism, whereas males showed higher gallstone prevalence under low TH condition. Gallbladder inflammation correlated with the sex-dependent gallstone prevalence. Under euthyroid conditions hepatic cholesterol, hepatic lipid accumulation, serum cholesterol and bile acid concentrations were higher in female compared to male mice. This reversed under low TH status. Furthermore expression of the nuclear receptor Fxr was increased in female but decreased in male livers by low TH. In hypothyroid males, diminished expression of the bile acid transporter Bsep is regulated by Fxr and correlated with the elevated serum bile acid concentration.

**Conclusions:** Our mouse data suggest that hypothyroidism increases gallstone prevalence in males but could be protective in female mice. This involves sex- and TH dependent changes in lipid and bile acid metabolism and secretion and is in agreement with data from epidemiological studies.

**OP-03-19**

**BENEFICIAL EFFECTS OF HYPOTHYROIDISM ON CHRONIC PRESSURE OVERLOAD MODEL IN MALE MICE**

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**Background:** The cardiovascular system is a prime target of thyroid hormones (TH) and thyroid dysfunction is associated with increased cardiovascular morbidity and mortality. Here we assessed the impact of TH excess and deprivation on heart disease using a chronic pressure overload mouse model to induce cardiac dysfunction.

**Methods:** To induce chronic left ventricular pressure overload, 8 weeks and 12 months old C57BL/6J male mice were subjected to transverse aortic constriction using a 27 or 25 gauge needle. Mice were followed up by echocardiography at 1, 3 and 5 weeks after surgery. TH excess was induced by 1 mg/ ml thyroxine and TH deprivation by 0.5% perchlorate and 0.04% methimazole in drinking water, starting one week after surgery. Hearts were investigated for changes in functional parameters, signal transduction, cardiomyocyte morphology and fibrosis.

**Results:** Hypothyroidism prevented progression of pressure induced pathological hypertrophy with a reduced thickness of the intraventricular septum and left ventricular posterior wall, reduced heart/tibia ratio and cardiomyocyte size. Improved cardiac function was indicated by increased fractional shortening (FS) and reduced fibrosis. Furthermore, hypothyroid hearts exhibited decreased mTOR signaling. In contrast, hyperthyroidism amplified cardiac hypertrophy and decreased FS. All effects were more pronounced in younger compared to older male mice.

**Conclusions:** In mice, hypothyroidism was associated with a protective effect on pressure overload induced chronic heart disease, in contrast to an adverse influence of hyperthyroidism.
concomitantly that the M256T-mutation resulted in a more pronounced reorientation of T3 than T4. In agreement with the model, TRα1-M256T reduced the affinity for T3 more than for T4 and had a larger effect on T3-dependent transcriptional activation. Interestingly, the Kd and EC50 for T4 and T4-dependent transcriptional activation were higher than that for T3 for WT but comparable for TRα1-M256T (Kd: WT 6-fold vs. M256T 0.3-fold, p < 0.001; EC50: WT 15-fold vs. M256T 0.9-fold, p < 0.001) also showed a similar trend. 

Conclusions: We report a novel TRα1-M256T mutation as a cause of RTHs. In vitro studies confirmed functional impairment of this mutant. Interestingly, this mutation abolishes the ability to discriminate between T3 and T4. This is the first naturally occurring mutation that confirms the importance of the Met256 residue for ligand binding and T3 vs. T4 selectivity of TRα1.

OP-03-21

PROTECTIVE AND DETRIMENTAL EFFECTS OF EXPERIMENTAL HYPO- AND HYPERTHYROIDISM ON MYOCARDIAL INFARCT SIZE AND FUNCTIONAL RECOVERY IN MOUSE HEART

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Background: Thyroid dysfunction is associated with increased cardiovascular morbidity and mortality whereby hyper- and hypothyroidism may have distinct impact. Both, the thyroid and cardiac system are sensitive to aging with increasing morbidity in advanced age. Here we studied the influence of thyroid hormone (TH) excess and deprivation on myocardial ischemia/reperfusion (I/R) injury in young and old mouse heart.

Methods: Chronic hyper- or hypothyroidism was induced over 3 weeks in 3-months-old (20 months old) male mice by T4 or methimazole/perchlorate addition to drinking water and confirmed by serum TH analysis. Control mice received sham treatment. Hearts were isolated and pressure-perfused. Spontaneous heart rate was determined within first 10 minutes, hearts were subsequently paced to 500 beats per minute and subjected to 30/120 min of global I/R. Left ventricular developed pressure (LVDP), coronary flow (CF) and infarct size (by triphenyltetrazoliumchloride-staining) were determined. Mitochondria were isolated under baseline conditions for functional measurements. Cardiac tissue samples after I/R were used for protein analysis.

Results: Spontaneous heart rate was elevated in hyperthyroid and decreased in hypothyroid hearts compared to controls. Chronic hyperthyroidism resulted in significantly increased infarct size and decreased functional recovery of LVDP but no changes in CF. In contrast, chronic hypothyroidism was associated with decreased infarct size and preserved functional recovery of LVDP and CF after ischemia. Furthermore, decrease in mitochondrial apoptosis signaling, ATP production and respiration were associated with TH deprivation. Of note, effects on infarct size were irrespective of age, however impaired functional recovery of old compared to young hearts was noted.

Conclusion: Chronic hypothyroidism reduced myocardial infarct size whereas chronic hyperthyroidism was detrimental and increased infarct size. This was independent of heart rate, as all hearts were equally paced. Thus, lack of TH may be protective rather than harmful in ischemic heart disease and influences mitochondrial function as an important relais in cardioprotection.

OP-03-22

THE METABOLIC AND THERMOREGULATORY PHENOTYPE OF MICE LACKING THE THYROID HORMONE RECEPTOR BETA

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Thyroid hormones (THs) are engaged in numerous physiological processes. The majority of these are governed by the nuclear TH receptors TRα1, TRβ1 and TRβ2, which regulate gene expression dependent on the availability of 3,3'-5-triiodothyronine (T3). Inactivating mutations for both receptors have been discovered in humans, leading to resistance to TH (RTH). In the case of RTHβ, patients present unsuppressed thyroid stimulating hormone concentrations despite elevated TH levels. TRβ knockout mice replicate the impairments in the feedback loop of the hypothalamic-pituitary-thyroid axis including elevated TH levels. Interestingly, however, no increase in body temperature was observed in these animals despite their increase in serum TH. Here we characterize the metabolic and thermoregulatory phenotype of TRβ knockout mice using infrared thermography, indirect calorimetry and nuclear magnetic resonance measurements. We found an increase in basal metabolic rate normalized to body weight in TRβ knockout mice compared to control littermates. In contrast, no changes in body composition were detectable between both groups and no increased heat dissipation via the tail was monitored in the TRβ knockout animals. Further analysis of the interscapular brown adipose tissue revealed no increased heat production measured by infrared thermography, which was in line with normal amounts of UCP1 in the tissue detected by western blot in both groups. The data suggest that the elevated obligatory thermogenesis can be compensated in TRβ knockout mice, causing no obvious elevation of oxygen consumption or adaptations in facultative thermogenesis.

OP-04-23

THE INFLUENCE OF METFORMIN AND HYPOCALORIC DIETING ON THYROID IODIDE UPTAKE IN HEALTHY VOLUNTEERS: A PILOT STUDY

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Background: Sufficient thyroid iodide uptake is needed to ensure effective RAI treatment, which is mediated by the expression of the sodium-iodide symporter (NIS). Previous research has shown that activation of AMP-activated-protein-kinase (AMPK) leads to decreased NIS expression and iodide uptake in in vitro studies and animal models. Clinically relevant conditions that lead to AMPK activation include metformin use, which is an important pharmacological modulator of AMPK, and hypocaloric conditions.

Aim of the Study: Here, we aim to assess the physiological effects of metformin and hypocaloric diet as modulators of AMPK activity, on thyroid iodide uptake in healthy volunteers.

Patients and Methods: We included 19 healthy male volunteers. Baseline measurements, including thyroid I-123 uptake and serum TSH, FT4 and T3 levels were performed. Subjects were randomized into 3 groups: Group
1 (n = 8) received metformin treatment; Group 2 (n = 7) followed a hypocaloric diet (1500 kcal/day); Group 3 (n = 4); no intervention (control). After two weeks, thyroid function and I-123 uptake measurements were repeated. During the trial, all subjects followed a moderately iodine restricted diet.

**Results:** Baseline characteristics were similar between all groups. Subjects were compliant with the study protocol. Levels of TSH and fT4 were similar before and after each intervention. T3 decreased significantly within the normal range after hypocaloric diet and metformin use (–0.2 ± 0.19 mmol/L resp. –0.12 ± 0.13 mmol/L; p < 0.05). The T3/rT3 ratio also significantly decreased after hypocaloric diet from 5.7 ± 1.5 to 4.5 ± 0.8 and after metformin use from 5.0 ± 1.2 to 4.5 ± 1.3. There was no significant difference in thyroid I-123 uptake after each intervention.

**Conclusion:** Both metformin treatment and hypocaloric diet resulted in a significant decrease in T3 levels and increased T3/rT3 ratios in healthy volunteers, without significant effects on thyroid iodide uptake. Based on this study, we did not find indications that metformin use or hypocaloric diets will have clinically relevant effects on RAI uptake in healthy volunteers. However, additional studies including a larger number of patients with benign and malignant thyroid pathology are needed in order to elucidate the role of AMPK modulation in the regulation of thyroid iodide uptake in thyroid disease.

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**OP-04-24**

**TRENDS, DETERMINANTS AND ASSOCIATIONS OF TREATED HYPOTHYROIDISM IN THE UNITED KINGDOM, 2005–2014**

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**Context:** Recent reports suggest that prescriptions for thyroid hormones have increased.

**Objective:** To analyse recent trends in and determinants of prevalence of treated hypothyroidism across the United Kingdom (UK).

**Design and Setting:** UK-wide data held by the National Health Service and the Office of National Statistics were examined.

**Main Outcome Measures:** Trends in prevalence of treated hypothyroidism between 2005 till 2014 were analysed. Furthermore, determinants of variation of treated hypothyroidism prevalence across health areas in the UK (n = 237) in 2014 and its association with other health conditions were explored by multivariate linear regression analyses.

**Results:** The prevalence of treated hypothyroidism increased from 2.3% (1.4 million) to 3.5% (2.2 million) of the total UK population between the years 2005–2014 and is projected to rise further to 4.2% (2.9 million) by 2025. There was large geographical variation of treated hypothyroidism across the UK with London having the lowest (1.4%) and the Western Isles of Scotland having the highest (6.3%) prevalence. Prevalence of treated hypothyroidism was independently related to health areas with higher proportion of individuals who were female, White, obese, and negatively associated with prevalent cigarette smokers. Prevalence of treated hypothyroidism was significantly associated with frequency of prevalent atrial fibrillation but not with other major health conditions including ischemic heart disease and osteoporosis.

**Conclusions:** Between 2005 and 2014, prevalence of treated hypothyroidism increased across the UK, with wide geographical variation, and is likely to increase further for the foreseeable future. Clinical effects and cost-effectiveness of the trend in increasing treatment of hypothyroidism remains to be evaluated.

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**OP-04-25**

**HYPERTHYROIDISM INCREASES THE RISK OF DEMENTIA, WHICH PARTIALLY RELATES TO PRE-EXISTING MORBIDITY – A REGISTER BASED COHORT STUDY OF TWO LARGE COHORTS**

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**Objectives:** Thyroid hormones within a narrow range are essential for normal brain function. Whether hyperthyroidism causes dementia is unclear. We hypothesized that patients with hyperthyroidism have increased risk of developing dementia.

**Methods:** Register-based cohort study of two groups of hyperthyroid patients. Cohort A comprises all patients registered with a hyperthyroid diagnosis (ICD-10) in the Danish National Patient Register (DNPR) from 1995–2014. Each patient was matched according to age and sex with four reference individuals, without known thyroid disease. Cohort B comprises all individuals who in the period 1995–2011 had at least one TSH measurement from general practices or hospitals on Funen, Denmark. Here, all individuals with a normal TSH were included in the reference population, whereas hyperthyroidism was defined as having a minimum of two decreased TSH values within a period of six months and at least 14 days apart. Pre-existing morbidity was calculated on an individual level, based on data extracted from DNPR. Dementia was identified with a relevant ICD-10 diagnosis in DNPR or treatment with relevant drugs according to the ATC-classification in The National Prescription Register (DNPR).

Using a Cox proportional hazards model, we calculated hazard-ratio (HR) for dementia comparing the two hyperthyroid patient cohorts with their respective reference population in a crude – and an adjusted for age, sex and pre-existing morbidity – model. We calculated the cumulative hazard of low TSH (<0.3 IU/L), in 6 month intervals, for the risk of developing dementia.

**Results:** Cohort A: 56,624 patients with a hyperthyroid diagnosis (median followup 7.3 yr), of whom 2,120 (3.7%) were subsequently diagnosed with dementia. In the reference population 7,547 (3.3%) out of 226,496 (median followup 8.1 yr) were diagnosed with dementia during followup. HR for dementia was 1.17 [95% confidence interval (CI): 1.12–1.23], but was non-significant when correcting for pre-existing morbidity HR 0.99 [95% CI: 0.94–1.04].

Cohort B: 234,218 patients; 2,772 with hyperthyroidism (median followup 7.2 yr) and 231,446 reference individuals (median followup 8.6 yr). 192 hyperthyroid patients (7.1%) and 6,431 reference individuals (2.8%) were diagnosed with dementia HR 1.21 [95% CI:1.05–1.40], which persisted after correcting for pre-existing morbidity HR 1.21 [95% CI: 1.04–1.40]. The cumulative HR for dementia, per 6 months of low TSH, was 1.17 [95% CI: 1.13–1.21].

**Conclusions:** Employing two hyperthyroid cohorts, an approximately 20% increased risk of being diagnosed with dementia is demonstrated. This is partially explained by pre-existing nonthyroid morbidity. Further evaluation of the association between different phenotypes of dementia and hyperthyroidism is warranted.
OBJECTIVE: To investigate the association between thyroid disease and mental vulnerability.

METHODS: Using Danish population-based studies, conducted in 1997–1998 and 2004–2005, including 8,219 adults between 18–75 years of age. After 11-years in 2008, 2,465 participants from the 1997 cohort were re-examined. The mental vulnerability of participants was recorded using a validated 12-item mental vulnerability questionnaire developed in Denmark. Persons with known thyroid disease and those with subclinical thyroid disease did not differ in their mental vulnerability. Women with known, optimally treated overt hyperthyroidism (OR 2.2 (CI 95% 1.3 to 3.8)) as well as optimally treated hypothyroidism (OR 2.4 (CI 95% 1.4 to 3.9)) compared with women without thyroid disease. Persons with unknown overt thyroid disease and those with subclinical thyroid disease did not differ in their Mental Vulnerability Score from persons without disease. In a multiple linear regression model there was no significant association between baseline thyroid peroxidase antibody (TPO Ab) status and change in Mental Vulnerability. TPO Ab did not predict a significant change in Mental Vulnerability Score from persons without disease. In a multiple linear regression model there was no significant association between baseline thyroxin (TSH) (P = 0.06) in a model adjusted for age, iodine intake and cohort.

CONCLUSION: Logistic regression analysis in cross-sectional data showed a significantly higher odds ratio (OR) of high mental vulnerability in women with known, optimally treated overt hyperthyroidism (OR 2.2 (CI 95% 1.3 to 3.8)) as well as optimally treated hypothyroidism (OR 2.4 (CI 95% 1.4 to 3.9)) compared with women without thyroid disease. Persons with unknown overt thyroid disease and those with subclinical thyroid disease did not differ in their Mental Vulnerability Score from persons without disease. In a multiple linear regression model there was no significant association between baseline thyroid peroxidase antibody (TPO Ab) status and change in Mental Vulnerability over time (P = 0.77). Baseline Mental Vulnerability was not associated with an 11-year change in serum thyroxin (TSH) (P = 0.06) in a model adjusted for age, iodine intake and cohort.

Mental Vulnerability of participants was recorded using a validated 12-item mental vulnerability questionnaire developed in Denmark. Persons with known thyroid disease and thyroid hormones within the treatment goals were classified as optimally treated. We found no evidence of a longitudinal association between Mental Vulnerability and TSH change. TPO Ab did not predict a significant change in Mental Vulnerability Score from persons without disease which may be explained by disease labeling.
Reduced Sensitivity to Thyroid Hormone as a Transgenerational Epigenetic Phenomenon Transmitted Along the Male Line

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Adult humans and mice exposed to high maternal thyroid hormones (TH) levels during fetal life, exhibit reduced sensitivity to TH (RSTH) which, based on mouse studies, appears to be caused by an increased expression of pituitary, but not hypothalamic deiodinase type 3 (D3). The latter accelerates TH inactivation which decreases the suppression of TSH resulting in RSTH. As the gene encoding for D3 is imprinted, we wondered if the effect is transmitted to subsequent generations without exposure to high TH levels. Therefore, we studied progeny of WT adults (second and third generations), descendents of grandmothers and great grandmothers, with RTH studied progeny of WT adults (second and third generations), descendent of RTH males with RSTH

**Table 1. Peak TSH response to TRH (pTSH) in the 3 generations studied, all WT for THRb (for Abstract OP-04-28)**

| Generation | Parental status | pTSH (mU/L) | p values
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<tr>
<td></td>
<td>Progeny of females with RSTH</td>
<td>Progeny of males with RSTH</td>
<td>p values</td>
</tr>
<tr>
<td>First</td>
<td>RTHβ</td>
<td>6.8±1.0*</td>
<td>1.6±0.5** &lt;0.003</td>
</tr>
<tr>
<td>Second</td>
<td>WT, RSTH</td>
<td>1.6±0.4</td>
<td>6.4±0.6 &lt;0.001</td>
</tr>
<tr>
<td>Third</td>
<td>WT, RSTH</td>
<td>1.3±0.2</td>
<td>4.6±0.6 &lt;0.005</td>
</tr>
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WT: Wild Type; RSTH: Reduced Sensitivity Thyroid Hormone; RTH Resistance to thyroid hormone. * Only this progeny was exposed to high TH levels during fetal life as mothers had RTHβ. ** Controls whose fathers had RTHβ and mothers were WT.

Dual Effects of Thyroid-Stimulating Hormone on Metabolic Syndrome and Its Components in Euthyroid Adults: A Population-Based Thyroid Study

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Objective: The association of thyroid-stimulating hormone (TSH) with risk of metabolic syndrome (MetS) and its components described previously is controversial. The present study aimed to investigate the relationship between thyroid function and metabolic disease risk in euthyroid subjects by a cross-sectional study.

Methods: A total of 48355 adults (25981 males and 22374 female) without thyroid disease were recruited and receive a comprehensive health examination including height, weight, waist circumference, blood pressure, and lipid profile. Furthermore, all participants underwent 75 g oral glucose tolerance test. MetS was identified using the 2009 International Diabetes Federation criteria. All participants were divided into three groups based on the tertiles of TSH levels.

Results: Generally, 30.5% males and 20.5% females were suffered from MetS in euthyroid population. Prevalence of central obesity, hypertension, and dyslipidemia increased significantly according to TSH tertiles, while that of hyperglycemia decreased. There was no significant difference between TSH tertiles in prevalence of MetS. Moreover, in partial correlation analysis, TSH was positively associated with body mass index (r = 0.027, P < 0.001), waist circumference (r = 0.019, P < 0.001), systolic blood pressure (r = 0.020, P < 0.001), diastolic blood pressure (r = 0.031, P < 0.001), triglyceride (r = 0.040, P < 0.001), and the number of MetS components (r = 0.036, P < 0.001), while negatively with fasting plasma glucose (r = –0.025, P < 0.001), two hours plasma glucose after glucose loading (r = –0.032, P < 0.001), and high-density lipoprotein cholesterol (r = –0.036, P < 0.001). After multivariable adjustment, there was a positive correlation between TSH and MetS risk (OR = 1.13[1.03–1.25], P = 0.014 for males; OR = 1.39[1.24–1.57], P < 0.001 for females). Similarly, TSH was positively associated with risks of central obesity; hypertension, and dyslipidemia. However, a negative correlation was observed between TSH and hyperglycemia in both males and females (OR = 0.871[0.79–0.96], P = 0.006 for males; OR = 0.91[0.82–1.00], P = 0.049 for females).

Conclusions: Within normal range, TSH decreased risk of hyperglycemia, but increased risk of the other components of metabolic syndrome, suggesting a dual role of TSH in metabolic regulation. This is a possible explanation of the inconsistency between previous studies.
OP-04-30
IMPAIRED QUALITY OF LIFE AFTER RADIOIODINE TREATMENT COMPARED WITH ANTI-ThYROID OR SURGERY TREATMENT FOR GRAVES’ HYPERThYROIDISM. A LONG-TERM FOLLOW-UP WITH THYPRO AND SF-36
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Objectives: To describe thyroid-specific and generic quality of life (QoL) 7–9 years after treatment of Graves’ disease (GD) with anti-thyroid drugs (ATD), radioiodine (RAI) or thyroidectomy.

Methods: Of 2244 patients with for hyperthyroidism due to GD who were registered 2003–05, 1143 volunteered to participate in a QoL follow-up study. The patients were treated in clinical routine at the seven participating centers. In 1143 patients valid clinical data from medical records were obtained and 975 patients returned the thyroid specific ThyPRO and/or the generic SF-36 questionnaire (n = 964) at follow-up. Scores from ThyPRO were compared with scores from a general population sample (n = 712), using multiple linear regression adjusting for age and gender as well as multiple testing. Similarly, with scores from a general population sample (n = 712), using multiple linear regression adjusting for number of treatments received, sex, age and for co-morbidities.

Results: At present, give and take the pro-et-cons from this study, the findings need to be considered when the doctor and patients chose treatment for GD.

Conclusions: QoL compared with ATD and surgery. Long-term impact of RAI on QoL needs to be considered when the doctor and patients chose treatment for GD.

OP-05-31
UNSATURATED FATTY ACID SYNTHESIS IS A METABOLIC FEATURE OF THYROID CANCER-ASSOCIATED MACROPHAGES
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Introduction: Tumor associated macrophages (TAMs) are the most abundant innate immune cells in non-medullary thyroid carcinoma (TC) and have been associated with poor prognosis. An important feature of macrophages is their high plasticity, which enables them to adapt to environmental changes by adjusting their cellular metabolism and immunological phenotype. Therapeutic approaches to reprogram pro-tumoral TAMs towards an anti-tumoral phenotype by targeting cell metabolism may represent an important therapeutic target, yet little is known about the metabolic reprogramming in TC-associated macrophages.

Aim: To study the metabolic and functional changes in TC-induced macrophages.

Methods: Transcriptomics, qPCR, immunofluorescent staining of neutral lipids and mass spectrometry were performed on monocytes co-cultured with TC cell lines in a transwell model. The impact of fatty acid (FA) uptake and biosynthesis, cholesterol biosynthesis and the transcription factor SREBP was assessed using pharmacological inhibitors.

Results: Transcriptome analysis in TC-induced macrophages identified increased inflammatory characteristics and rewiring of cell metabolism as key functional changes. Next to an increase in aerobic glycolysis, FA synthesis and desaturation were upregulated. Furthermore, the intracellular concentrations of the FA precursor Acetyl-CoA were increased, and the upregulation of enzymes involved in FA synthesis was validated by qPCR. Immunofluorescent staining confirmed an increase of neutral intracellular lipids in TC-induced macrophages. Whereas inhibition of FA uptake and the transcription factor SREBP did not affect the inflammatory characteristics, inhibition of FA synthesis led to a decrease of the inflammatory response. The concept of an important change of FAs in TC-associated macrophages was supported by validation through mass spectrometry of the increase in unsaturated fatty acids in TC-induced TAMs.

Conclusions: Fatty acid synthesis of unsaturated FAs is upregulated in TC-induced macrophages. Furthermore, FA synthesis contributes to the inflammatory characteristics of TAMs.

OP-05-32
CXCL9 AND CXCL11 CHEMOKINES MODULATION BY IFN-GAMMA, TNF-ALPHA AND PPAR-GAMMA IN PAPILLARY THYROID CANCER
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Objectives: Chemokines have a pivotal role in tumor progression, angiogenesis and metastasis. To date no findings are reported in literature about the regulation by cytokines (IFN-gamma and TNF-alpha) of chemokines (C-X-C motif) ligand 9 and 11 (CXCL9 and CXCL11) in primary cell cultures of papillary thyroid carcinoma (PTC), as well as about the effect of peroxisome proliferator-activated receptor-gamma (PPAR-gamma) activators on these chemokines, or regarding the effect of the stated chemokines on PTC proliferation.

We aimed to test: 1) the effect of IFN-gamma and TNF-alpha stimulation on CXCL9 and CXCL11 secretion in primary cell cultures obtained from
PTC, in comparison with non-neoplastic thyroid cells (TFC); 2) to estimate the effect of PPAR-gamma activation on CXCL9 and CXCL11 secretion and proliferation in these cell types; 3) to evaluate the effect of CXCL9 and CXCL11 on proliferation and migration of PTC cells.

**Methods:** Firstly we measured CXCL9 and CXCL11 basally, then after 24 h of IFN-gamma- and/or TNF-alpha stimulation in presence/absence of thioucidinediones and/or PPAR-gamma knocking down by RNA interference technique in PTC. Proliferation and migration were assessed in PTC cells after PPAR-gamma agonists, or CXCL9 or CXCL11 treatment.

**Results:** We observed that: 1) CXCL9 and CXCL11 were basally absent in TFC and in PTC cells; 2) IFN-gamma induced CXCL9 and CXCL11 secretion in both cell types in a dose-dependently way; 3) TNF-alpha alone induced a significant chemokines secretion only in PTC cells; 4) IFN-gamma plus TNF-alpha induced a synergistic chemokines release in PTC, whereas at a lower level in TFC; 5) thioucidinediones suppressed dose-dependently IFN-gamma plus TNF-alpha induced chemokines release in TFC, while stimulated it in PTC; 6) PPAR-gamma knocking down abolished the effect of PPAR-gamma agonists on chemokines release; 7) PPAR-gamma agonists reduced proliferation, and CXCL9 or CXCL11 (100 and 500 pg/mL) reduced proliferation and migration (P < 0.01) in PTC.

**Conclusion:** To sum up we have shown that the cytokines (IFNgamma+TNF-alpha) induced a significant release of CXCL9 and CXCL11 in PTC cells. We have observed that PPAR-gamma agonists stimulated chemokines secretion, while inhibited proliferation in PTC cells. Furthermore PTC cells proliferation and migration were inhibited by these chemokines.

**OP-05-33**

**EXPRESSION OF TERT IN PAPILLARY THYROID CANCER AND BIOLOGICAL EFFECTS OF hTERT SILENCING IN HUMAN PAPILLARY THYROID CANCER CELLS**

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TERT promoter mutations carry out an important role in the tumorigenesis of less differentiated human thyroid carcinomas, in which are present with high prevalence making TERT an eligible molecular target for the treatment of these neoplasms. Less clear is the role of TERT in the papillary thyroid cancer (PTC). Recently, a significant association of the co-presence of TERT promoter mutations and BRAF V600E mutation with several aggressive clinicopathological characteristics of PTC has been described.

Aim of this study was to analyze the expression levels of TERT in a series of PTC tissues and its pathogenic role by evaluating the effects of hTERT silencing on the growth and migration properties of two human PTC cells, both carrying the BRAF V600E mutation. In addition, we investigated the molecular mechanism underlying hTERT silencing action.

Expression levels of TERT transcript were measured in 48 PTC tissues collected from patients subjected to total thyroidectomy by real time RT-PCR. The effects of RNA-mediated silencing of hTERT were analyzed in BCPAP and K1 cells, by MTT and migration assays, while western blot analysis was performed to detect the expression levels of phospho-AKT, phospho-ERK and β-catenin.

mRNA hTERT expression was detected in 22/48 (45.8%) PTC tissues, including tumors either positive (n = 6) or negative (n = 16) for the presence of hTERT promoter mutations. Three cases carried also a BRAF V600E mutation.

A relationship between mRNA hTERT expression levels and an aggressive phenotype was present (according to ATA risk of recurrence). In BCPAP and K1 cell lines, hTERT silencing determined a significant reduction of the growth and migration properties (about 70% vs controls). Such an effect was associated with a reduction of AKT phosphorylation and β-catenin expression levels.

Our findings demonstrate that in subgroups of aggressive PTCs, TERT expression can be detected even in the absence of gene promoter mutations. Moreover, the anti-proliferative and anti-migration effects on PTC cells suggest that hTERT may represent an optimal candidate to be targeted also in selected PTCs.

**OP-05-34**

**VAV3 ACTS AS A TUMOR SUPPRESSOR IN THYROID CANCER**

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**Introduction:** The VAV family of proteins is a highly conserved group of tyrosine phosphorylation-regulated signaling molecules that function as GTPase exchange factors of the RhoA family of proteins. Furthermore their ability to interact with many different partner proteins and to generate multiple second messenger molecules point them as central regulators of signaling events arising from both transmembrane and intracellular tyrosine kinase proteins. VAV mutations have not been reported in human cancer however their role in the progression of different types of cancer has been clearly established. A possible involvement of VAV proteins in thyroid cancer progression has not been investigated but interestingly an association between VAV3 SNPs (single nucleotide polymorphisms), hypothyroidism and PTC susceptibility has been reported (Nat Commun. 2017, 13; 8:15966).

**Objective:** Our purpose in this project was to analyze the role of VAV3 in the progression of thyroid cancer and in the control of thyroid differentiation.

**Methods:** Analysis of Thyroid Cancer Genome Atlas (TGCAna) database. Human thyroid tumor-derived cell lines and differentiated rat-derived cell lines expressing different versions of VAV3 protein of human origin or with impaired VAV3 expression. Immunoblot and immunofluorescence, RT-qPCR, cell viability, migration and invasion assays.

**Results:** By TCGA database analysis we found that VAV3 mRNA is highly downregulated in mutant BRAF vs. mutant RAS or RET/PTC human PTCs. Furthermore high VAV3 levels correlate with a higher differentiation state and increased expression of TG, DUOX1, DUOX2 and FOXO1. Decreased VAV3 expression is associated with a higher degree of extrathyroidal extension and recurrence of the disease. Ovarexpression of VAV3 modifies cytokine architecture and regulates migration, invasion and proliferation of ATC-derived human cell lines. In addition VAV3 controls the differentiation state of rat-derived cell lines by increasing the expression of thyroid differentiation markers.

**Conclusion:** VAV3 is a novel tumor suppressor in thyroid cancer and it is involved in the control of the differentiated state of thyroid cells. VAV3 could be a marker of good prognosis in the progression of thyroid cancer.

**OP-05-35**

**EMBRYONIC THYROID CELLS RESIST BRAFV600E-INDUCED DEDIFFERENTIATION**

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**BRAFV600E** mutation is the most common oncogenic driver in papillary thyroid cancer (PTC). Besides inducing neoplastic growth constitutive activation (CA) of the MAPK pathway by mutant Braf confers loss of thyroid function by repressing the expression of the sodium-iodide symporter (NIS), which explains resistance of BRAFV600E positive thyroid tumors to radioactive iodine (RAI) treatment. Raf kinase inhibitors restore radioactive iodine uptake in mutant human PTCs. Recent studies in animal models indicate that proper organ and tissue development during embryogenesis is remarkably robust to perturbations of MAPK signaling, buffered by yet poorly characterized compensatory mechanisms. In this study, searching for novel means to antagonize oncogene-induced thyroid dedifferentiation, we addressed the possibility that embryonic thyroid cells might respond differently to BrafV600E than adult thyroid cells.

**Objectives:** To investigate the effect of mutant Braf on developmental thyroid growth and differentiation in mouse embryos.

**Methods:** Mice carrying BrafV600E (BrafW500E) were recombined with Nkx2-1 Cre (constitutive) or TgCreERT2(T2) (inducible with tamoxifen) mice to generate embryos in which BrafV600E is conditionally expressed in, respectively, Nkx2-1 and Ptc1 thyroid progenitors from embryonic day E9.5 and differentiated follicles expressing thyroglobulin (Tg) as Cre driver from E15.5 onwards.
Lineage tracing using a double fluorescent (mTmG) reporter mouse confirmed thyroid-specific transgene expression. Thyroids in embryonic (E12.5, E18.5), postnatal (P0, P10, P30) and adult (3–12 mo) mutant and wildtype mice were investigated by immunofluorescence. Thyroid gene expression was analyzed with qRT-PCR.

**Results:** Nkx2-11 progenitors expressing mutant Braf showed accelerated proliferation leading to a 4-fold increased size of the thyroid primordium. BrafV600E did not disturb the normal morphogenetic program resulting in a giant thyroid gland that had a normal anatomical shape and position at birth (P0). Remarkably, mutant cells synchronously expressed Tg and formed follicles corresponding to the natural process of de novo thyroid differentiation. Moreover, wildtype and Braf mutant thyroid cells showed equal transcript levels of Pax8, Nis, Tpo ad Tg at P0. Nkx2-11/CreBrafV600E mice died neonatally due to defective lung development. In TgCreBrafV600E mice mutant Braf repressed all thyroid differentiation genes except TSHR already at P10, and eventually generated metastatic PTC tumors.

**Conclusions:** Mouse thyroid progenitors expressing mutant Braf differentiate normally to follicle cells. Thyroid genes including NIS are not downregulated although constitutive MAPK signaling drives proliferation of these cells. This uncovers novel features of thyroid differentiation mastered by developmental cues that might be exploited to counteract RAI-refractoriness in thyroid cancer.

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**OP-05-36 DEPENDENCE OF THYROID TUMORIGENESIS ON miRNA PROCESSING BY DICER1 IN VIVO**

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Perturbed microRNA (miRNA) regulation accompanies thyroid cancer suggesting a possibility that altered miRNA expression might impact on tumor development and progression. Indeed, germline mutations of DICER1 encoding an endoribonuclease of crucial importance for pre-miRNA processing confer familial multinodular goiter with an increased risk of developing papillary thyroid cancer (PTC). It is also known that BrafV600E, the most common thyroid oncogenic mutation, induces distinct changes in the miRNA expression profile that promote growth of cultured thyroid cells. However, functional in vivo studies on the putative impact of Dicer1 and miRNAs on thyroid tumorigenesis are lacking.

In murine models, constitutive inactivation of Dicer1 in thyroid progenitors or embryonic follicle cells does not influence thyroid development but progressively destroys thyroid morphology and impairs function leading to overt hypothyroidism postnatally. In contrast, deletion of Dicer1 in adult mouse thyroid cells by inducible Cre, expressed by the thyroglobulin promoter, generates more subtle glandular changes suitable for functional studies. Recently, Dicer1 deficiency was found to strongly inhibit thyroid growth in vitro and in vivo but whether neoplastic thyroid growth is Dicer1-dependent is unknown.

**Objectives:** To investigate the contribution of miRNA in BrafV600E-induced thyroid tumorigenesis.

**Methods:** Dicer1 was conditionally deleted (ko) simultaneously with activation of mutant Braf in TgCreBrafV600E and TgCreBrafV600E/Dicer1fl/fl mice, either globally by tamoxifen injection (tam+) at 4 weeks of age or multifocally by spontaneous Cre activation (tam−) occurring in a minority of cells. Thyroids excised after 3, 6 and 12 months (mo) were processed for HE-staining and immunohistochemistry on serial sections and quantitative RT-PCR analysis of gene expression.

**Results:** Mutant Braf stimulated follicle cell proliferation and generated CK19 tumors with a papillary histotype after 6–12 mo most notably in the sporadic (tam−) tumor model. Dicer1 ko inhibited sporadic tumor growth at all time points with preserved follicular architecture among few pre-malignant lesions. Dicer1 ko retarded tam+ global thyroid growth although tumors eventually developed. Notably, this was accompanied by altered numbers of Ki67+ cells, reduced after 3 mo but increased after 6 mo in comparison to age-matched TgCreBrafV600E mice. Thyroid genes (TSHR, Tg, NIS, TPO) were repressed in TgCreBrafV600E/Dicer1fl/fl but not in TgCreDicer1fl/fl mice. Hemizygous deletion of Dicer1 did not reduce tumorigenesis by mutant Braf.

**Conclusions:** This study provides proof of concept that tumor initiation and early development of thyroid cancer in vivo require the normal machinery for miRNA biogenesis. Nonetheless, impaired Dicer1 function may promote growth of tumor clones progressing to PTC.

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**OP-05-37 PROTEOMIC CHANGES IN BENIGN FOLLICULAR ADENOMA VERSUS MALIGNANT FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA**

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The tumor and adjacent nontumor thyroid tissue fragments from the resected thyroid glands were collected and analyzed from 18 females (17–66 years) divided into two groups, one with benign FTA (n = 9, average age 52 ± 9 years) and the other with FVPTC (n = 9, average age 45 ± 16 years). Control thyroid tissue (CTA and CFVPTC) was collected by the hospital pathologist and defined as adjacent to the site of lesion with no histological markers of abnormal pathology. Tumor and nontumor adjacent samples were analyzed by liquid chromatography mass spectrometry, and protein abundance was evaluated by label-free quantitation. Western blotting and quantitative real-time polymerase chain reaction were used to validate and complement the mass spectrometry data. The differentially expressed proteins in CTA and CFVPTC were merged and retained for further comparative benign versus malignant analysis. Thus, 604 proteins were found to be uniquely and differentially altered in FTAs compared with their reference thyroid tissue (CTA/CTFTA), while 318 proteins presented a significantly altered abundance only in the follicular variant of papillary thyroid carcinoma (FVPTC/CFVPTC). 1120 proteins were differentially expressed in both groups. To be noted is that the majority of proteins were found to be up-regulated in both CTA and FVPTC groups when compared with their respective controls. Six proteins involved in this signaling pathway repetitively presented a significant alteration of spectral abundance in benign follicular adenoma or FVPTC versus adjacent control thyroid tissue. The results demonstrated deregulated expression of four endoplasmic reticulum chaperones (78 kDa glucose-regulated protein, endoplasmic, calnexin, protein disul-fide-isomerase A4) of glutathione peroxidase 3 and thyroglobulin, all of them involved in thyroid hormone synthesis pathway. The altered tissue abundance of endoplasmic reticulum chaperones in thyroid cancer was correlated with serum biomarkers of abnormal pathology. Tumor and nontumor adjacent samples are available via ProteomeXchange with identifier PXD004322.

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**OP-05-38 THE SIX1 HOMEOPROTEIN REGULATES THE SUPPRESSIVE AND ONCOGENIC EFFECT OF TGFB PATHWAY**

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The SIX1 homeodomain protein is a developmental transcription factor that has been related to tumour initiation and progression. A low SIX1 expression has been described in normal epithelial adult tissues, whereas in some...
epithelial cancer types is increased. SIX1 acts as a transcriptional repressor or activator depending on protein interactions. Some of the SIX1 targets are ZEB1, CDH1, CCND1, CCNA1, and MYC, which are related with cell proliferation and epithelial to mesenchymal transition (EMT). In addition, TGFβ pathway has been described as an activator of SIX1 expression in cancer samples.

Our objectives were to study the role that SIX1 plays in the thyroid cancer progression and its connection with the TGFβ pathway as a possible EMT regulator.

We observed that normal thyroid differentiated rat cell line PCC13 and human control cell line Nthy-ori 3-1 expressed lower SIX1 mRNA and protein levels than human thyroid cancer cell lines. TGFβ decreased SIX1 mRNA and protein levels in normal PCC13 cells, Nthyori 3.1 and some of the cancer cell lines whereas in other cancer cell lines TGFβ increased SIX1 levels. In these last cell lines, we found that TGFβ binds to the SIX1 promoter by electrothropic mobility shift assay (EMSA) and chromatin immunoprecipitation (ChIP) and ZEB1 overexpression increased SIX1 mRNA expression. We next generated stable SIX1 cell lines by retroviral infection and observed that SIX1 increased cell proliferation and cell migration.

These findings reveal a hypothetical loop in which ZEB1 is able to upregulate or downregulate the levels of SIX1 depending on TGFβ context and consequently regulating the expression itself. Therefore, SIX1 has an important role in how TGFβ affects the follicular thyroid cell function.

Monday, 17th September 2018

Oral Session 6: Update in Treatment of Thyroid Cancer

OP-06-39
ACTIVE SURVEILLANCE IN LOW RISK PAPILLARY THYROID CARCINOMA: A MULTICENTER COHORT STUDY IN KOREA

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Context: Recently, the concept of active surveillance has been introduced as a management option for low-risk papillary thyroid carcinoma (PTC) due to its indolent nature.

Methods: This is a multi-center cohort study including 369 low-risk PTC patients who underwent active surveillance rather than immediate surgery. Significant tumor size increase on ultrasonography (US) was defined as maximum diameter increase over 3 mm or significant volume increase over 50% from the baseline.

Results: The mean age of patients at diagnosis was 51.1 years and 284 patients (77.0%) were female. The initial maximum diameter and volume of PTCs in US were 5.8 ± 1.7 mm and 79.0 ± 68.1 mm³. During median 32.0 months of follow-up, 83 patients (22.5%) experienced tumor size increase and 13 patients (3.5%) had maximum diameter increase over 3 mm. The cumulative incidence of tumor size increase gradually increased overtime (6.0% at 2 years, 16.4% at 3 years, 28.2% at 4 years, 36.3% at 5 years, and 47.7% at 6 years). The risk for tumor size increase in patients younger than 45 years was two times higher than in older patients (p = 0.003). There was no significant difference in tumor size changes according to sex, hashimoto’s thyroiditis or thyroxine replacement during active surveillance. During the follow-up, 58 patients (15.7%) underwent delayed thyroid surgery due to anxiety (37.9%), tumor size increase (32.8%), appeared new cervical lymph node (LN) metastasis (8.6%), and location of the tumor (6.9%). After delayed surgery, 29.3% of patients had LN metastasis on the final pathology.

Conclusions: A significant number of PTCs might grow during active surveillance and tumor volume change was a more sensitive index to evaluate the size change of tumor. Active surveillance should be carefully applied in selected patients and may not be appropriate for younger patients.

OP-06-40
HYPOTHALAMIC-PITUITARY-ADRENAL AXIS DYSFUNCTION IN PATIENTS RECEIVING TYROSINE-KINASE INHIBITORS FOR ADVANCED THYROID CANCER

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Background: Fatigue is a major and frequent side effect occurring during treatment with two tyrosine-kinase inhibitors (TKIs), Lenvatinib and Vandetanib, widely used for advanced radioidine refractory differentiated (RAI-R-DTC) and medullary thyroid (MTC) carcinomas. To relief patients from this side effect, which strongly affects quality of life, an increase in the daily physical activity has been suggested, but in most cases the reduction of the drug dosage is needed. A possible effect on adrenal function has been reported for some TKIs, but not for Lenvatinib and Vandetanib.

Methods: We evaluated 12 patients (7 females/5 males, mean age 57 yrs) with advanced RAI-R-DTC and MTC during treatment with Lenvatinib (n = 7) and Vandetanib (n = 5) and followed up at a single Institution. All patients were submitted to a basal evaluation of adrenal function and were administered with a questionnaire (CTCAE Version 4.0.) aimed to evaluate the degree of fatigue. Moreover, in 10 of them the serum cortisol response to 250 μg ACTH test was tested, too.

Results: After an average of 8.8 ± 1.09 months of treatment, 8/12 (67%) patients showed a progressive increase in ACTH levels with cortisol basal levels within normal limits: 2/5 patients were on Vandetanib and 6/7 patients on Lenvatinib.

Moreover, 5/11 patients (45%) showed an impaired response of cortisol upon ACTH infusion, thus allowing to confirm the diagnosis of primitive adrenal insufficiency. All patients underwent abdominal ultrasound and the presence of adrenal gland lesions was ruled out.

Patients with an established diagnosis of adrenal insufficiency were given cortisone acetate replacement therapy at the standard dosage, leading to a significant improvement in the degree of fatigue (from Grade 2 to Grade 1 in all cases). Nevertheless, the 6 patients receiving cortisone acetate therapy (25–35 mg/d) showed a persistence of elevated ACTH values.

Conclusions: Our data indicate for the first time the occurrence of primary adrenal insufficiency during Lenvatinib and Vandetanib treatment, which is likely responsible for the fatigue documented in the majority of patients. The administration of cortisone acetate is significantly associated with the relief of symptoms. Therefore, it seems crucial to evaluate the hypothalamic-pituitary-adrenal axis and, upon diagnosis of primary adrenal insufficiency, to start a replacement treatment.
OP-06-41
RECOMBINANT HUMAN THYROTROPIN VS THYROID HORMONE WITHDRAWAL IN RADIOACTIVE IODINE THERAPY OF THYROID CANCER PATIENTS WITH NODAL METASTATIC DISEASE: A LARGE MULTICENTER RETROSPECTIVE MATCHED COHORT STUDY
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Context: Recombinant human thyrotropin (rhTSH) has been shown to be as effective as thyroid hormone withdrawal (THW) in the preparation for radioactive iodine (RAI) therapy in differentiated thyroid cancer patients (DTC) without distant metastasis, including patients with nodal metastatic disease (N+ DTC). However, there is lack of consensus regarding the degree of nodal involvement which is optimal for rhTSH stimulation.

Objectives: The primary objective of the study was to demonstrate non-inferiority of rhTSH vs. THW in terms of disease-free status (basal ultrasonography Tg <0.2 mg/L and/or stimulated-Tg ≤ 1 mg/mL, absence of TgAb and normal neck US) at the first follow-up control performed at 6–18 months post RAI therapy in the real-life setting in N+ DTC. Other objectives included identification of predictors (age, tumor size: pT1-T2/pT3, number of N+: ≤5 or >5, size of the largest N+: ≤1 cm, N1a/N1b…) of disease status using a logistic regression model, and description of clinical and biological medium-term outcomes.

Design: Patients: This was a French multicenter retrospective, matched cohort study. Groups were matched in each participating center according to the age (<45 vs. ≥45 years), number of metastatic lymph nodes (≤5 vs. >5 nodes) and stage of tumour (pT1-T2 vs. pT3 according to pTNM 2010).

Results: The cohort consisted of 458 pT1-T3 thyroid cancer patients with lymph node metastases and no evidence of distant metastasis at the time of RAI therapy, prepared with either rhTSH stimulation (n = 205) or THW (n = 193). Patients and tumors characteristics and initial administrated radiiodine activities (3.27 ± 1.00 GBq) were similar between the two groups. Most patients had 5 N+ or less (90.7% and 91.9%, in rhTSH and THW respectively). On the initial post-therapy scan, 4.9% (rhTSH group) and 6.6% (THW group) had persistent iodine-avid lymph nodes and a single patient (THW group) had distant metastasis. At the first follow-up control, disease-free patients rate was not inferior in the rhTSH group (75.1% [95% CI: 68.6; 80.9]) compared to the THW group (71.9% [95% CI: 65.1; 78.0]). The last follow-up control (29.7 ± 20.7 in rhTSH group and 23.7 ± 23.8 months in the THW group), 83.5% (rhTSH group) and 81.5% (THW group) of patients achieved a complete remission status. None of these prognostic factors were found to affect the difference between rhTSH and THW on patient outcomes after RAI therapy.

Conclusions: rhTSH was non-inferior to THW for RAI therapy in our series of DTC patients staged pT1-T3/N1/M0.

OP-06-42
TAILORING LENVATINIB TREATMENT TO INCREASE RESPONSE AND TO LOWER SIDE EFFECTS
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Objectives: Lenvatinib has been approved for the treatment of progressive radioiodine refractory differentiated thyroid cancer. However, patients often present adverse events requiring a dose reduction.

Methods: From July 2015 to March 2018, seven patients treated with Lenvatinib were followed-up for a mean period of 12.6 months.

Results: The seven patients treated (four women, median age at Lenvatinib initiation: 67 years) had papillary (three patients), follicular (two patients), and insular (two patients) thyroid cancer. All patients had ECOG performance status ≤ 1. Lenvatinib treatment was started on average 27.6 months (range 1–83) after the appearance of the lesion/s for which we decided to start the treatment. Due to the possible risk of fistulization, two patients with tracheal infiltration started Lenvatinib at a low dose (10 mg/day). The other five patients started Lenvatinib at a 20 mg/day dose. Two of them reduced the dosage: one patient from 20 to 10 mg, after a two-week period of drug interruption, because of reversible posterior leukoencephalopathy; the other patient from 20 to 14 mg due to uncontrolled adverse events.

The most frequently observed side effect was hypertension (six patients). It was controlled in all patients by a combination treatment with ACE-inhibitor and calcium antagonist drugs and in two patients with the addition of diuretics. Diarrhea was recorded in five patients and controlled by loperamide, accompanied by appropriate diet and fluid and electrolyte replacement. Fatigue was also frequent (five patients) and was associated to primary hypothyroism. It improved after the introduction of cortisone acetate. Stomatitis (three patients) was treated by cytoprotectors (such as hyaluronic acid gel) and sodium bicarbonate mouthwashes. Weight loss (three patients) required nutritional changes and was managed by a nutritionist. Two patients complained of hemorrhoids, in one case (grade 3) a hemorrhoidectomy was required. Palmar-plantar erythrodysesthesia syndrome (two patients) was treated with sensitive skin moisturizer. Skin ulceration, nausea, arthralgia, and hoarseness were less frequent or occasional.

Mean progression free survival was 12.6 months; no patients had progressive disease. Tumor response, according to RECIST criteria, was a partial response in 42.9% and a stable disease in 57.1% of patients. Thyroglobulin levels paralleled radiologic imaging and were extremely useful to indicate the effectiveness of treatment.

Conclusions: Lenvatinib treatment is affected by the occurrence of adverse events. A close monitoring and management of these side effects is crucial to continue the treatment and to limit the need of dose reduction, which may affect the treatment response.

OP-06-43
EFFECTICITY OF TYROSINE-KINASE INHIBITORS (TKI) AS SECOND-LINE TREATMENT IN ADVANCED THYROID CANCER
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Introduction: Tyrosine kinase inhibitors (TKI) represent treatment of choice in patients with advanced metastatic thyroid cancer for more than ten years. In phase II/III clinical trials treatment with TKI was able to determine an objective response [stable disease (SD) and/or partial response (PR)] in 60–70% of cases. However, an important limit of these therapies is the development of drug resistance. In clinical practice a second TKI is usually employed in case of progressive disease (PD) occurred after 1st TKI treatment, but so far few data are available on the TKI’s efficacy when used as second-line drugs.

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Objective: Aim of the study was to evaluate the efficacy ("best response" -BR) and the length of treatment with TKIs used as salvage therapy after the therapeutic failure of 1st TKI. The study group consisted of patients with differentiated or medullary advanced thyroid cancer treated with more than one TKI (n = 17 – Group-1) or with only one TKI (n = 39 – Group-2).

Results: In Group-1 the “BR” with the 1st TKI was evaluable in all patients [PR: 11.7%, SD: 70.6% and PD: 17.7%]. The median length of treatment was 28.1 months. Treatment was discontinued in 13/17 (76.4%) for PD and in 4/17 (23.6%) patients for adverse events. In Group-1, the “BR” with the 2nd TKI was evaluable in 13/17 patients [PR: 23.1%, SD: 50.0% and PD: 26.6%]. “BR” was not different between 1st TKI and 2nd TKI in Group-1, while with the 2nd TKI the length of treatment was lower respect to that observed with the 1st TKI (median 14.2 months). In Group-2 the “BR” was evaluable in 34/39 patients [PR: 29.4%, SD: 50.0% and PD: 20.6%]. “BR” was not different between Group-1 and Group-2. Last follow-up was available in 48/51 (94.1%) patients. The mortality rate in the total group was 66.6%; the median survival, calculated as the time between the start of therapy with TKI and patient death, was significantly higher in Group-1 [38.5 versus 13.5 months (p = 0.01)].

Conclusion: Second-line treatment with TKIs as salvage therapy allows to obtain a similar, but shorter objective response compared to that obtained during the 1st treatment. Therefore, patients who experienced PD during 1st TKI treatment should always be treated with other TKI, if available.

OP-06-44

RADIODINE TREATMENT AFTER THYROID HORMONE WITHDRAWAL OR RHTSH STIMULATION – A SINGLE CENTRE RETROSPECTIVE STUDY IN DISSEMINATED THYROID CANCER IN PAEDIATRIC PATIENTS

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Distant metastases are diagnosed in about 20% of children with DTC. Radioiodine is the treatment of choice, however there are limited data on optimal preparation for it.

The aim of our retrospective study was to evaluate effectiveness of radioiodine treatment after thyroid hormone withdrawal (THW) and rhTSH stimulation in metastatic paediatric DTC.

Patients: From 501 children diagnosed with DTC during the years 1988–2018, 72 (14.4%) had distant metastases (lungs – 66, bones – 2, both – 4). All 72 children were treated with radioiodine after THW (group A: 46 patients) or combination of rhTSH and THW cycles (group B: 26 patients). Median cumulated radioiodine activity was 16.8 GBq.

Results: Median time of observation in the whole group of patients was 11.5 years and was longer in group A (13 vs. 5 years, p < 0.05). During the last radioiodine treatment complete scintigraphic response was achieved in 63% and biochemical CR (Tg <2 ng/ml) in 24% (p < 0.05). Complete scintigraphic and biochemical response increased respectively to 86% and 40% during last follow-up on TSH stimulation. During last follow-up supressed Tg decreased below 1 ng/ml in 70% of children.

When we compared last radioiodine treatment in group A and B there was no statistically significant difference in scintigraphic (58% vs. 72%) or biochemical (25% vs. 18.5%) complete response. However, during last follow-up on TSH suppression complete biochemical response was higher in group A (84% vs. 46%, p < 0.05). In 6 patients treated under rhTSH stimulation only complete biochemical and scintigraphic response was achieved respectively in 1/6 (17%) and 5/6 (83%) patients.

No lung fibrosis nor secondary malignancies were diagnosed during follow-up

Conclusions: Our study confirms that radioiodine treatment of disseminated DTC in children/adolescents is safe and effective. To confirm complete remission long follow-up is necessary since response is extended over time. rhTSH seems not to decrease response rate to radioiodine treatment and observed difference between groups are probably related to shorter follow-up after rhTSH.
the 16 tumor foci was 79% (range 22–100%); 6 tumors (37%) were no longer identifiable by sonography.

**Conclusions:** UPEA for PTM was well tolerated and was substantially cheaper than conventional surgery. Our results suggest that, for PTM patients who do not wish neck surgery and are uncomfortable with “active surveillance”, UPEA likely represents an attractive and “minimally invasive” definitive management option.

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**OP-07-47**

**CORTICOSTERONE AFFECTS THYROID HORMONES INDUCED MODIFICATION OF THE METHYLMOME**

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**Objectives:** Acting on DNA methylation is an important means of regulating the expression of gene clusters and a central mechanism for coordinating developmental transitions. However, DNA methylation is dynamic and also integrate signals from the constantly changing environment. Thus, certain variation of DNA methylation at these developmental transitions can confer on the genome a risk situation that can have lifelong consequences (mental and behavioral illness, cardiovascular and metabolism diseases, cancer or decreased quality of life). In this context, thyroid hormones are both master regulator of developmental transitions and regulate the expression of genes coding for DNA methylation modifying enzymes. Furthermore, the diversity of thyroid hormone effects may be due to the integration of other physiological signals. One of them is the glucocorticoids, mediators of response to stress and essential for the survival of an organism and its adaptation in case of developmental transition and changes in the environments. Our objectives is to locate thyroid hormones and glucocorticoids effects on DNA methylation profiles to characterize potential determinants for certain pathologies and / or adaptation to a variation of the environment.

**Methods:** We have initiated the mapping of DNA methylation following treatment with T3 and corticosterone independently or in combination, using a method for capturing methylated DNA (MethylCap) combined with high-throughput sequencing (MethylCap-Seq). Our model of developmental transition is the amphibian metamorphosis, a post-embryonic process regulated by thyroid hormones and intertwined with glucocorticoids mediated stress. Indeed, metamorphosis can be either delayed or accelerated, making glucocorticoids an important interface between environmental cues and thyroid hormone controlled developmental process. Additionally, stress during metamorphosis might also induce potential phenotype propagation to adult forms, highlighting its importance in driving adaptation to fluctuating environments. We have also compared hormones induced methylation profiles in the hind limb and caudal epidermal, two organs with contrasted fate (respectively morphogenesis and cell death).

**Results:** The presence of the two hormones does not have the effect of adding the effects of these hormones alone. A strong tendency for DNA methylation markers to be removed following treatment with T3 and corticosterone is observed. The majority of differential methylated regions (DMR) are tissue specific. However, some DMRs are found in both tissues and show either identical or opposite variations. The DMRs are generally not localize near genes regulated or not by the two hormones.

**Conclusions:** Several tissue specific variations of the methyleome and cross-effects of the T3 and corticosterone were observed.
thyroid explants from CD1 mice embryos were collected at embryonic day E8.5 and E14.5, respectively (ex vivo model). Thereafter the explants were exposed or not to IE treatment (10^-6 M) for 24 h or 48 h. Gene and protein expression were evaluated by RT-qPCR and Western Blotting, respectively. Furthermore, the involvements of epigenetic mechanisms were also analyzed.

Our results showed that mESC were successfully differentiated to thyrocytes and in thyroid explants. Finally, we demonstrated an increase of DNA methyltransferases expression as well as hypermethylated regions of histone H3 after IE exposure which suggest that an epigenetic mechanism is involved in the gene repression triggered by IE treatment in the ex vivo and in vitro models. In conclusion, these data report that IE treatment is deleterious for embryonic endoderm differentiation, and reinforce that IE programs endoderm and thyroid gene expression through epigenetic mechanisms during embryonic life.

Patients with an inactive thyroid hormone (TH) transporter MCT8 manifests severe failure of psychomotor retardation in combination with abnormal TH concentrations in the circulation (so-called Allan-Herndon-Dudley Syndrome (AHDS)). The neurological symptoms are most likely due to an impaired TH transport in the CNS and, consequently, a disturbed differentiation and maturation of neural cells. Passage of TH across the blood-brain barrier is also impeded in mice lacking the TH-transporters Mct8 and Oatp1c1. These so-called M/O dko mice display a delayed cerebellar development, diminished myelination and a disturbed maturation of GABAergic interneurons thereby replicating the abnormalities found in MCT8 patients.

Treatment of TH analogs with TH in the brain but are not dependent on MCT8 have been suggested as a therapeutic approach. Indeed, the analogs Triac and Dita have both been tested in animal models as well as in patients and were both able to normalize the peripheral thyrotropic state. Moreover, when applied to M/O dko mice both substances were able to partially restore normal brain development with Triac being more efficient than Dita.

Here, we tested the efficacy of four novel TH analogs for the treatment of AHDS. These compounds are different prodrugs of sobetirome (GC-1) that are known to partially restore normal brain development with Triac being more efficient in both mESC-derived endoderm cells and thyroid explants. Interestingly, the main thyroid markers were also reduced in mESC-derived thyrocytes and in thyroid explants. Finally, we demonstrated an increase of DNA methyltransferases expression as well as hypermethylated regions of histone H3 after IE exposure which suggest that an epigenetic mechanism is involved in the gene repression triggered by IE treatment in ex vivo and in vitro models. In conclusion, these data report that IE treatment is deleterious for embryonic endoderm differentiation, and reinforce that IE programs endoderm and thyroid gene expression through epigenetic mechanisms during embryonic life.

**OP-07-50**

**THYROMIMETIC POTENTIAL OF NOVEL TH ANALOGS IN PRIMARY NEURONS AND IN TH TRANSPORTER DEFICIENT MICE**

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**OP-07-51**

**3-IODOTHYRONAMINE AMELIORATES ISCHEMIA-INDUCED SYNAPTIC DYSFUNCTION IN MOUSE ENTORHINAL CORTEX**

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**Objectives:** Abnormalities in thyroid hormone (TH) availability and/or metabolism have been hypothesized to contribute to Alzheimer’s disease (AD) and to be a risk factor for stroke. Recently, 3-iodothyronamine (T1AM), an endogenous amine putatively derived from TH metabolism, gained interest for its ability to promote learning and memory in the mouse. In the present work we investigated the effect of T1AM on ischemia-induced synaptic dysfunction in the entorial cortex, a brain area crucially involved in learning and memory and early affected during AD.

**Methods and Results:** Field excitatory post-synaptic potential (fEPSP) were recorded in EC/hippocampal horizontal slices obtained either from WT mice (C57Bl) or mice overexpressing a human mutant form of anyloid precur- sor protein (mhAPP). Slices were exposed to an oxygen-glucose deprivation protocol (OGD) for 10 min and then recorded for 50 min after reperfusion. T1AM was perfused to slices at the concentration of 5 μM for 10 min during the application of OGD. The effect of T1AM was compared to that of RO5166017 (250 nM), a specific agonist of trace amine-associated receptor 1 (TAAR1), which is considered as the chief molecular target of T1AM. A long-lasting synaptic depression was induced by OGD in WT slices. As previously reported, OGD effect was enhanced in EC slices form mhAPP mice (mean fEPSP amplitude in the last 10 min of recording was of 59 ± 4% of baseline n = 6 slices, 5 mice). However, T1AM perfusion was capable of preventing the long lasting synaptic depression after OGD either in WT slices or mhAPP slices (mean fEPSP amplitude in mhAPP+T1AM was 104 ± 2% of baseline; p < 0.001 vs mhAPP untreated slices; n = 4, 3 mice). A similar protective effect was achieved by the perfusion with RO5166017 (mean fEPSP amplitude was 108%±3% of baseline in mhAPP+RO5166017, p < 0.001 vs. mhAPP untreated slices; n = 4, 3 mice).

**Conclusions of the Study:** T1AM ameliorates ischemia-induced synaptic dysfunction in the EC. This effect was confirmed in an amyloid enriched environment. RO5166017 demonstrated a similar efficacy, suggesting the involvement of TAAR1 in T1AM-mediated neuroprotection.
somewhat higher body mass index. The endocrine function of the adult pancreas was assessed by real-time PCR at 7 months, showing that both insulin and glucagon mRNA expression was drastically upregulated in Dio2KO fish. Moreover, immunohistochemical staining of pancreas cryosections for insulin showed a strong increase in signal intensity, indicative of elevated protein content, as well as a higher number of insulin-producing β cells. Measurement of insulin and glucagon receptor expression in different tissues is ongoing. We also measured blood glucose at 8 and 11 months of age and found significantly higher levels in fasted as well as fed Dio2KO fish.

Conclusion: These combined results indicate that hypothyroid Dio2KO zebrafish are hyperglycemic and show signs of insulin resistance, two putative aspects associated with diabetes type 2. This indicates the potential use of our Dio2KO zebrafish line as a disease model to study the mechanisms underlying the link between adverse DIO2 polymorphisms and sugar metabolism.

OP-07-53

THE THYROID HORMONE RECEPTOR B DEPLETS THE BREAST CANCER CELL POPULATION IN ESTROGEN-DEPENDENT MCF-7 CELLS

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More than 70% of breast cancers express high levels of the estrogen receptor (ERα), and require estrogen for sustained growth and progression. A subpopulation of highly tumorigenic cancer cells that display stem cell properties (cancer stem cells or CSCs) show activation, progression and relapse of breast tumors. CSCs have the capacity for self-renewal, can form mammospheres under non-adherent conditions and can be identified by a CD44+/CD24- and ALDH+ phenotype. Since expression of the thyroid hormone receptor β (TRβ) in the ERα-luminal MCF-7 cell line decreases tumor growth in immunodeficient mice (Park et al., 2013. Am.J.Cancer.Res. 3:302–11), we have analyzed the possibility that the receptor could affect the CSC population. Treatment of TRβ-expressing MCF-7 cells (MCF7-TRβ) with T3 decreased significantly the population of CD44+/CD24- and ALDH+ cells, indicating a reduction in the number of CSCs. Accordingly, T3 reduced the efficiency of mammosphere formation, showing that the hormone decreases the number of CSCs with self-renewal capacity. T3 also reduced the expression of the pluripotency factors Sox2, Nanog or ALDH in the mammospheres, as well as the expression of ERα. In contrast TRβ expression was higher in the mammospheres than in the adherent cultures, suggesting that CSCs could be highly responsive to the hormone. T3 also inhibited activation of NF-κB and SMAD signaling pathways essential for breast CSC self-renewal and tumorigenesis and decreased migration and invasion of MCF7-TRβ cells, a hallmark of CSCs. Furthermore, TRβ-expressing cells showed strongly reduced tumor initiating capacity when injected at limiting numbers into the fat mammary pads of immunodeficient mice. Transcriptome analysis of mammospheres confirmed downregulation of ER-responsive genes upon T3 treatment. Furthermore, among the repressed genes in response to T3 there was an enrichment in genes containing binding sites for other transcription factors such as FOXA1, FOXM1, GATA3 or ZNF217 that are key determinants of luminal-type breast cancers and are required for ER binding to chromatin. These results indicate a novel role of TRβ in the biology of CSCs that may be related to its action as a tumor suppressor in ERα+ breast cancer tumors.

OP-07-54

IDENTIFICATION OF THYROID HORMONE TRANSPORTERS IN A HUMAN PLACENTAL CELL MODEL

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Introduction: Fetal development in the first half of pregnancy is dependent on maternal thyroid hormone (TH). This highlights the importance of the placenta as a human placental TH transport. Of the known TH transporters, the monocarboxylate transporters MCT8 and MCT10, the L-type amino acid transporters LAT1 and LAT2, and the organic amino acid transporting peptides OATP1A2 and OATP4A1 are expressed in human placenta. In this study, we used pharmacological inhibitors to identify the major TH transporters in a human placental cell model (BeWo cells).

Methods: mRNA expression levels of the known TH transporters in BeWo cells were measured by quantitative PCR. To measure TH uptake, cells were incubated with 1 nM 125I-T3 or 125I-T4 and the amount of radioactivity in the cell lysates was measured in a gamma counter. To determine the efficacy and specificity of the pharmacological inhibitors, we first overexpressed TH transporters in COS1 cells and determined TH uptake and cellular toxicity at different inhibitor concentrations. We then tested TH uptake in BeWo cells in the presence or absence of the optimal inhibitor concentrations.

Results: Quantitative PCR analysis indicates that all tested TH transporters except MCT8 are expressed in BeWo cells. In COS1 cells overexpressing these TH transporters, 2-Amino-2-norbornancarboxylic acid (BCH) specifically inhibited LAT1 and LAT2 while L-tryptophan inhibited LATs and at the highest dose (10 nM) also MCT10. Verapamil inhibited both MCTs and OATP1A2 but not LATs. Both rifampicin and naringin inhibited OATP1A2. Furthermore, silychristin strongly inhibited MCT8, but not MCT10, at a low dose (100 nM) and OATP1A2 at the highest dose (10 μM). In BeWo cells, verapamil, BCH and 1 mM L-tryptophan reduced T3 uptake by 27%, 30% and 42% respectively. The combination of BCH and verapamil or BCH and 10 μM L-tryptophan further decreased T3 uptake by 56% and 59% respectively, suggesting a major role for MCT10 and LATs in T3 uptake. The role of MCT10 was confirmed by transfecting BeWo cells with MCT10-specific siRNA, which resulted in a 19% reduction in T3 uptake. Verapamil also decreased T4 uptake by 28%, indicating part of the T4 uptake is facilitated by verapamil sensitive transporters.

Conclusion: TH uptake assays with the inhibitors indicate that MCT10 and LATs play a major role in T3 uptake in BeWo cells. T4 is partially dependent on verapamil sensitive transporters, however, the majority of T4 transport is still unaccounted for.

Oral Session 8: Autoimmunity, Graves’ Orbitopathy, Genetics

OP-08-55

T AND B CELLS INFILTRATING ORBITAL TISSUES IN GRAVES’ ORBITOPATHY (GO) AND THEIR RELATION WITH GO ACTIVITY. A POSSIBLE EXPLANATION FOR GO RESPONSE TO IMMUNOSUPPRESSIVE TREATMENTS

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Graves’ orbitopathy (GO) responds to immunosuppressive treatments when active but poorly when inactive. In other autoimmune diseases, response has been ascribed to a reduction in lymphocytes infiltrating the target organ. To investigate whether this occurs also in GO, we designed an observational, cohort study, aimed at assessing the extent and immunohistochemical pheno-
type of orbital lymphocytes and relate it with the ophthalmological features of GO, especially its clinical activity score (CAS). The population included 8 men and 12 women, all Caucasians (age: 46 ± 13 yr), who underwent orbital decompression surgery. Orbital tissues samples were collected and subjected to histology and immunohistochemistry. Having established a cut-off value of 300 lymphoid cells per sample, lymphocytes above this value were found in 9/20 patients (45%), often organized into distinct foci. They comprised a mixture of T (CD3-positive) and B (CD20-positive) cells, suggesting a mature, polyclonal autoimmune response. In a simple linear regression model, the total number of lymphocytes, as well as the number of CD3- and CD20-positive subsets, correlated with CAS (R: 0.63, 95% CI: 0.27–0.84, P = 0.003; R: 0.59, 95% CI: 0.20–0.82, P = 0.006; and R: 0.65, 95% CI: 0.30–0.85, P = 0.002, respectively). In a multiple linear regression model, lymphocytes maintained their effect on CAS when adjusted for smoking and GO duration, two additional variables that were also correlated with CAS, highlighting even more the important role that orbital lymphocytes play in affecting CAS (total number: R: 0.58, 95% CI: 0.18–0.82, P = 0.01; CD3-positive: R: 0.58, 95% CI: 0.17–0.82, P = 0.01; CD20-positive: R: 0.59, 95% CI = 0.19–0.83, P = 0.01). This study shows a correlation between T and B lymphocytes infiltrating orbital tissues and the activity of GO, possibly enhancing our understanding of the relation between GO immunological features and clinical expression.

OP-08-56
DILUTION ANALYSIS OF THYROID STIMULATING ANTIBODIES DIFFERENTIATES BETWEEN Graves’ THYROIDAL AND ORBITAL DISEASE
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Objective: Serum levels of TSH receptor (TSH-R) stimulating antibodies (TSAb) correlate with clinical activity and severity of Graves’ thyroidal disease (GD) and associated orbitopathy (GO). We hypothesized a highly significant differentiation between patients with GD versus GD+GO by analyzing TSAb levels in serially diluted serum samples.

Methods: Twenty well-characterized patients with GD without GO (median, 25th-75th percentile, 38.1 years, 31.5–50.3, 15 female), and 20 well-differentiated patients with GD+GO (55.7 years, 43.7–65.8, 18 female) were investigated. Serial 1:3 dilutions were performed on each patient sample (200 μl) into TSAb-negative control serum (400 μl) up to a final dilution of 1:6561. Results from the TSAb bioassay (Thyretain, Queidel, cut-off SRR% 140) were compared with five TSH-R-Ab binding immunoassays: Kronus ELISA (1 IU/L), Dynex ELISA (2 IU/L), Cobas (Roche, 1.75 IU/L), Immulite (Siemens, 0.55 IU/L), and Kryptor (Thermofisher, 1.8 IU/L).

Results: All undiluted samples of hyperthyroid patients with GD only were positive in the TSAb bioassay (median SRR% 237, range 217–336) and became negative at dilution 1:27. In contrast, all undiluted samples of hyperthyroid patients with GD+GO were positive in the TSAb bioassay (627, 576–752) and all remained positive at dilutions 1:3 (626, 528–871), 1:9 (590, 520–874), 1:27 (525, 463–627), and 1:81 (347, 292–442), all p < 0.001. The positivity rate of TSAb at dilution step 1:3 between patients with GD versus GD+GO was markedly different (p = 0.004). At very high dilutions, 1:243 (259, 195–314), 1:729 (159, 150–249), 1:2187 (162, 162–162), the rate of TSAb-positivity for GD+GO patients was 75%, 35% and 5%, respectively (all p < 0.001). All of the GD+GO samples became negative at a dilution of 1:6561. TSH-R-Ab positivity with the Cobas binding assay was 85% (5.9 IU/L, 3.3–7.8) in undiluted GD samples only and 50% (2.6, 2.3–3.8) at dilution 1:3 whereas TSH-R-Ab positivity of undiluted GD+GO samples and at dilutions 1:3–1:243 was 100%, 85%, 85%, 75%, 15% and 5%, respectively. Even after metamizole treatment, all GD+GO samples were still positive at the very high dilution of 1:729. The five binding ELISA and/or automated immunoassays confirmed this marked difference of anti-TSH-R-Ab detection between GD versus GD+GO observed in all GD+GO samples were still positive at the very high dilution of 1:729. TSH-R-Ab positivity in GD samples only and 50% (2.6, 2.3–3.8) at dilution 1:3 whereas TSH-R-Ab positivity of undiluted GD+GO samples and at dilutions 1:3–1:243 was 100%, 85%, 85%, 75%, 15% and 5%, respectively. Even after metamizole treatment, all GD+GO samples were still positive at the very high dilution of 1:729. The five binding ELISA and/or automated immunoassays confirmed this marked difference of anti-TSH-R-Ab detection between GD versus GD+GO observed in all GD+GO samples were still positive at the very high dilution of 1:729.

Conclusions: This novel TSAb dilution analysis significantly differentiates between GD and GD+GO. It also emphasizes the higher sensitivity of anti-TSH-R-Ab detection in the TSAb bioassay versus all ELISA and automated binding assays.

OP-08-57
BLOCKING THE TSH RECEPTOR WITH THE HUMAN MONOCLOAL AUTOANTIBODY K1-70(TM) IMPROVES GRAVES’ OPHTHALMOPATHY AND AIDS CONTROL OF ADVANCED FOLLICULAR THYROID CARCINOMA – RESULTS OF LONG-TERM TREATMENT UNDER THE FIRST IN HUMAN SINGLE PATIENT EXPANDED USE THERAPY
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Introduction: The human monoclonal autoantibody to the TSH receptor (TSHR) K1-70™, inhibits cyclic AMP mediated TSHR signaling by TSH or stimulating TSHR autoantibodies (TRAbs). Expression of the TSHR in orbital fibroblasts may be linked to the pathogenesis of Graves’ ophthalmopathy (GO). Therefore K1-70™ has potential therapeutic use to control the TSHR activity in Graves’ disease (GD) and GO and to block TSHR signaling in advanced well differentiated thyroid cancers. The results of the first in human, single patient expanded use therapy with K1-70™ in a patient with advanced, well differentiated follicular thyroid carcinoma (FTC) complicated by high levels of stimulating TRAbs and severe GO are reported.

Clinical Case: A 54 year old female smoker presented with GD, GO and locally advanced and distant metastatic well-differentiated FTC. Her disease progressed rapidly despite multiple neck operations, thoracotomies and high dose I-131 therapies. She had severe GO with diplopia, clinical activity score (CAS) 6 (of 7) and exophthalmometry of 21 bilaterally with chemosis, injection, lid swelling, pain with eye movement, spontaneous pain, and lid erythema. TRAb levels were 80 IU/L with thyroid stimulating immunoglobulin (TTSI) levels of 11 (reference <1.3 U/ml).

There was a partial structural response of disease following 4 months of lenvatinib (24 mg) with an initial decrease followed by a slow increase in serum thyroglobulin. However GO continued to progress with proptosis at 97 remaining 21 bilaterally. Quality of life (QoL) was 6/10.

The patient was initiated on 3-weekly intramuscular injections of K1-70™ in combination with 20 mg lenvatinib on a FDA-authorized single patient PIV of GD and advanced FTC, K1-70™ therapy, the rate of tumor progression was attenuated on K1-70 alone and her QoL score improved to 9/10.

There was an overall structural response of disease following 4 months of lenvatinib (24 mg) with an initial decrease followed by a slow increase in serum thyroglobulin. However GO continued to progress with proptosis at 97 remaining 21 bilaterally. Quality of life (QoL) was 6/10.

The patient was initiated on 3-weekly intramuscular injections of K1-70™ in combination with 20 mg lenvatinib on a FDA-authorized single patient PIV of GD and advanced FTC, K1-70™ therapy, the rate of tumor progression was attenuated on K1-70 alone and her QoL score improved to 9/10.

Conclusions: These observations indicate that blocking TSHR activity with K1-70™ may be an effective strategy to control GO. Furthermore, in patients with Graves’ disease and advanced FTC, K1-70™ may have an additional suppressive effect on tumor progression, either alone or in combination with other anti-neoplastic therapies.
THE OPTIMAL IODINE INTAKE IS THE PROTECTIVE FACTOR FOR THE POSITIVE THYROID AUTOANTIBODIES: AN EPIDEMIOLOGICAL SURVEY OF 31 PROVINCES IN CHINA

Objective: To investigate the changes of thyroid antibody in China after 20 years of universal salt iodization

Methods: A stratified cluster sampling method was adopted to investigate 71,229 cases of Chinese people over 18 years old, covering 31 provinces in China from 2015–2017. Serum TPOAb, TgAb, TSH were measured using electrochemiluminescence immunoassays on a Cobas 601 analyzer (Roche Diagnostic, Switzerland); Urine iodine concentration, were measured on Inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7700x, Agilent Technologies, USA)

Results: The median of urinary iodine in school-age children (MUI) was 197.8 μg/L. The MUI of the general survey population was 182.7 μg/L. 15 provinces were classified as adequate iodine intake, 9 provinces were more than adequate iodine intake and 4 provinces were excessive iodine intake. Now China is an area with adequate iodine intake. The positive rate of TPOAb was 10.78% and the positive rate of TgAb was 12.11% in whole cohort. The TPOAb positive rate of iodine deficiency (<100 μg/L), iodine adequacy (100–199 μg/L), more than adequate (<200–299 μg/L) and iodine excess (>300 μg/L) group was 13.47%, 10.84%, 9.54% and 9.84%, respectively. The positive rate of TgAb was 14.96%, 12.01%, 10.59% and 11.69% respectively.

Conclusions: Mortality due to suicide and unknown causes, but not accidents and homicide, was increased in HT. These findings indicate that HT may have a significant role in the pathophysiological mechanisms of suicidal behavior. Beyond independent confirmation, the high dissatisfaction rate and reduced quality of life in HT patients need to be explored in order to introduce preventive measures.

COMPARISON OF THE TREATMENT EFFECT BETWEEN THIAMAZOLE AND POTASSIUM IODIDE FOR NEWLY DIAGNOSED GRAVES’ DISEASE

Objectives: The efficacy of potassium iodide (KI) therapy for Graves’ disease has already been reported, although only a few clinical reports have compared the treatment effect between thiamazole (MMI) and KI.

Methods: This prospective clinical study enrolled 368 patients newly diagnosed with mild to moderate Graves’ disease, defined as FT4< 5.0 ng/dL, between July 2014 and June 2016. Patients were randomly divided into two groups, the MMI and KI groups, and written consent was obtained from all patients in the KI group. Medication was started with a dose of 15 mg of MMI or 50 mg of KI respectively, and if FT4 values did not decrease after the initiation of treatment, the doses were increased by 5 mg in the MMI group and 50 mg in the KI group. Patients whose thyroid hormone levels could not be controlled with 30 mg of MMI or 100 mg of KI were regarded as non-responders.

Results: In total, 200 patients were included in the MMI group and 168 patients in the KI group. Seventy-one patients in the MMI group and 53 patients in the KI group were excluded for various reasons, and 129 patients in the MMI group and 115 in the KI group were analyzed. Comparison of baseline parameters at the initial visit in the two groups showed that FT3, FT4 and TRAb values were significantly higher in the MMI group. All patients in the MMI group responded well, such that 61/129 (47.3%) patients could stop the medication, and 68/129 (52.7%) patients were controlled with MMI. Nineteen of the 129 patients stopped taking MMI because of side effects. On the other hand, in the KI group, 72/115 (62.6%) patients were controlled with KI, 25 of whom could stop the medication and 74 of whom remained on maintenance KI therapy. The remaining 43/115 (37.4%) patients had a few clinical responders. Multiple logistic regression analysis performed on the parameters measured at the initial visit indicated that FT4 (OR 0.44, 95% CI 0.25–0.75) and TRAb (OR 1.07, 95% CI 1.00–1.15) were significant factors related to KI responsiveness. ROC curve analysis of the relationship between FT4 value and KI responsiveness indicated a cut off FT4 value of 3.16 ng/dL.

Background: Hashimoto’s thyroiditis (HT) is associated with excess psychiatric and somatic comorbidity, with possible profound effects on mental health and quality of life. In fact, the majority of HT patients experience some psychiatric symptoms such as, sadness, poor concentration and sometimes even altered personality. Lately, much focus has been on the hitherto largely unexplained many complaints, including cognitive dysfunction, despite being biochemically euthyroid on a number of thyroid hormone combinations. The negative impact on quality of life connected with an increased psychiatric vulnerability raises the question of whether HT patients could have an increased risk of unnatural manners of death. However, little is known about risk and distribution of unnatural manners of death in HT. This study investigated the risk of death by accidents, suicide, violence/homicide, and unknown causes in patients with HT, compared to a matched control population.

Methods: Cohort study covering all adult Danes (218 years) diagnosed with HT during 1995–2012. Utilizing the Danish National Patient Registry, 111,565 cases with HT were identified and matched for age and sex with four subjects from the background population. The manner of death was identified by linking the study population with the Danish Register of Causes of Death. The hazard ratios (HR) for mortality – due to death by accidents, suicide, violence/homicide, and unknown causes – were calculated using Cox regression analysis, adjusted for pre-existing somatic and psychiatric morbidity. Median follow-up time was 5.9 years (range 0–17.5 years).

Results: Compared to controls, HT patients had an increased frequency of death caused by suicide (0.10% vs 0.07%, p < 0.001) and unknown causes (0.05% vs 0.02%, p < 0.001). There were no significant differences between controls and HT in risk of death by accidents (0.36% vs 0.37%, p = 0.384) or homicide (0.004% vs 0.005%, p = 0.749). After adjustment for pre-existing somatic and psychiatric morbidity HT patients still had an increased risk of suicide [HR = 1.31, 95% confidence interval (CI) 1.04–1.65] and death by unknown causes [HR = 1.65 (1.17–2.34)] whereas risk of death caused by accidents was reduced by 32%, [HR = 0.68 (0.61–0.77)].
Background: A growing number of patients with non-small cell lung cancer (NSCLC) are treated with programmed cell-death protein 1 (PD-1) blockade. Although programmed cell death-ligand 1 (PD-L1) expression has been a standard biomarker to predict clinical response, there are many limitations. Thyroid dysfunction, the most common immune-related adverse event, which is closely related to antitumor mechanism, was recently reported as a prognostic factor of PD-1 blockade treatment. We hypothesized that incorporating thyroid dysfunction into PD-L1 expression would better predict clinical outcomes.

Methods: A total of 73 patients with NSCLC treated with PD-1 blockade who measured PD-L1 expression and regular thyroid function test were enrolled. Patients were categorized according to thyroid function (thyroid dysfunction vs. euthyroid group) and PD-L1 expression (PD-L1 positive vs. PD-L1 negative group). The primary outcome was progression-free survival (PFS). Patients, tumor, and medication factors were adjusted using Cox proportional hazard modeling.

Results: Thyroid dysfunction developed in 15 patients (20.5%) with the median 40.2 days to development of thyroid dysfunction. Both thyroid dysfunction and PD-L1 expression independently predicted treatment response, there are many limitations. Thyroid dysfunction, the most common immune-related adverse event, which is closely related to antitumor mechanism, was recently reported as a prognostic factor of PD-1 blockade treatment. We hypothesized that incorporating thyroid dysfunction into PD-L1 expression would better predict clinical outcomes.

Conclusions: Thyroid dysfunction during PD-1 blockade independently predicted treatment response and improved prediction efficacy of PD-L1 expression in early course of PD-1 blockade treatment in patients with NSCLC.
Three inadequate cases (Bethesda class I) were wild type (WT) and TERTp alterations alone may be responsible for the aggressive course of the disease. Nonetheless, accumulating evidence suggests that this limitation can be overcome by molecular diagnostic approaches that definitely allow to better classify the nodular lesion. Aim of the present study was to characterize the clinical impact of TERTp mutations alone. However, patients harboring only TERTp mutations displayed significantly more advanced age at the time of PTC diagnosis. Our results are in line with previous studies and suggest that BRAF-TERTp duo may have prognostic value. However, more patients with TERTp mutations only need to be studied in order to give the answer whether TERTp alterations alone may be responsible for the aggressive course of the disease. The contribution of three new TERTp alterations in PTC progression and their potential association with poorer outcome need further evaluation.

HYPERTHYROIDISM AND PAPILLARY THYROID CARCINOMA IN THYROID STIMULATING HORMONE RECEPTOR D633H MUTANT MICE

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Objectives: An overactive thyroid in the course of non-autoimmune hyperthyroidism may affect virtually any organ system, can lead to excess comorbidity and mortality, and is potentially lethal, if not treated. Most commonly, it is caused by constitutively activating mutations of the thyroid stimulating hormone receptor (TSHR). All known TSHR activating mutations have been shown to increase basal cAMP production via the G protein GS and few mutations can additionally mobilize the release of intracellular calcium via Gq/11. Thus far, the functionality of these mutations has been exclusively tested in vitro, but appropriate in vivo models are lacking.

Methods: To understand the pathophysiology and the role of different signaling cascades of activating TSHR mutations in vivo we generated a knock-in mouse model carrying TSHR variant D633H by homologous recombination. The development and progression of non-autoimmune hyperthyroidism was monitored over a one year period.

Results: In this model we observed both subclinical and overt hyperthyroidism depending on age and sex. At 2 months of age homozygous (HOM) female and male mice developed overt hyperthyroidism, indicated by low TSH and high thyroid hormone serum concentrations, while heterozygous (HET) females showed subclinical hyperthyroidism. Hyperthyroidism in HOM mice is transient as a normalization of serum thyroid hormone concentration was observed at the age of 6 months. Histological changes in the thyroid of both sexes at 2 weeks of age were marginal. At 4 weeks of age all mice, regardless of sex and genotype, developed colloid goiter associated with flattened thyroid epithelium and increased size of the follicular lumen. At 12 months of age nearly all HOM mice presented large papillary thyroid carcinomas (PTC) associated with an overactive thyroid in HOM females. These PTC areas were well differentiated and showed increased numbers of proliferating thyrocyte nuclei and Ki67 stainings. Besides the introduced activating TSHR mutation additional alterations in common PTC oncogenes (Braf, Neas and Kras) were not found.

Conclusions: Taken together, our results from the TSHR D633H knock-in mouse model show that non-autoimmune hyperthyroidism is not as stable as expected but rather a dynamic condition involving age-, sex- and genotype-dependent compensatory mechanisms. Furthermore, our data strongly suggests that a permanently active TSHR can lead to the transformation of thyrocytes into cancer cells.
**OP-09-66**

**MUTATIONAL PROFILE OF A LARGE SERIES OF SPORADIC MEDULLARY THYROID CARCINOMAS BY NEXT GENERATION TARGETED SEQUENCING**

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**Objectives:** About 60% of sporadic Medullary Thyroid Carcinomas (sMTC) harbour mutually exclusive somatic mutations in the RET and RAS genes. A few recent studies performed in limited series and using next generation sequencing (NGS) methods found very rare novel mutations, including gene fusions in RET and ALK genes. Taking into account the results of these studies, up to 30–40% of sMTC remain orphan of a genetic driver mutation. The aim of this project was to characterize the mutational landscape of a large series of sMTC by targeted NGS sequencing.

**Methods:** Genomic DNA obtained from a total of 166 sMTC tissues was targeted sequenced in a Ion Torrent S5 Platform using a NGS custom panel able to sequence the whole RET, H-, K- and N-RAS genes gene and hotspot exons in the TP53, GNAS, PPM1D, PTEN, MET, BRAF, EIF4A1X, AKT1, CHEK2, CTNNB1, STK11, PIK3CA, TSHR genes. C228 and C225 hotspot mutations in the promoter of the Telomerase Reverse Transcriptase (TERT) gene were evaluated by Sanger sequencing.

**Results:** Sequencing with our custom panel we found 137/166 (82.5%) cases that were positive for somatic mutations. Eighty-eight/137 (64.2%) presented a single RET mutation: 48 M918T, 15 in codon C634, 3 D898_E901del, 2 C620R, 1 A883F, 1 C630R, 1L790F, 1 S891A, 1 L629_D631delinsH, 1 T636_V637insCRT, 1 E632_L633del. Another 37/166 (22.3%) presented mutations in other genes: 3 RET+RET, 4 RET+RAS, 3 RET+PPM1D, 1 RET+TP53, 1 RET+MET, 1 RET+RAS+PTEN, 2 RAS+MET, 1 RAS+PPM1D, 1 RAS+RET+TSHR. Finally, 29/166 (17.5%) remained negative for all mutations studied. Mutations in the TERT gene promoter were absent in all cases studied.

**Conclusions:** Applying NGS targeted sequencing we confirmed RET and RAS somatic mutations as principal drivers in sporadic MTC and the rate of negative cases is limited to 20%. The prevalence of RAS mutations appears to be higher with respect to previously reported. Rare mutations found in other genes will be further investigated in order to assess their role in sMTC pathogenesis. Finally, TERT promoter mutations do not have a role in sMTC.

**OP-09-67**

**TARGETING CLAUDIN-1 OVEREXPRESSING PAPILLARY THYROID CARCINOMA BY MODIFIED CLOSTRIDIUM PERFRINGENS ENTEROTOXIN**

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**Objectives:** Papillary thyroid cancer (PTC) is the most common endocrine malignancy, which is treated by surgery with or without radioiodine therapy and normally associated with a good prognosis. However, some patients develop recurrence and/or show distant metastases with absence of response to conventional radioiodine therapy. To overcome their poor prognosis, novel treatment options are needed. Clostridium perfringens enterotoxin (CPE) is a suitable biological tool for targeted cancer therapy. CPE can specifically interact with certain members of the claudin-family (Cldn3 and Cldn4) that result in rapid cell death. In non-transformed cells, claudins are localized in tight junctions. Structure-guided mutagenesis led to a CPE-variant with high Cldn1 binding affinity. In PTC, Cldn1 is overexpressed with pronounced plasma membrane localization and could therefore be targeted by the CPE-variant for PTC therapy.

**Methods:** Immunohistochemistry and immunoblot analysis were used to investigate Cldn1 expression in human PTC tissue and human surrounding normal thyroid tissue as well as in the human thyroid cell lines K1 (PTC) and Nthy-ori (thyroid follicular epithelial). The CPE-S231R/S313H variant (high Cldn1 affinity) and CPE-wildtype (wt, low Cldn1 affinity) were generated in E.coli. For in vitro binding affinity and cytotoxicity HEK293 transiently transfected with Cldn1, K1 and Nthy-ori cells were used. In a cell derived xeno-transplant (CDX) model K1 cells were subcutaneously injected into female NMRI mice. Eighteen days post injection, mice were intratumorally injected either with vehicle-control, CPE-wt or CPE-S231R/S313H one day for 10 days. Tumor growth and tumor histology were investigated.

**Results:** In human PTC tissue and K1 cells high Cldn1 expression was observed, whereas human normal thyroid tissue and Nthy-ori cells revealed weak Cldn1 expression. The CPE-S231R/S313H variant showed high Cldn1 binding and cytotoxicity in Cldn1-transfected HEK293 cells. Furthermore, CPE-S231R/S313H treatment resulted in a strong cytotoxic effect with elimination of approx. 80% of K1 cells, whereas cell viability of Nthy-ori was not affected. Both CPE-wt and vehicle-control treatment of CDX mice did not suppress tumor growth leading to 5-fold increase of tumor volume within 10 days. In contrast, CPE-S231R/S313H application attenuated tumor growth down to 25% those of CPE-wt and vehicle-control. Tumor histology showed necrosis in CPE-S231R/S313H, but neither in CPE-wt nor vehicle-control treated tumors.

**Conclusions:** Our data suggest that the novel CPE-variant with increased Cldn1-binding is a suitable tool to target selectively Cldn1-overexpressing PTC as potential therapeutic approach.
GENETIC VARIANTS OF PARP4 GENE IN PATIENTS AFFECTED WITH MULTIPLE PRIMARY TUMORS INCLUDING THYROID CANCERS

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Two or more tumors that arise simultaneously or at regular intervals in one patient are defined as primary multiple cancers. Interestingly, individuals affected with a primary thyroid cancer have a high incidence to develop a second primary cancer, and a possible cause could be a shared genetic pathway. Recently, the PARP4 gene, which codifies for a member of poly (ADP-ribose) polymerases family, has been identified as a possible susceptibility gene of primary thyroid and breast cancers. In particular, two germline PARP4 variants were found significantly associated with the risk of the development of these two cancers. In 2017, 11701G and G496V (43% of cases vs 0.5% of controls) were found in exon 29 and 13, respectively. Moreover, the T899A variant in exon 22 was detected in a patient with a familial history of thyroid and breast cancers. Little is known about the biological function of PARP4, but it is suspected to be involved in the DNA repair pathway and a role as a tumor-suppressor has been suggested. The aim of this study was to investigate the presence of PARP4 variants in a cohort of patients affected with multiple primary cancers including a thyroid cancer. DNA was extracted from blood samples of 51 patients with multiple primary cancers, 61 patients with papillary thyroid cancer (PTC) alone and 90 healthy donors. Exons 13, 22 and 29 were analyzed by means of PCR amplification and direct sequencing. The previously reported T11701G and G496V variants were absent in our series, whereas T899A variant was frequently detected in both patients and controls. Interestingly, we found a rare variant (c.1481C>A) within exon 13 in one patient affected with PTC, medullary thyroid carcinoma, kidney carcinoma and colorectal cancer. This variant was absent either in 57 PTC patients or in 87 healthy controls. Moreover, we detected two rare intronic variants: c.534±447C>T within the IVS29 and c.2758±9G>A in IVS22. The first variant was found in 2 out of 49 (4%) cases with multiple cancers and in 2 out of 61 (3.3%) patients affected with PTC alone. The other variant was detected in one patient affected with both primary PTC and non-Hodgkin lymphoma, and absent either in 39 patients with PTC alone or in 34 healthy controls. In conclusion, germline PARP4 variants appears to be a risk factor for the development of multiple primary cancers, PTC among them, and further studies on larger series are warranted.

MULTINODULAR GOITER IN CHILDHOOD: A DIAGNOSTIC GATEWAY FOR SCREENING DICER1 SYNDROME

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Background: DICER1 is a member of the Ribonuclease III family that plays a crucial role in the biogenesis and the maturation of microRNAs. Pathogenic germline DICER1 variants cause a hereditary cancer predisposition syndrome with a variety of manifestations: in addition to first described pleuropulmonary blastoma (PPB) and ovarian sex cord-stromal tumours, individuals may also develop benign (multinodular goiter MNG, cystic nephroma) or malignant tumours as differentiated thyroid carcinoma from infancy to adolescence and early adult. Average penetrance seems low to 15% except for MNG recently described as 15 to 75% at 40 years.

Objectives: To investigate whether MNG could be a pointer for familial DICER1 mutation screening

Methods: We report a series of 9 families whose diagnosis for Dicer1 variants was done on childhood MNG or in index patient or in siblings presenting benign (15) and malignant (9) tumours. We screened DNA sample from probands and families’ members (25) for DICER1 variants using Next Generation Sequencing tools. For 3 families the unique manifestation over generations was related to MNG. Patients’ and family history, clinical examination, thyroid ultrasonography, thyroid function and autoimmunity were evaluated.

Results: In all cases but one, the DICER1 pathogenic variants associated to MNG have been already described in the literature or located in the enzymatic site of the enzyme. In one family, infant history of pulmonary cystic adenomatoid malformation in the context of MNG at 11 for the proband but also father and uncle, led us to explore the DICER1 gene and identified an new heterozygous variant in the exon 20, c.3104C>G, p.Pro1035Arg. Histological sections rereading in view of the familial thyroid history corrected the initial diagnosis in PPB.

Conclusion: MNG is uncommon in children. Its recurrence within a family or its association with children benign or malignant tumours should make them suspect of anomalies in the DICER1 protein as proposed in recent international recommendations. Early detection of DICER1 variants has important consequences in terms of therapeutic strategy, early tumours screening and genetic counselling.

DICER1 SYNDROME

MULTINODULAR GOITER IN CHILDHOOD: A DIAGNOSTIC GATEWAY FOR SCREENING DICER1 SYNDROME

OP-09-68

OP-09-07

THE COMPARISON OF CLINICAL AND GENETIC FEATURES BETWEEN PEDIATRIC AND ADULT PAPILLARY THYROID CARCINOMAS

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Objectives: Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer. Our aim was to compare the clinical and genetic parameters between our cohorts of pediatric and adult PTC patients.

Methods: Our cohorts contained 73 pediatric (5–18 years) and 460 adult PTC patients. DNA and RNA were extracted from cancer tissue samples. DNA was used for sequencing of TERT promoter C228T and C250T mutations with CEQ8000 (Beckman Coulter) and BRAF and RAS mutations by Nextera XT kit with MiSeq (Illumina). RNA was used for detection of RET/PTC1 and RET/PTC3 rearrangements using Real Time PCR (LC 480, Roche). Clinical and pathological data were compared between both cohorts.

Results: In the pediatric cohort, significantly more often categories T3 (12.8% vs. 37% in adult, p < 0.001), extrathyroidal invasion (26.2% vs. 14.0%, p = 0.026) were present in comparison with adult PTC. Mutations in RAS genes were detected only in pediatric patients – mutation Q61K in N-RAS gene and Q61R in H-RAS (3% vs. 8% in adults, p = 0.09) and BRAF V600E mutation in 9 pediatric patients (12.2% vs. 37% in adult, p < 0.001). No TERT mutations were found in pediatri PTC in contrast to 12% in the adults (p = 0.004). RET/PTC rearrangements were found in 14 patients (20.9% vs. 5% in adults, p = 0.001) – 9 RET/PTC1, 5 RET/PTC3 and one RET/PTC1e9 were detected. RET/PTC1e9 in 8 years old boy with aggressive classical variant of PTC (T4N1M1) was created by fusion of exon 1 of CCDC6 with exon 9 of extracellular domain of RET followed by
Conclusions: In comparison of pediatric and adult PTC patients, pediat-
tric patients had more aggressive features than adults, mainly more frequent
advanced T3 and T4 in TNM classification, lymph node metastasis, extra-
thyroidal extension and angioinvasion. The genetic analysis revealed sig-
ificantly higher prevalence of the RT/PTC fused genes in pediatric PTC
compared with adult PTC, in contrast to significantly lower prevalence of the
BRAF V600E and TERT mutations.

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Tuesday, 18th September 2018

Oral Session 10: Young Investigators / Clinical and Translational

OP-10-71
DURATION OF HYPERTHYROIDISM AND LACK OF TREATMENT ARE ASSOCIATED WITH INCREASED RISK OF CARDIOVASCULAR DISEASE AND DEATH

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Objectives: Well accepted, all-cause mortality is increased in hypothy-
roid patients, and cardiovascular disease remains the most prevalent cause of
death in hyperthyroidism. However, the effects on cardiovascular risk of vary-
ing thyroid status and that of treatment remain unclarified. We investigated the
association between hyperthyroidism and the risk of cardiovascular disease
dead and in treated and untreated hyperthyroid individuals, and the impact of
cumulative periods of hyperthyroidism on cardiovascular risk.

Patients and Methods: A case-control study nested within a cohort of
239 768 individuals who had at least one serum-TSH measurement in the
period of 1995–2011. Incident cases of cardiovascular disease (myocardial
infarction, atrial fibrillation, heart failure, stroke, and cardiovascular death)
were matched with three healthy controls from the cohort according to sex
and age. Conditional logistic regression analyses were performed to calcu-
late odds ratios (OR) for exposure to hyperthyroidism, adjusting for preexist-
ing comorbidities, using the Charlson Comorbidity Index. Hyperthyroidism
was defined as at least two measurements of decreased serum TSH within 6
months, separated by at least 14 days, in an effort to exclude non-thyroidal ill-
ness. Cumulative periods of decreased TSH were included in the analyses as a
time-dependent covariate.

Results: 20 651 individuals experienced a cardiovascular event [9.5%
incidence rate 13.2/1000 person years, 95% confidence interval (CI) 13.0–
13.4]. Conditional logistic regression showed an increased risk of cardio-
vascular disease in untreated hyperthyroid patients compared to euthyroid
individuals [OR 1.23, 95% CI 1.06–1.48, p = 0.007], but not in treated hyper-
thyroid patients [OR 1.04 (95% CI 0.96–1.22, p = 0.57)]. OR for cardiovas-
cular disease per 6 months of decreased TSH was 1.09 (95% CI 1.05–1.14,
< 0.001) in treated hyperthyroid individuals, and 1.10 (95% CI 1.05–1.15)
in untreated hyperthyroid individuals. After stratification for gender and age
≥65 years and <65 years, the above findings persisted in females and patients
older than 65, but not in males and those younger than 65 years, due to lack of
power.

Conclusion: Risk of cardiovascular disease is increased in untreated
hyperthyroid patients. Duration of decreased TSH is associated with increas-
ing risk of cardiovascular outcomes in both treated and untreated hyperthy-
roid individuals. Our results point at the importance of initiating treatment
and of maintaining biochemical euthyroidism in hyperthyroid patients in order
to reduce the risk of cardiovascular disease and death. Confirmation of this
hypothesis will require a randomized clinical trial, which is unlikely to be car-
ried out.

OP-10-72
DIGOXIN TREATMENT INDUCES TUMOR REDDIFFERENTIATION AND AUGMENTS RADIOACTIVE IODIDE UPTAKE IN A MOUSE MODEL OF BRAFV600E-INDUCED THYROID CANCER

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Objectives: Non-medullary thyroid cancer (TC) treatment is based on the
ability of thyroid follicular cells to accumulate radioactive iodide (RAI). How-
ever, in a subset of TC patients expression of the sodium iodide sym-
porter (NIS) is lost due to tumor dedifferentiation, leading to RAI resistance.
Currently, for RAI-refractory TC treatment options are limited and not cura-
tive. Previously, the cardiac glycoside digoxin has been demonstrated to
activate autophagy, to restore NIS expression and to increase iodide uptake
capacity in vitro in poorly differentiated TC cell lines, termed redifferen-
tiation. However, the in vivo effects of digoxin treatment on TC differentiation
remain unclear. In the present study, the in vivo effects of digoxin are investi-
gated in TPO-Cre/LSL-BrafV600E mice that spontaneously develop BrafV600E-
induced papillary TC.

Methods: Mice with established TC were subjected to 3D ultrasound for
monitoring tumor growth and 124I PET/CT for measurement of intratumoral
radioactive iodide uptake at baseline and 5, 12 and 19 days after start of treatment with
either vehicle control, 20 μg digoxin or 60 μg digoxin daily. Post-mortem
analyses on tumor tissue comprised gene expression profiling and measure-
ment of intratumoral autophagy activity and protein expression of the prolif-
eration marker Ki-67.

Results: Tumor growth is inhibited by digoxin treatment which is accom-
panied by a reduced protein expression of Ki-67. Furthermore, 124I accumula-
tion in the tumor was increased after digoxin treatment, both after 24 hours
and 72 hours after 124I injection at all post-treatment time points. Post-mortem
analyses revealed that digoxin treatment increased expression of thyroid-
specific genes incorporated in the Thyroid Differentiation Score as well as
autophagy related genes. In addition, autophagy activity in tumor tissues of
digoxin-treated mice was increased compared to vehicle-treated mice.

Conclusion: Digoxin treatment in transgenic mice with BrafV600E
induced TC results in inhibited tumor growth and increased iodide uptake capacity
by activated autophagy and restored expression of genes involved in iodide
metabolism. All together, digoxin treatment emerges as promising adjunc-
tive therapeutic strategy for restoring RAI sensitivity in dedifferentiated
BrafV600E-driven TC.
MATERINAL IODINE STATUS AND CHILD IQ: A META-ANALYSIS OF INDIVIDUAL-PARTICIPANT DATA FROM THREE POPULATION-BASED BIRTH COHORTS

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Methods: We included data from three large European, population-based birth cohorts: INMA (Spain), Generation R (The Netherlands) and ALSPAC (United Kingdom). The urinary iodine to creatinine ratio (I/Creat) was measured at a median (interquartile range, IQR) gestational age of 13.0 (12.4–14.1) weeks, 13.1 (12.1–14.8) weeks, and 12.0 (8.0–16.0) weeks in INMA, Generation R, and ALSPAC, respectively. Iodine deficiency was defined as an I/Creat below 150 μg/g, iodine sufficiency as an I/Creat between 150 to 500 μg/g, and excessive iodine as an I/Creat above 500 μg/g. Non-verbal and verbal IQ were assessed at 15–8 years of age. Coefficient specific effects estimates were combined using random-effects individual data meta-analysis after adjusting for potential confounding variables.

Results: In total 6,179 mother-child pairs were included. The median I/Creat was 152, 301, and 124 μg/g in INMA, Generation R, and ALSPAC, respectively. There was a linear association between iodine I/Creat and non-verbal IQ (P = 0.01), without evidence for differential effects according to gestational age at thyroid function measurement. In contrast, there was a non-linear association for I/Creat with verbal IQ (P < 0.001). When stratifying the association of iodine status with verbal IQ according to tertiles of gestational age, the association was driven by iodine status measured in early pregnancy. Further prospective analyses are needed to compare any beneficial impact. The differences were of magnitudes normally deemed clinically relevant.

Conclusions: Iodine status in pregnancy was associated with child IQ and our results suggest that the fetus may be vulnerable to mild-to-moderate iodine deficiency during early pregnancy for the development of verbal IQ.
Enrichment of cell-free circulating tumour DNA (ctDNA) in plasma has been shown to be a useful biomarker in other solid tumours. We hypothesized that ctDNA may represent a minimally invasive biomarker with the potential to permit personalized treatment plans in thyroid cancer. This proof-of-concept study was a multi- mutational analysis of ctDNA to test this hypothesis in patients with advanced thyroid cancer over multiple time-points.

Methods: Mutation analysis of archival tumour tissue was performed on an NGS platform using a validated gene panel targeted to known cancer hotspots. Custom Taqman assays for discovered variants were designed for plasma ctDNA testing using digital droplet PCR. Concentrations of detected ctDNA were correlated with conventional biomarker concentration and axial imaging status defined by RECIST criteria.

Results: Tumours were obtained from 51 patients, with the following histologies: 17 papillary, 15 follicular, 15 medullary, 3 poorly differentiated and 1 anaplastic. Variants were detected in 42 (82%) of the tumour tissue samples. Detected rates of mutation in genes per histological subtype were broadly in line with published data. Plasma was assayed for ctDNA in 190 samples from 42 patients. Circulating tumour DNA was detected in the plasma of 28 of 42 (67%) tested patients. Earlier detection of disease progression was noted in 2 patients with medullary thyroid cancer (MTC). In a further 2 cases conventional biomarkers were not detected due to thyroglobulin antibodies and de-differentiated disease, yet ctDNA was detected and also showed increasing levels prior to confirmed disease progression. Changes in ctDNA concentration were noted to occur more rapidly than for conventional markers in response to disease progression in multiple patients receiving targeted therapies.

Conclusion: Detectable levels of ctDNA were found in the plasma of the majority of patients with advanced thyroid cancer. Sub-analysis suggests that ctDNA measurement may offer superiority over conventional markers in several clinically relevant scenarios. These include earlier detection of progression in MTC; use as an alternative biomarker when conventional markers are not available due to auto-antibodies or de-differentiated disease; and more rapid assessment of disease status in response to targeted therapies thereby potentially allowing prompter discontinuation of futile therapies. These early results are promising and support the hypothesis that ctDNA may be a clinically useful biomarker in thyroid cancer. A planned multi-centre study will aim to confirm this.

OP-10-76

CIRCULATING TUMOUR DNA AS A POTENTIAL DISEASE PROGRESSION BIOMARKER FOR ADVANCED THYROID CANCER

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Introduction: Conventional biomarkers in thyroid cancer (thyroglobulin, calcitonin, CEA) are not disease specific and can fluctuate in advanced disease making interpretation difficult. Cell-free circulating tumour DNA (ctDNA) has been shown to be a useful biomarker in other solid tumours. We hypothesized that ctDNA is a potential candidate for a disease specific, minimally invasive biomarker with the potential to personalise treatment plans in thyroid cancer. This proof-of-concept study was a multi- mutational analysis of ctDNA to test this hypothesis in patients with advanced thyroid cancer over multiple time-points.

Methods: Mutation analysis of archival tumour tissue was performed on an NGS platform using a validated gene panel targeted to known cancer hotspots. Custom Taqman assays for discovered variants were designed for plasma ctDNA testing using digital droplet PCR. Concentrations of detected ctDNA were correlated with conventional biomarker concentration and axial imaging status defined by RECIST criteria.

Results: Tumours were obtained from 51 patients, with the following histologies: 17 papillary, 15 follicular, 15 medullary, 3 poorly differentiated and 1 anaplastic. Variants were detected in 42 (82%) of the tumour tissue samples. Detected rates of mutation in genes per histological subtype were broadly in line with published data. Plasma was assayed for ctDNA in 190 samples from 42 patients. Circulating tumour DNA was detected in the plasma of 28 of 42 (67%) tested patients. Earlier detection of disease progression was noted in 2 patients with medullary thyroid cancer (MTC). In a further 2 cases conventional biomarkers were not detected due to thyroglobulin antibodies and de-differentiated disease, yet ctDNA was detected and also showed increasing levels prior to confirmed disease progression. Changes in ctDNA concentration were noted to occur more rapidly than for conventional markers in response to disease progression in multiple patients receiving targeted therapies.

Conclusion: Detectable levels of ctDNA were found in the plasma of the majority of patients with advanced thyroid cancer. Sub-analysis suggests that ctDNA measurement may offer superiority over conventional markers in several clinically relevant scenarios. These include earlier detection of progression in MTC; use as an alternative biomarker when conventional markers are not available due to auto-antibodies or de-differentiated disease; and more rapid assessment of disease status in response to targeted therapies thereby potentially allowing prompter discontinuation of futile therapies. These early results are promising and support the hypothesis that ctDNA may be a clinically useful biomarker in thyroid cancer. A planned multi-centre study will aim to confirm this.

OP-11-77

GESTATIONAL AND EARLY POSTNATAL HYPOTHYROIDISM ARREST ANGIogenesis AND GLYPHOMATIC SYSTEM DEVELOPMENT IN THE NEOCORTEX OF RATS

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Thyroid hormones (TH) regulate the expression of key genes involved in the development and maturation of the cerebral cortex. However, data reporting the role of TH in angiogenesis and glympastic system development are scarce. We studied early postnatal development of cortical vessels and glympatic system, affecting extracellular water and metabolite diffusion in the parietal cortex of control (C) and hypothyroid (H) rats. Hypothyroidism was induced with 0.02% methimazole and 1% KC104 from embryonic day 10 until sacrifice at postnatal (P) days ranging from P0-40. Fixed coronal sections of the parietal cortex of C and H pups were used to study: (i) density, length and diameter of vessels and (ii) cell characterization by immunohistochemistry and in situ hybridization using Co44, NeuN, GFAP, VEGF, Flk1, AQP1 antibodies and mCo44a and mAQP4a probes. The expression of HIF1a, ARNT, VEGF, Co44a and AQP4a was studied in fresh dissected parietal cortex using ELISA. Furthermore, in vivo water diffusion was studied with MRI at P40.

OP-10-75

LENVATINIB THERAPY IN PROGRESSIVE, RADIOIODINE-REFRACTORY, DIFFERENTIATED THYROID CARCINOMA: ANALYSIS OF 74 CASES FOLLOWED IN A SINGLE CENTRE

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Objectives: Lenvatinib is an oral multi-thyrosine kinase inhibitor (TKI) approved for the treatment of progressive radioiodine-refractory differentiated thyroid carcinoma (DTC). Primary endpoint was to confirm, in the clinical practice, the efficacy of Lenvatinib therapy in a big series of patients followed in a single centre; secondary endpoint was to evaluate its safety.

Methods: we analyzed the clinical, biochemical and pathological data of 74 patients who, for progressive DTC according to RECIST 1.1, started Lenvatinib therapy.

Results: in our study group no epidemiological, clinical and pathological differences have been found to respect the SELECT study (median age at diagnosis 65.5 vs 64 years; male ratio 51% vs 48%; prior treatment with other TKI in 28% vs 25%; presence of lung metastases in 89% vs 87%). At the moment of first control, after a median of 2 months of Lenvatinib therapy, 100% of patients had e clinical benefit: 34% had a partial response (PR) and 66% had a stable of disease (SD). After a mean of 16 months of follow-up, 30/74 (40.5%) patients were still being treated: 14/30 (47%) patients remained in PR; 12/30 (40%) patients remained in SD, 4/30 (13%) had a progressive disease (PD). We noticed not only a radiological response but also a decreasing in serum thyroglobulin (Tg) value or in the titer of anti-Tg antibodies (TgAbs): at the screen- ing, the median Tg value was 452 ng/ml and the median titer of TgAbs was 193 U/ml vs the median Tg value of 219 ng/ml and the median titer of TgAbs of 54 U/ml at the moment of the best response. Treatment-related adverse events (AE) occurred in 93% of patients. The most frequent AE were fatigue (81%), nausea and anorexia (74%), weight loss (68%), arterial hypertension (67%), dysgeusia (45%), diarrhea (33%) and proteinuria (20%). Regarding the AE, a mean of 84% of patients had grade 1/2 AE according to the Common Terminology Criteria for Adverse Events (CTCAE) and only 14% of patients had grade 3/4 (AE). Five/39 deaths, occurred during Lenvatinib therapy, were most likely considered to be drug-related.

Conclusions: these data confirmed that, in the clinical practice, Lenvatinib therapy is effective and associated with a progression-free survival similar to the SELECT study. Adverse events are manageable and associated with a high quality of life in patients treated with Lenvatinib.
The vessel density in both groups was 35.8% at P0-13 and at P20-40 it increased to 56.6% and 45.1% (P < 0.001) in C and H rats, respectively. The total vessel length (on average, 8,800 ± 400 μm) and the vessel length diameter distribution was similar in both groups at P0. However, both parameters differed from P10 onwards. On average, vessel length in H rats at P10-40 was 22,000 ± 5,000 μm vs 31,000 ± 6,000 μm in controls. At P10-20, the total length of vessels with a diameter of ~4.5 μm in C rats was 7,300 ± 5,000 μm while in H rats these diameters were not observed. At all ages, C and H rats showed VEGF, mCol4a1 and mAQP4 expression in neurons and astrocytes, while Flk1 and AQP1 in ependymocytes/tenocytes. Moreover, the expression of HIF1α, ARNT, VEGF, Col4a1 and AQPR4 decreased (P < 0.05; on average, 21.4, 23.3, 15.4, 18.7 and 12.2%, respectively) in H rats respect to controls. In concordance, water diffusivity at P40 also decreased (P < 0.01; on average, 20.1%) in H rats respect to C rats.

Our data shows that developmental hypothyroidism decreases the expression of pro-angiogenic and transporter molecules that impair cortical angiogenesis and the glymphatic system, affecting water diffusion. These alterations may help to explain the histopathology and physiopathology of neurological and psychiatric diseases comorbid in children suffering gestational and early postnatal TH deficiency. MINECO-SAF2014-58256-R.

**OP-11-78**

**RAPID VASODILATION IS A PHYSIOLOGICAL EFFECT OF NONCANONICAL THYROID HORMONE RECEPTOR ALPHA ACTION**

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**Introduction:** Thyroid hormone (TH) is crucial for physiological homeostasis and its cardiovascular effects are mainly mediated by TH receptor (TR) α. TRs can either influence gene transcription (canonical action) or rapidly active cellular signaling pathways (noncanonical action). The physiological relevance of noncanonical TH/TRα action is unknown. As triiodothyronine (T3) has been shown to decrease blood pressure in mice within minutes, we hypothesized that rapid vasodilation could be a physiological effect of noncanonical TRα action. Therefore, the aim of our study was to characterize the underlying mechanism of T3 induced vasodilatation.

**Material and Methods:** Mesenteric arteries were isolated from wild-type (WT) mice, TRα knockout (TRαKO) mice and a knock-in mouse model (TRαKOC) with a mutation in the DNA-binding domain which abrogates canonical TRα action while noncanonical signaling is preserved. In a wire myograph system the isolated vessels were pre-constricted with noradrenalin (10–5 M). The response to T3 (10–5 M) was measured and resulting vasodilation (% vs 31,000 ± 6,000 μm in controls) was normalized to maximum contraction with noradrenalin and expressed as percent. To investigate the underlying mechanism, arteries were pretreated with the endothelial NO-synthase (eNOS) inhibitor N(G)-nitro-L-arginine methyl ester (L-NAME) (10–4 M) and the phosphorylidyinositol 3-kinase (PI3K) inhibitor Wortmannin (10–5 M), respectively. To study the role of functional endothelium and determine whether T3 acts in the endothelium or in smooth muscle cells, the endothelium was removed from isolated rat mesenteric arteries and the T3 effect was compared to that in intact arteries.

**Results:** T3 treatment induced vasodilatation in arteries from WT mice (22 ± 2%) within 5 minutes. This effect was absent in arteries from TRαKO mice (5 ± 1%, TRαKO vs. WT < 0.0001). Strikingly, T3 mediated vasodilatation was preserved in TRαKO mice (17 ± 1%, TRαKO vs. WT n.s.), demonstrating that DNA binding of TRα is not required. T3 induced vasodilation was endothelium-dependent (arteries with intact endothelium 37 ± 5% versus arteries without intact endothelium 3 ± 6%; p < 0.0001). In mouse mesenteric arteries the T3 mediated vasodilatation was reduced by eNOS inhibition with L-NAME (28 ± 5% vs. 47 ± 5% without L-NAME, p < 0.05). Furthermore, T3 mediated vasodilatation was inhibited by pretreatment with the PI3K inhibitor Wortmannin (untreated 47 ± 5% vs. Wortmannin 19 ± 3%, p < 0.05).

**Conclusion:** T3 and TRα induce vasodilatation within minutes by PI3K and eNOS activation in the endothelium of WT and TRαKO mice. Thus, TRα mediates rapid TH effects on vascular physiology independent from gene transcription.

**OP-11-79**

**BROWNING OF WHITE ADIPOSE TISSUE IS MEDIATED BY CANONICAL THYROID HORMONE RECEPTOR BETA SIGNALING**

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**Introduction:** Thyroid hormone (TH) regulates energy metabolism, especially through regulation of white adipose tissue (WAT). TH receptors (TR) α and β can act either as ligand dependent transcription factors, promoting gene expression (canonical, type 1 signaling), or by activation of cellular signaling pathways (noncanonical, type 3 signaling). Aim of this study was to determine which receptor, TRα or TRβmediated effects are not necessarily mediated by the predominantly expressed TRα isoform. The aim of our study was to characterize the underlying mechanism of T3 induced vasodilatation.

**Material and Methods:** We determined the roles of TRα and TRβ and the underlying mechanism in browning of WAT in several mouse models: WT, TRβKO (global TRβ deficiency to eliminate all TRβ effects), TRβKO (abrogated type 1 but intact type 3 action) and TRβKO (preserved type 1 but abrogated type 3 signaling). Mice of all genotypes were rendered hypothyroid and half of the groups were treated with T3 (1 μg/ml via drinking water). After 7 days, browning was studied histologically and biochemically by determination of gene expression and western blot analysis in subcutaneous (sc)WAT.

**Results:** TRα expression in WT was >5-fold higher than that of TRβ. In WT mice, but not in TRβKO mice, adipocyte cell size was decreased and populations of multilocular brite (brown-in-white) adipocytes were detected, indicating browning of scWAT. These histological changes were accompanied by an increased expression of Ucp1, Pgc1a, Pdgfa and Dio2, genes known to be involved in browning. Staining of Ucp1 as well as western blot analysis confirmed browning of scWAT. As presence of TRα could not compensate for lack of TRβ, these results demonstrate complete dependence of brite adipose tissue activation on TRβ. T3 induced WT browning in TRβKO mice to the same extent as in WT mice, but not at all in TRβKO mice. Thus, canonical, type 1 TRβ signaling is the underlying mechanism of TH signaling in WAT.

**Conclusion:** Browning of WAT by TH is mediated by TRβ, although TRα is more abundant. Therefore, our results demonstrate that organ specific TH effects are not necessarily mediated by the predominantly expressed TR isoform. Moreover, we identified the type 1 TRβ signaling as the underlying mechanism of brite adipocyte formation.

**OP-11-80**

**ECTOTIC EXPRESSION OF THE HUMAN TRBETA2 AFFECTS THE COMMITMENT OF L-CONE IDENTITY IN THE ZEBRAFISH, IN AN ISOFORM-SPECIFIC MANNER**

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In zebrafish, the TH action is mediated by different receptors (TRα1 and TRβ2, TRβ1 and TRβ2) encoded by two genes (THRA and THRB), with differing tissue distribution. The proper functioning of sensory organs requires the generation of appropriate numbers and proportions of neuronal subtypes that encodes distinct information. Perception of colour relies on signals from multiple cone photoreceptor types. In zebrafish retina, each cone expresses a single opsin type with peak sensitivity to long (L) (red), medium (M) (green), short (S) (blue) or ultra-short (UV) wavelengths. It has been reported that the zebrafish cone photoreceptors are produced by symmetric division of dedicated precursors, in which the activity of TRβ2 is critical. In this work, we micro-injected wild-type and mutant (R243Q, PV) human TRβ2 transcripts
into zebrafish 1–2 cell embryos. The specification of the different photoreceptors were assessed by qPCR and in situ hybridization (ISH) of the opsin genes: sws1 (UV-cone); lws1 and lws2 (L-cone); rh2-1, rh2-2, rh2-3 and rh2-4 (M-cone); sws2 (S-cone). The knock-in (KI) of both hTrβ2 mutants severely reduced the number of L-cones and caused a corresponding increase in UV cones. By contrast, the number of S- and M-cones were not affected. Interestingly, the overexpression of hTrβ2 wild-type allele allows the only generation of the L-opsin cones. Our experiments suggest that the cone precursors have the potential to develop as UV-cone and that a correct Trβ2 dosage appears essential in the commitment to an L-cone identity. To analyse the specificity of Trβ2 controlling photoreceptor specification, we microinjected also the wild-type and mutant (E403X) hTrα1 mRNAs into 1–2 cell stage embryos. Interestingly, both hTrα1-KI embryos did not display any defects during retinal development. According to the micro-injection of the only hTrβ, but not hTrα, mutants was associated with the typical RTHβ biochemical signature (high T4/T3 with unsuppressed TSH concentrations) indicating the existence of a dominant-negative effect on the pituitary negative feedback. Since the human transcripts should be ubiquitously expressed in the zebrafish tissues after micro-injections at 1–2 cell stage embryos, the whole of our findings support the existence of distinct Trα1 or Trβ2 pathways in which specific molecular interactions at the cellular/nuclear level control the access of the different receptors at specific regulatory sites of gene expression. Our KI embryos could represent an useful model to test and identify the domains and specific interactions responsible for the α- or β-dependent action at tissue and molecular level.

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**OP-11-81**

**TAZ/WWTR1 AND PAX8 ELICIT A CROSSTALK MECHANISM ON NIS EXPRESSION AND FUNCTION**

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Despite the highlighted involvement of the Hippo Pathway in the control of cell proliferation, the mechanisms that modulate this pathway in the thyroid gland remain poorly understood. However, a role for its transcriptional cofactor TAZ has been described as a coactivator of Pax8 on the thyroglobulin promoter. Pax8 is a key driver of thyroid differentiation and it targets a large number of genes crucial for the thyroid function, such as NIS. The aim of this work was to study the role of the Hippo pathway and its mediator TAZ in NIS expression, and hence in thyroid differentiation.

By chromatin immunoprecipitation (ChIP) and luciferase reporter assays, we unexpectedly determined that TAZ is co-repressing Pax8 activation of the NIS promoter by decreasing its binding to the NUE. Furthermore, by Western Blotting and immunoprecipitation we observed that TAZ expression levels are regulated by TSH and TGFβ in an opposite way to the main differentiation markers in thyroid follicular cells. TSH has appeared to be an activator of the Hippo signalling pathway: by stimulation of MST1/2 phosphorylation it promotes TAZ translocation to the cytoplasm and its degradation by proteasome. On the contrary, TGFβ induces higher TAZ nuclear levels, thus stabilizing its active form and reducing NIS transcription. In accordance to this, TAZ silencing by RNAi partially impairs TGFβ-induced NIS repression and allows NIS membrane location, improving iodine uptake. Besides, the absence of TAZ is able of increasing Pax8 levels in the nucleus, also reinforcing its interactions with several binding partners as was checked by Proximity Ligation Assays. This last could be the cause of the aforementioned effects of TAZ on NIS expression.

All these data establish a novel role of the Hippo pathway, and particularly the cofactor TAZ, in the regulation of NIS expression in thyroid cells by the crosstalk on this factor with one of the main transcription factors involved in thyroid differentiation.

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**OP-11-82**

**MCT8 DEFICIENCY DISTURBS EARLY RETINAL DEVELOPMENT AND RESULTS IN A SHIFT TO MORE BLUE LIGHT-SENSITIVE CONES AT THE EXPENSE OF GREEN/RED LIGHT-SENSITIVE CONES**

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**Objectives:** Patients carrying inactivating mutations in the SLC16A2 gene encoding the thyroid hormone (TH) transporter MCT8 suffer from severe psychomotor retardation. Widespread brain lesions originating during development are the predominant cause for this phenotype. Some reports also mention impaired visual function, but whether or not MCT8 deficiency affects the development of the neuroretina has not yet been studied in detail. Based on the strong expression of MCT8 in chicken retinal precursor cells, we hypothesized that MCT8 may be important for retinal development.

**Methods and Results:** The retinal cyto-architecture is evolutionary conserved, and comprises 7 cell types organised in distinct layers which arise during consecutive phases in embryonic development. Chicken embryonic development takes 21 days and MCT8 expression in retinal precursor cells starts from embryonic day 4 (E4). We induced MCT8 knockdown by electroporating a pRFP-MCT8-RNAi vector into the retinal neuro-epithelium at this stage and used an empty pRFP-RNAi vector as control. Rapid knockdown of MCT8 was confirmed at E5 by showing a clear reduction in MCT8 mRNA transcripts in regions transfected with the pRFP-MCT8-RNAi vector. 5-ethyl-2'-deoxyuridine (EdU)-pulse labelling at E6 revealed reduced cell proliferation, suggesting that MCT8-dependent TH uptake is necessary for stimulating retinal cell genesis. In addition, immature MCT8-deficient photoreceptor cells displayed delayed migration towards the presumptive photoreceptor layer, and retinal ganglion cell differentiation was impaired, suggesting that early neurodevelopmental processes are hampered in a cell-specific manner. We then examined whether these early defects caused persistent disruption in the structure of the mature retina. A thinner inner nuclear layer and inner plexiform layer together with a reduced number of RFP-positive cells at E18 reflected the reduced expansion of the MCT8-deficient precursor pool at an early stage. This caused a general decrease in the number of all major retinal cell types, as observed using cell-specific markers, but without shifting the ratio between them. However, changes were found within the photoreceptor population. While the number of rods was unaffected, MCT8 deficiency caused an increased generation of blue light-sensitive cones at the expense of green/red light-sensitive cones, a shift that might interfere with normal colour perception.

**Conclusion:** MCT8-dependent TH uptake in retinal precursor cells seems pivotal to guide different cell processes during retinal development. We also showed that MCT8 has a role in generating normal cone diversity, providing a first hint on why visual function in MCT8-deficient patients may be impaired.
Oral Session 12: Clinical Features and Diagnostic Approach of Thyroid Cancer

**OP-12-83**

**IS SERUM TSH A MARKER OF THYROID NODULAR DISEASE? – A DANISH MULTICENTRE STUDY**

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**Objective:** The preoperative level of s-TSH has been reported to be higher in patients with differentiated thyroid cancer (DTC), as compared with patients with benign thyroid nodular disease (TND). Since most previous studies were performed in iodine-sufficient areas, we investigated whether such a relationship between s-TSH and thyroid malignancy exists in a Danish cohort.

**Methods:** Patients undergoing thyroid surgery for TND were included retrospectively from three tertiary surgical departments. After excluding individuals with overtly coexisting thyroid disorders, patients were compared with the Danish background population, employing previous data from the DanThyr study.

**Results:** 998 patients [cases/controls: 265/733; female/male: 794/204; age (mean ±sd): 51 ± 15 years] were included. S-TSH was significantly higher in the DTC group [median (IQR): 1.3 (0.9–1.9 IU/l)] compared with the benign TND group [0.9 (0.6–1.5 IU/l)] (p < 0.0001). The median s-TSH in the background population was similar to that found among DTC patients (p = 1.00), but markedly higher than the s-TSH level in the benign TND group (p < 0.0001). There was no association between s-TSH and DTC stage (p = 0.08–0.87).

**Conclusion:** s-TSH was significantly higher in patients with DTC than among those with benign TND. However, this difference can be explained by an abnormally lower s-TSH level in the latter group, probably caused by subtle nodular functional autonomy. Due to the huge overlap and the small difference in median s-TSH between patients with benign and malignant TND, s-TSH is not suitable as a biomarker of DTC in a clinical setting.

**OP-12-84**

**CALCITONIN DOUBLING TIME (CT-DT) MAY NOT BE INDICATIVE OF DISEASE PROGRESSION AND SURVIVAL IN PATIENTS WITH METASTATIC MEDULLARY THYROID CARCINOMA (MTC)**

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**Objectives:** A short Ct-DT is considered as an unfavorable prognostic factor for disease progression in MTC patients. However, the role of Ct-DT in disease course of metastatic MTC (meta-MTC) patients undergoing intensive locoregional and/or systemic therapy is not well established. We evaluated disease course in relation to Ct-DT in MTC patients followed-up in our Unit since 1979.

**Methods:** Of all MTC patients (n = 280), 49 (17.5%) presented with distant metastases at the time of diagnosis and/or during follow-up. In 41 (14.6%) Ct-DT was available. Patients were classified in 2 groups according to Ct-DT: group 1 Ct-DT <12 months: 24/41 (58.5%), group 2 Ct-DT ≥12 months: 17/41 (41.5%).

**Results:** Of 41 meta-MTCs (89.5% sporadic), 28 (68.3%) were men. Age at diagnosis was 5–78 yrs (mean:47.8 ± 17.7). Tumor size:3.3 ± 1.9 cm, cervical lymph node infiltration:100.0%, capsular invasion:84.6%, soft tissue invasion:76.5%, multifocality:45.0%. Ct-DT range was 2–36 months (median:8;mean:10.8 ± 8.3); 9/41 (22.0%) presented with distant metastases at diagnosis, while metastases during follow-up occurred within 0.8–25 yrs from diagnosis (median:5 yrs). Patients underwent locoregional therapies (55.3%), Tyrosine Kinase Inhibitors (TKIs) administration (26.4%, vandetanib 21.1%) or combined therapy (10.5%). The therapeutic strategy did not differ between the two groups. During a follow-up of 0.2–10 yrs (median:2) biochemical (H) and structural (S) response was as follows: partial response (B:4.9%,S:9.8%), stabilization (B:26.8%,S:31.7%), progression (B:68.3%, S:58.5%). No differences were observed between the two Ct-DT groups. New metastatic lesions occurred in 28/41 patients (68.3%) mainly in ≥2 loci (46.4%) and lungs (25.0%). The majority of patients received TKIs (65.1%, vandetanib 57.5%) while 23% underwent locoregional therapies. During a follow-up of 0.3–9 yrs (median:2) response was: partial response (B:22.2%, S:11.1%), stabilization (B:29.6%, S:51.9%), progression (B:48.1%, S:37.0%). Again no differences were observed between the two Ct-DT groups. Overall, patients presented with locoregional lesions (29.6%, S:31.7%), progression (26.4%, S:45.5%). No difference was found between the two Ct-DT groups. Overall, TKIs were administered in 34/41 patients (82.9%), Vandetanib (28/41, 68.3%). Response to vandetanib therapy during a follow-up of 0.3–7 yrs (median:2) was: partial response (25.0%), structural stabilization (41.7%), progression (33.3%), with no difference between the two Ct-DT groups. Overall response to the various therapeutic interventions during a follow-up of 1–29 yrs (median:10) was: partial response (6/41, 16.7%), stabilization (11/41, 30.6%), progression (11/41, 30.6%) while 8/41 (22.2%) died, and did not differ between the two Ct-DT groups; accordingly there was no difference in the survival curve (Kaplan-Meier).

**Conclusions:** Targeted therapeutic interventions at the right time can restrain disease progression in metastatic MTC patients. Ct-DT may not be used as an index of disease progression and survival when appropriately combined local and systemic therapies are used.
OP-12-85
PRESENTATION AND CLINICAL OUTCOME OF FAMILIAL NON-MEDULLARY THYROID CARCINOMA (FNMTC) ACCORDING TO THE NUMBER OF AFFECTED FAMILY MEMBERS
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Introduction: Familial non-medullary thyroid carcinoma (FNMTC) is defined as the presence of the disease in two or more first-degree relatives, without associated genetic syndromes. Concerns exist about the definition of FNMTC. Some authors reported that families with only two affected members may represent only a fortuitous association of this disease and not a FNMTC. On the contrary, there are agreements about the increased aggressiveness of FNMTC when compared with sporadic form of papillary thyroid cancer (PTC). On these bases, we hypothesized that clinical presentation as well as clinical outcome of PTC should not be different between families with two affected first-degree relatives (FNMTC-2) and families with three or more affected first-degree relatives (FNMTC-3), if both FNMTC-2 and FNMTC-3 are familial.

Objective and Methods: To validate our hypothesis, we retrospectively identified 101 patients, 75 females and 26 males, belonging to 40 kindred with FNMTC followed for a mean period of 106.7 months. We analyzed the clinical presentation and outcome of FNMTC patients at diagnosis, including gender, age at diagnosis, tumor diameter, extrathyroidal extension, multicentricity, cytological diagnosis of mPTC, familiarity should be considered a negative prognostic factor also in mPTC. The majority of patients were treated with total thyroideotomy should be considered a negative prognostic factor also in mPTC. The rate of intermediate risk patients rose from 33.7% in the whole cohort to 44.3% in patients with non incidental mPTC (p = 0.000). FmPTC was associated with a higher rate of intermediate risk only in non incidental mPTC. The rate of intermediate risk patients rose from 33.7% in the whole cohort to 61.3% in patients with non incidental FmPTC (p = 0.03). Regarding the clinical status, evaluated two years after the initial therapy, CHAID algorithm first splitted the patients exclusively according to the presence/absence of lymph node metastases, the presence of familial disease significantly increased the rate of structural incomplete response (p = 0.004). In SmPTC patients without lymph node metastases, the non incidental diagnosis increased the rate of structural incomplete response from 1.9% to 2.9% (p = 0.01).

Conclusions: This study suggests that familiarity should be considered as a negative prognostic factor also in mPTC. According to this, in the presence of cytological diagnosis of mPTC, familiarity should be taken into account in the management of mPTC.

OP-12-86
FAMILIARITY AS A NEW PROGNOSTIC FACTOR IN THE RISK STRATIFICATION OF THYROID MICROCARCINOMA
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Introduction: The incidence of papillary thyroid microcarcinoma (mPTC) is constantly increasing. Also familial forms of mPTC (FmPTC) are increasing. It is controversial if the FmPTC has a different clinical behavior than the sporadic form (SmPTC).

Objective: Aim of our study was to address the question if FmPTC has a different clinical presentation and outcome compared to SmPTC and if familiarity should be considered a negative prognostic factor also in mPTC.

Methods: We retrospectively analyzed 291 patients with mPTC followed for 110.7 ± 61.3 months. The majority of patients were treated with total thyroideotomy ± 131. The FmPTC was defined as the presence of this tumour in two or more first-degree relatives, after excluding hereditary syndromes associated with PTC.

Results: FmPTC patients had more frequently bilateral tumors (32.6%, p = 0.01) and lymph node metastases at diagnosis (30.2%, p = 0.02) than SmPTC (16.5% and 14.9%, respectively). Two years after the initial therapy, FmPTC patients had a higher rate of structural disease and a lower rate of remission than SmPTC (p = 0.007). On the contrary, the final clinical outcome was not different between the two groups (p = 0.9). We analyzed whether the familial disease was associated with clinical presentation and outcome also in a multivariate model, using a “CHAID tree-building algorithm”. The CHAID algorithm first splitted the patients exclusively according to the incidental/non incidental diagnosis. The rate of intermediate risk patients rose from 33.7% in the whole cohort to 44.3% in patients with non incidental mPTC (p = 0.000). FmPTC was associated with a higher rate of intermediate risk only in non incidental mPTC. The rate of intermediate risk patients rose from 33.7% in the whole cohort to 61.3% in patients with non incidental FmPTC (p = 0.03). Regarding the clinical status, evaluated two years after the initial therapy, CHAID algorithm first splitted the patients exclusively according to the presence/absence of lymph node metastases, the presence of familial disease significantly increased the rate of structural incomplete response (p = 0.004). In SmPTC patients without lymph node metastases, the non incidental diagnosis increased the rate of structural incomplete response from 1.9% to 2.9% (p = 0.01).

Conclusions: This study suggests that familiarity should be considered as a negative prognostic factor also in mPTC. According to this, in the presence of cytological diagnosis of mPTC, familiarity should be taken into account in the management of mPTC.
**OP-12-88**

**OBESITY AND DIFFERENTIATED THYROID CANCER (DTC): CORRELATION BETWEEN BODY MASS INDEX (BMI) AND HISTOPATHOLOGICAL FEATURES**

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**Background:** The role of obesity in the incidence of DTC is still debated and it is unclear if higher BMI could be associated with more aggressive presentation of DTC. The aim of this study was to investigate the relationship between BMI and histopathological features of a consecutive series of DTC patients.

**Patients and Methods:** We retrospectively evaluated the data of 805 consecutive DTC patients who underwent total thyroidectomy (TTx) and radioiodine remnant ablation (RRA) in years 2010–2011 at our institution. Patients were divided into three groups accordingly to their BMI [normal weight (Nw), overweight (Ow), obese (Ob)], at the time of the first control after TTx (median 5 months). For each group clinico-pathological and histological features and risk of recurrence (according to 2009 ATA Guidelines) were evaluated.

**Results:** Out of 805 pts, 360 were Nw (median age 41.5 y, 83.3% females), 285 were Ow (median age 49.0 y, 59.6% females) and 160 were Ob (median age 50.0 y, 64.4% females). Age and BMI were positively associated (p < 0.01). Papillary thyroid cancer, classic variant, was the most frequent histotype observed (48.3% of Nw, 41.5% of Ow, 41.2% of Ob), followed by follicular variant (24.2% of Nw, 29.9% of Ow, 26.2% of Ob). Tumor size was >4 cm in 5.3% of Nw, in 8.9% of Ow, and in 10.1% of Ob. DTC was multifocal in 56.6% of Nw, 55.6% of Ow and 59.9% of Ob. Metastatic lymph nodes (N1a/a/o N1b) were observed in 24.3% of Nw, 23.2% of Ow and in 18.4% of Ob. Accordingly to the ATA 2009, about one half of the pts had an intermediate risk of recurrence (51.4% of Nw, 51.2% of Ow, 50% of Ob) and the other half had low risk (46.9% of Nw, 47.4% of Ow, 48.1% of Ob); as expected, very few were the high risk patients. The post therapeutic whole body scan (pWBS) showed the presence of metastasis in 3.3% of N, 4.9% of Ow and 1.2% of Ob. The above reported differences among the three groups were not statistically significant.

**Conclusions:** 1) In our series increased BMI was significantly associated with older age; 2) there were no statistically significant differences in the histological presentation of DTC among Nw, Ow and Ob pts; 3) No differences of metastatic disease revealed at pWBS were observed in the 3 groups.

**OP-12-89**

**PREDICTORS OF PERSISTENT OR RECURRENT DISEASE IN 4,292 PATIENTS WITH DIFFERENTIATED THYROID CANCER**

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**Context:** Differentiated thyroid cancer (DTC) is generally associated with an excellent prognosis, however, up to 20% of patients have disease events after surgery, diagnosed “ab initio” or during follow-up. Disease status assessment at diagnosis has important clinical implications for planning: 1) tailored treatment strategies, and 2) long term follow-up procedures.

**Objective:** To evaluate predictors of persistent or recurrent disease, according to clinical and pathological data, in a continuous series of DTC patients, followed-up in our Thyroid Clinic.

**Design and Patients:** We retrospectively reviewed a consecutive series of 4,292 patients undergone thyroidectomy for DTC. According to the time of post-surgical events, patients were subdivided into two groups: with persistent disease (occurrence up to one year from surgery) and with recurrent disease (later than one year).

**Results:** Among 805 pts, 360 were Nw (median age 41.5 y, 83.3% females), 285 were Ow (median age 49.0 y, 59.6% females) and 160 were Ob (median age 50.0 y, 64.4% females). Age and BMI were positively associated (p < 0.01). Papillary thyroid cancer, classic variant, was the most frequent histotype observed (48.3% of Nw, 41.5% of Ow, 41.2% of Ob), followed by follicular variant (24.2% of Nw, 29.9% of Ow, 26.2% of Ob). Tumor size was >4 cm in 5.3% of Nw, in 8.9% of Ow, and in 10.1% of Ob. DTC was multifocal in 56.6% of Nw, 55.6% of Ow and 59.9% of Ob. Metastatic lymph nodes (N1a/a/o N1b) were observed in 24.3% of Nw, 23.2% of Ow and in 18.4% of Ob. Accordingly to the ATA 2009, about one half of the pts had an intermediate risk of recurrence (51.4% of Nw, 51.2% of Ow, 50% of Ob) and the other half had low risk (46.9% of Nw, 47.4% of Ow, 48.1% of Ob); as expected, very few were the high risk patients. The post therapeutic whole body scan (pWBS) showed the presence of metastasis in 3.3% of N, 4.9% of Ow and 1.2% of Ob. The above reported differences among the three groups were not statistically significant.

**Conclusions:** 1) In our series increased BMI was significantly associated with older age; 2) there were no statistically significant differences in the histological presentation of DTC among Nw, Ow and Ob pts; 3) No differences of metastatic disease revealed at pWBS were observed in the 3 groups.

**Table 1. Total events, persistent and recurrent disease in 4,292 DTC patients**

<table>
<thead>
<tr>
<th></th>
<th>Total events n (%)</th>
<th>Persistent n (%)</th>
<th>Recurrent n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total events</strong></td>
<td>639</td>
<td>498</td>
<td>141</td>
</tr>
<tr>
<td>Biochemical</td>
<td>254/639 (39.7%)</td>
<td>171/498 (34.3%)</td>
<td>83/141 (58.9%)</td>
</tr>
<tr>
<td>Structured</td>
<td>385/639 (60.3%)</td>
<td>327/498 (65.7%)</td>
<td>58/141 (41.1%)</td>
</tr>
<tr>
<td>LN mets</td>
<td>170</td>
<td>136</td>
<td>34</td>
</tr>
<tr>
<td>Distant mets ± LN mets</td>
<td>215</td>
<td>191</td>
<td>24</td>
</tr>
<tr>
<td>Disease free at last visit</td>
<td>151 (23.7%)</td>
<td>71 (14.3%)</td>
<td>80 (56.7%)</td>
</tr>
</tbody>
</table>

**Results:** After a median follow-up of 4.9 yrs, 639/4292 (14.9%) patients presented a disease event. Most of them (78%, 498/639) showed persistent disease vs. few patients (22%, 141/639) with recurrent disease. Average age at diagnosis was significantly higher in the group with persistent disease (46.9 years) than in the disease-free group (45.7 years). The female/male ratio was significantly lower in the group with persistent disease (F/M = 1.9/1) vs. the group with either disease free (F/M = 4.4/1) or recurrent disease (F/M = 4.8/1). Moreover, structured disease was significantly more frequent in the group with persistent disease (65.7%) than in the group with recurrent disease (41.1%). The occurrence of distant metastases was especially different in the two groups (38.4% vs 17.0%). At multivariate analysis, several variables were independently associated with persistent disease: male gender (OR = 1.7), age (OR = 1.02), follicular histotype (OR = 1.5), T-status (T3: OR = 3) and N-status (N1b: OR = 7.7). N-status was the sole variable independently associated with recurrent disease (N1b: OR = 2.5).

**Conclusions:** In DTC patients, persistent disease is more common than recurrent disease, it is often due to structural disease and distant metastases, and is linked to several independent risk factors. Conversely, recurrent disease is more frequently due to local lymph-nodal spread. Post-operative DTC status is helpful in planning short- and long-term follow-up procedures and in predicting long-term outcome.

*Eur Thyroid J 2018;7(suppl 1):1–118 DOI: 10.1159/000491542*
Table 1. Malignancy Rates Before/After Reclassification of NEFVPTC as NIFTP (OP-12-90)

<table>
<thead>
<tr>
<th>Bethesda Category</th>
<th>Whole sample/Submitted to surgery (n)</th>
<th>Malignant cases before/after NIFTP (n)</th>
<th>Risk of malignancy, %</th>
<th>Submitted to surgery</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before NIFTP</td>
<td>After NIFTP</td>
<td>Relative ΔROM, %</td>
<td>Before NIFTP</td>
<td>After NIFTP</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>514/180</td>
<td>65/55</td>
<td>12.6 10.7 –15.1</td>
<td>36.1 30.6 –15.2</td>
<td>0.002</td>
</tr>
<tr>
<td>FN/SFN</td>
<td>182/114</td>
<td>27/25</td>
<td>14.8 13.7 –7.4</td>
<td>23.7 21.9 –7.6</td>
<td>0.500</td>
</tr>
<tr>
<td>SFM</td>
<td>46/29</td>
<td>21/18</td>
<td>45.7 39.1 –14.4</td>
<td>72.4 62.1 –14.2</td>
<td>0.250</td>
</tr>
<tr>
<td>Malignant</td>
<td>30/25</td>
<td>21/21</td>
<td>70.0 70.0 0</td>
<td>84.0 84.0 0</td>
<td>NA</td>
</tr>
</tbody>
</table>

ROM, rate of malignancy; NA, not applicable.

348. We found 180 patients with a cytopathologic diagnosis of AUS/FLUS (10 NIFTP), 29 with FN/SFN (2 NIFTP), 25 with SFM (3 NIFTP) and 25 within BSRTC VI (no NIFTP). The complete results of the series can be found in Table 1. Among the 15 patients with NIFTPs, 93% underwent total thyroidectomy and 20% received radioiodine.

**Conclusion:** Reclassification as a NIFTP resulted in a decrease in overall malignancy rate, and the Bethesda categories most affected were III (AUS/FLUS) and V (SFN). The majority of NIFTP lesions were found on AUS/FLUS category, in which we should take into consideration the reduced risk of malignancy in our approach. Besides reducing the psychological burden associated with a cancer diagnosis, the NIFTP category has the potential for decreasing risks associated with surgery and health costs.

### Oral Session 13:
The Thyroid and Thyroid Hormone

**OP-13-91**

**CRYSTAL STRUCTURE OF LIGAND-FREE TSH RECEPTOR**

*Jennifer Miller-Gallacher*, Paul Sanders*, Stuart Young*, Andrew Sullivan*, Stuart Baker*, Samuel Reddington*, Matthew Clue*, Katarzyna Kabelis†, Jill Clark†, Jane Wilmut†, Daniel Thomas†, Monika Chlebowska†, Francesca Cole†, Emily Pearson†, Emma Roberts†, Matthew Holly†, Michele Evans†, Ricardo Núñez Miguel†, Michael Powell†, Jane Sanders†, Jadwiga Furmaniak‡, Bernard Rees Smith‡

†Firs Laboratories, RSR Ltd, Cardiff, UK.‡Firs Laboratories, RSR Ltd, Cardiff, UK.

**Objective:** The crystal structures of the thyroid stimulating hormone receptor (TSHR) leucine-rich domain (amino acids 22–260; TSHR260) have been solved in complex with both a stimulating human monoclonal autoantibody (M22™) and a blocking human monoclonal autoantibody (K1-70™). However, attempts to purify and crystallise ligand-free TSHR260 have been unsuccessful due to the poor stability of TSHR260. Our aim was to generate a stable TSHR260 construct that could be purified and crystallised without antibodies bound.

**Methods:** Stable TSHR260-JMG55 was produced by mutagenesis, expressed in insect cells and purified using a combination of ion exchange chromatography, affinity chromatography, nickel-affinity chromatography and size-exclusion chromatography. Purified TSHR260-JMG55 was deglycosylated and crystallised by hanging drop vapour diffusion without autoantibodies bound and the data was collected at the European Synchrotron Radiation Facility.

**Results:** Ligand-free TSHR260-JMG55 remained stable through three rounds of purification, deglycosylation and a further two purification steps. TSHR260-JMG55 was approximately 900 times more thermostable than the wild type TSHR260. Purified TSHR260-JMG55 bound human TSHR monoclonal autoantibodies and patient serum TSHR autoantibodies with similar affinity to wild type TSHR260. Furthermore, full-length TSHR containing the TSHR260-JMG55 domain responded to stimulation by TSH or human TSHR monoclonal autoantibodies in a similar manner to full-length wild type TSHR. The crystal structure of unbound TSHR260-JMG55 was solved to 2.83 Å with two molecules in the asymmetric unit and good electron density observed for residues 24–260.

**Conclusion:** The ligand-free TSHR260-JMG55 structure and the TSHR260 structures in complex with M22™ or K1-70™ are remarkably similar except for small changes in side-chain conformations, with root-mean-square deviations of the Cα atoms of 0.42–0.71 Å for residues 30–256 of TSHR260. The main difference in the structures is at the N-terminus where flexibility in the protein gives rise to dispersed electron density and varying conformations. The similarity in structures suggests that the binding of autoantibodies does not alter the rigid leucine rich repeat structure of TSHR260. Therefore, stimulation of the TSHR by M22™ and blocking of TSH stimulation of the TSHR by K1-70™ must involve changes in other domains of the receptor. This is the first reported structure of a glycoprotein hormone receptor crystallised without a ligand and should be helpful in understanding the interactions of glycoprotein hormones with their receptors. Thermostable TSHR260-JMG55 may also be useful in designing new methods for TSHR autoantibody detection and in developing new drugs for controlling the autoimmune response to the TSHR.

**OP-13-92**

**PRO-INFLAMMATORY EFFECT OF HYALURONAN OLIGOSACCHARIDES (6-MER-HA) IN HUMAN THYROCYTES AND FIBROBLASTS: ROLE OF TOLL-LIKE 2 (TLR-2) AND 4 (TLR-4) RECEPTORS**

*Rosaria Ruggeri*, Teresa Manuela Vicchio†, Alfredo Campennì‡, Angela Avenoso‡, Salvatore Campo‡, Giuseppe Maurizio Campo‡, Francesco Frasca‡, Francesco Trinarchi†, Angela D’Ascolab

†Department of Clinical-Experimental Medicine and Pharmacology, Division of Endocrinology, University of Messina, AOU Policlinico di Messina, Messina, Italy; ‡Department of Human Pathology in Adulthood and Childhood, University of Messina, AOU Policlinico di Messina, Messina, Italy; ‡Department of Biomedical and Dental Sciences, and Morfo-Functional Images, Nuclear Medicine Unit, University of Messina, AOU Policlinico G. Martino Messina, Messina, Italy; §Department of Biomedical and Dental Sciences, and Morfo-Functional Images, University of Messina, Messina, Italy; §Department of Biomedical and Dental Sciences, and Morfo-Functional Images, University of Messina, Messina, Italy; §University of Catania, Endocrinologia, Garibaldi Nisima, Catania, Italy; †University of Messina, Accademia Peloritana Dei Pericolanti, Messina, Italy.

**Objectives:** Lymphocytic infiltration and inflammation in autoimmune thyroid diseases (AID) results in accumulation of hyaluronan (HA) that contributes to the pathogenesis of extra-thyroidal manifestations of AIDs, namely ophthalmopathy, pretibial dermopathy and mixedema. Indeed, hyaluronan fragments (originating from native HA during tissue inflammation) are able to up-regulate pro-inflammatory genes by interacting with the Toll-like receptor...
2 (TLR-2), Toll-like receptor 4 (TLR-4) and CD44. In particular, TLRs activation activates a signaling mediated by adapter molecules, including myeloid differentiation primary response (MyD88) and tumor necrosis factor receptor associated factor 6 (TRAF-6), that results in the nuclear factor kappa-B (NF-kB) activation. NF-kB, in turn, modulates the expression of inflammasome mediators, as interleukin-1 beta (IL-1 beta) and interleukin-6 (IL-6). This study was aimed at investigating the effect of very small HA oligosaccharides (6-mer HA) on human thyrocytes and fibroblasts in vitro.

**Methods:** Primary thyrocytes and fibroblasts were obtained from patients who thyrodectomized for benign thyroid diseases (solitary thyroid nodule). Cultured cells were treated for 24 h with increasing concentrations of O-6-mer HA (12.5, 25, 50 μg/ml), with and without TLR-2 and TLR-4 blocking antibodies. mRNA and proteins expression for TLR-2, TLR-4, MyD88 and TRAF-6 were evaluated by real-time PCR and Western Blot, respectively. Protein quantification was assessed by densitometry analysis. NF-kB p50/65 activation was determined in nuclear extracts by DNA binding activity assay. IL-1 beta and IL-6 levels were measured by ELISA.

**Results:** In cultured thyrocytes, 6-mer HA induced the increase in both mRNA and protein of TLR-2, TLR-4, MyD88 and TRAF-6, as well as the activation of NF-kB and, in turn, the increase in IL-1beta and IL-6 levels, at 25 and 50 μg/ml concentrations (p < 0.05 and p < 0.01, respectively). A similar effect of O-6-mer HA was observed in cultured fibroblasts also at the lowest concentration (p < 0.05; p < 0.01; p < 0.001 for HA 12.5, 25 and 50 μg/ml, respectively). Incubation with TLR-2 and/or TLR-4 specific blocking antibodies prevented the up-regulation of MyD88 and TRAF-6, and significantly reduced NF-kB activation and pro-inflammatory cytokine production in both cell types (p < 0.05 anti-TLR-2; p < 0.01 anti-TLR-4; p < 0.001 anti-TLR-2 + anti-TLR-4).

**Conclusions:** HA (6-mer HA) oligosaccharides induce an inflammatory response, via TLR-2 and TLR-4 activation, in both thyrocytes and fibroblasts in vitro. Hence, accumulation of HA oligosaccharides may play an important role in the pathogenesis of extra-thyroidal manifestations of AID, such as orbitopathy, pretibial myxedema and myxedema.

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**OP-13-93**

**CLASS III PI3K/VPS34 IS CRUCIAL FOR THYROID HORMONENOSIS**

**Grieco Giuseppina**, Wang Tongsong, Gaie Chevornay Héloïse, Janssens Virginie, Liao Xiao, Samuel Refetoff, Courtoy Pierre, Christophe Pierre

1De Duve Institute, Brussels, Belgium; 2Chicago, USA; 3University of Chicago, Medicine/Endocrinology, Chicago, USA; 4De Duve Institute, Université Catholique de Louvain, Bruxelles, Belgium

The production of thyroid hormones (T3, T4) depends on thyroid organization in follicles, lined by a monolayer of thyrocytes with strict apico-basal polarity. Polarization not only supports vectorial transport of thyroglobulin (Tg) to storage into, and recapture from, the colloid but also allows selective dispatching of channels, transporters, pumps and enzymes to their appropriate basolateral (NIS and NaKATPase) or apical membrane domain (pendrin, anocytamin, DUOX2, DUOX2 and TPO). How do these actors of T3/T4 synthesis reach their final destination has been poorly studied. Type III PI3K/Vps34 is now recognized as a main component in the general control of vesicular trafficking and cell homeostasy via autophagy. Here, we selectively inactivated Vps34 in thyrocytes using the Pax8-Cre deleter strain. Vps34 cKO mice were born at the expected Mendelian ratio and showed normal growth until postnatal day 14, then stopped growing and died at around 1 month of age. We thus analyzed thyroid Vps34 cKO at postnatal day 14. We found that loss of Vps34 in thyrocytes causes: (i) disorganization of thyroid parenchyma with abnormal thyrocyte and follicular shape, (ii) reduced PAS colloidal spaces and impaired luminal iodothyroglobulin/thyroglobulin ratio, (iii) severe hypothyroidism with very low T4 levels (0.75 ± 0.62 μg/dL) and huge plasma TSH (19.31 ± 10,482 μIU/mL), (iv) intense signal in thyrocytes for the lysosomal membrane marker, LAMP-1, and the autophagy marker, p62. These data suggest that Vps34 is crucial for thyrocyte homeostasis and thyroid hormonogenesis, by controlling biosynthetic and autophagic routes.

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**OP-13-94**

**COMPLEX CHROMOSOMAL REARRANGEMENT AND SEGMENTAL MATERNAL UPD AT CHROMOSOME 7 IN A PATIENT WITH PENDRED SYNDROME AND SILVER-RUSSELL SYNDROME-LIKE FEATURES**

**Laura Fugazzola**, Chiara Castronovo, Valentina Giorgini, Alessandra Sironi, Silvia Russo, Palma Finelli, Susan Marelli, Luca Persani, Valentina Cirelo

1Division of Endocrine and Metabolic Diseases, IRCCS Istituto Auxologico Italiano, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy; 2Laboratory of Medical Cytogenetics and Molecular Genetics, IRCCS Istituto Auxologico Italiano, Milan, Italy; 3Laboratory of Medical Cytogenetics and Molecular Genetics, IRCCS Istituto Auxologico Italiano, Department of Medical Biotechnologies and Translational Medicine, University of Milan, Milan, Italy; 4Neuropsychiatry and Neurorehabilitation Unit, Scientific Institute, IRCCS Eugenio Medea, Bosisio Parini, Lecco; 5University of Milan, IRCCS Istituto Auxologico Italiano, Ospedale San Luca, Milan, Italy; 6Division of Endocrine and Metabolic Diseases, IRCCS Istituto Auxologico Italiano, Milan, Italy

Pendred syndrome (PS) is an autosomal recessive disorder characterized by the association of sensorineural hearing loss, inner ear malformations, and a partial iodide organification defect at the thyroid level, though the phenotype is extremely variable. The clinical features of PS are due to an impaired function of pendrin, a transmembrane protein encoded by the SLC26A4 gene on chr7q22.3. Mutations in SLC26A4 are found in compound heterozygosity or in homozygosity in PS patients. Silver-Russell syndrome (SRS) is a heterogeneous syndrome with severe intrauterine and postnatal growth retardation, and typical dysmorphic features. A minor epigenetic mechanism leading to SRS is a maternal uniparental disomy either of the whole chromosome 7 (matUPD7) or restricted to 7q (matUPD7q). The clinical features of these cases are less characteristic: the growth is less retarded, the morphological abnormalities are slight, whereas delayed development and speech are more common. Three imprinted loci, GRB10 at 7p12.1, PEG10 at 7q21.3 and MEST at 7q32.2 have been identified, though no imprinted genes have been conclusively implicated in SRS. Here, we report the genetic characterization of a female child affected with PS and a slight postnatal growth retardation. Nucleic Acids were extracted from whole blood samples of the child and her parents. Molecular analysis of SLC26A4, cytogenetic analyses, SNPs Array and MS-MLPA were performed. A gross homozygous deletion of SLC26A4 exons 17–20 was found in the child, but the father resulted wild type and the mother heterozygous for the deletion. The sequencing analysis of junction fragments showed the presence of an insertion of about 1 kb of the IVS3 of the SLC26A4 and a partial deletion on chromosome 7. To exclude apparently balanced complex structural chromosome aberrations between chromosom 7p and 7q, which might have mediated the formation of the del/ins rearrangement within SLC26A4, a cytogenetic analysis was performed on both the child and her mother, which did not reveal any abnormality in chromosome 7 homologues. The suspect of a matUPD7 in the child was confirmed by SNPs array, which showed a segmental duplication of almost the long arm of maternal chromosome 7. Moreover, an increased methylation signal of MEST gene was detected in the child by MS-MLPA. In conclusion, we report the first case of a female child affected with PS and SRS-like features harboring a complex chromosomal rearrangement and a maternal segmental UPD of chromosome 7.
PARTIAL THYROID-FUNCTION SPECIFIC G PROTEIN ALPHA S DEFICIENCY LEADS TO SEVERE HYPOTHYROIDISM, HYPERPLASIA AND PAPILLARY THYROID CARCINOMA-LIKE LESIONS IN MICE

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The thyroid function is controlled by the thyroid-stimulating hormone (TSH), which binds to its G protein-coupled receptor (TSHR) and subsequently activates the Gs- and Gq/11-mediated signaling cascades. Consequently, the iTGαsKO mice show decreased white adipose tissue were decreased only in the iTGαsKO males. Surprisingly, at the age of 6 months, neoplastic lesions with increased proliferation and slightly increased phosphorylated extracellular signal-regulated protein kinase 1 and 2 (pERK1/2) staining were found in iTGαsKO mice. These tumors developed from non-recombined thyrocytes still expressing Gαs, in the presence of highly elevated serum TSH. In summary, we report that partial thyrocyte-specific Gαs deletion leads to severe hypothyroidism, but can also trigger tumor development in the thyroid of iTGαsKO mice. Thus, these mice are a novel model to elucidate the pathophysiological consequences of hypothyroidism and also TSHR/Gαs-mediated signaling.

SOX9 REGULATES WNT/BETA-CATENIN PATHWAY Activity THROUGH MODULATION of TCF4 IN THYROID FOLLICULAR CELLS

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The sex-determining region Y (SRY)-box (SOX) family of transcription factors are involved in the regulation of many developmental processes such as organogenesis and maintenance of stem cells. Among these factors, Sox9 has been studied in a wide variety of tissues due to its role in cell differentiation, proliferation and survival, and it has been shown to have a correlation with the Wnt/β-catenin signaling pathway. However, whether this transcription factor is an activator or an inhibitor of this pathway is not clear yet, as it seems to play a different role depending on the tissue studied. Here we present our results on this matter obtained in thyroid follicular cells.

We performed Sox9 gain and loss of function experiments in PCC13 cells to analyse its role on several components of the Wnt/β-catenin signaling pathway. The data obtained indicate that TCF4, a transcription factor that exerts its function when the pathway is activated, is the most affected gene by Sox9. Downregulation of Sox9 leads to a reduction in both TCF4 mRNA and protein levels while its overexpression had the reverse effect. Furthermore, protein levels of β-catenin were diminished after silencing of Sox9. In order to test whether TCF4 had an effect on the expression of Sox9, an in silico analysis of its promoter was done identifying several TCF4 binding sites. Protein/DNA binding assays showed functional binding of TCF4 to Sox9 promoter suggesting a regulation of its transcriptional activity. Moreover, downregulation by RNA silencing of TCF4 resulted in a reduction of Sox9 protein levels.

In conclusion, we found that Sox9 regulates TCF4, one of the main components of the Wnt signaling pathway, and this in turn controls Sox9 expression. These findings suggest the existence of a regulation loop controlling the expression of Sox9 and Wnt/β-catenin pathway target genes. Future experiments will clarify the role of this regulation in thyroid physiology.

A FEEDBACK LOOP BETWEEN THE TUMOR SUPPRESSOR DICE R1 AND THYROID DIFFERENTIATION TRANSCRIPTION FACTORS PLAYS AN IMPORTANT ROLE IN THYROID TUMORIGENESIS

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Background: Thyroid cancer is a common endocrine malignancy that has rapidly increased its global incidence in recent decades. It is known that when thyroid cancer progress there is a marked downregulation of differentiation and consequently a decreased expression of thyroid transcription factors. In addition, thyroid tumors loss their response to TSH and to its downstream signaling. In the last years, the role of miRNA in cancer progression has been well established and its functional maturation requires the enzyme DICE R1. Since low levels or loss of function mutations in DICE R1 have been described in thyroid cancer, the aim of this work was to study the function and implications of DICE R1 down-regulation as well as its transcriptional regulation in this pathology.

Methods: DICE R1, NX2.1, PAX8 and CREB1 miRNA levels were evaluated in FTC patients analysing The Cancer Genome Atlas (TCGA). DICE R1 was suppressed or silenced in immortal thyroid cells and functional assays were performed to assess proliferation, migration and invasion. Transcription factor binding sites within the DICE R1 promoter were identified by ECR browser bioinformatic tool. Transcription factors functional activity was analysed by protein/DNA binding assay and luciferase promoter activity.

Results: We found that transcription of DICE R1 is positively regulated by NX2.1 and PAX8 two transcription factors involved in thyroid differ entiation. In accordance, we observed that TSH, the main regulator of thyroid differentiation, increases DICE R1 by a mechanism involving CREB1 transcription factor. We confirm that NX2.1, PAX8 and CREB1 are all decreased in thyroid cancer, suggesting that DICE R1 downregulation in this tumor type is mediated, at least in part, through the impairment of its transcription.

Our analysis of TCGA revealed an association between low DICE R1 expression and thyroid metastasis, high risk, and extrathyroidal extension. Functionally, DICE R1 downregulation promoted proliferation, migration, invasion and worse clinicopathological transition in thyroid cancer cell lines. However, it suppressed the expression of pro-differentiation transcription factors PAX8 and NX2.1 supporting the existence of a positive feedback loop. Importantly DICE R1 silencing also decreased the expression of the hallmark of thyroid differentiation, NIS, and reduced the cell iodine uptake, essential for thyroid cancer treatment.

Conclusions: Overall, our data establish DICE R1 as a new tumor suppressor in thyroid cancer bearing downregulation associated with worse clinical outcome in patients with this cancer. In addition, we show that DICE R1 transcription is dependent on NX2.1, PAX8 and CREB1, three transcription factors known to be markedly decreased in thyroid cancer.
In zebrafish, we observed the expression of glis3 transcript since the early developmental stages, and in particular it well localized in the pharyngeal endoderm, in the developing pancreas and in the pronephric ducts suggesting a direct role of glis3 in the commitment and growth of these organs, but is absent in the differentiated thyrocytes.

Transient knockdown zebrafish embryos, obtained by morpholino micro-injection (called glis3 MOs) revealed a reduced expression of the early thyroid genes nkx2.4 and pax2a, thyroid hypoplasia with low T4 production and high TSH, demonstrating that glis3 is involved in thyroid development. The Sonic hedgehog (Shh) pathway is a critical regulator of embryonic development, which sets off a chain of events in target cells, regulating gene expression by transcription factors of the Gli-family. It has been reported that GLIS3 physically interacts with the Shh-suppressor Sufu, although the link between Shh and GLIS3 is presently unknown. By ISH, we observed that the expression of the Shh was significantly reduced in the pharyngeal endoderm of glis3 MOs. The injection of a morpholino against shh transcripts abolished the expression of glis3 in the endodermal layer, confirming their association during the endocrine cells specification. Furthermore, the treatment with Cyclopamine (Shh-antagonist) resulted in a reduced or absent expression of glis3.

In conclusion, this is the first evidence of Shh-Glis3 possible interactions during the early specification of thyroid primordium. These data suggest a major role of glis3 in regulating the commitment of the thyroid precursor cells and provide novel insights into the molecular mechanisms involved in CH pathogenesis.
Objectives: The human monoclonal autoantibody K1-70™ to the TSH receptor (TSHR) blocks the stimulation of cyclic AMP production by TSH and thyroid stimulating autoantibodies (TSAb). The toxicity of K1-70™ IgG following weekly intravenous (iv) or intramuscular (im) administration to rats and to cynomolgus monkeys for 29 days was determined. An assessment of delayed onset toxicity and/or reversibility of toxicity was made during a 4 week treatment-free period. The pharmacokinetic profile of K1-70 was analysed.

Methods: The study was conducted under the requirements of the Animals (Scientific Procedures) Act 1986 and local ethical approval. Rats were dosed iv with 0, 10, 30 and 100 mg/kg or im with 5 mg/dose. Animals were dosed on days 1, 8, 15, 22 and 29. Delayed onset toxicity and/or reversibility of toxicity was assessed during a subsequent 4 week treatment-free period. Blood samples for pharmacokinetic analysis were taken on days 1 and 22 of the dosing phase, pre-dose, 5 min and at 8, 24, 72 and 168 hours post dose.

Results: In rats a direct effect of K1-70™ was a decrease in T3 and T4 with 0, 10, 30 and 100 mg/kg or im with 5 mg/dose. Animals were dosed on days 1, 8, 15, 22 and 29. Delayed onset toxicity and/or reversibility of toxicity was assessed during a subsequent 4 week treatment-free period. Blood samples for pharmacokinetic analysis were taken on days 1 and 22 of the dosing phase, pre-dose, 5 min and at 8, 24, 72 and 168 hours post dose.

Conclusions: In the studies with monkeys and rats, the toxicological findings were consistent with the pharmacology of K1-70 and were consistent with the hypothyroid state. Based on the rat toxicity data the highest maximum dose of K1-70 should be 145 mg for the first in human phase I safety, tolerability, pharmacokinetic and pharmacodynamics study in subjects with Graves' disease.
**P1-01-03**

**SERUM LEVELS OF THE SOLUBLE RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS ARE REDUCED IN CHILDREN SUFFERING FROM HASHIMOTO’S THYROIDITIS**

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**Objectives:** Advanced glycation end products (AGEs) increased oxidative stress and promote inflammation, resulting in the cellular damage, by interacting with the their receptor (RAGE) on cell membrane. By contrast, the soluble receptor for AGE (sRAGE), that is proteolytically cleaved from cell surface receptor via matrix metalloproteinases, sequester RAGE ligands and act as a cytoprotective and anti-inflammatory agent. AGEs-RAGE/sRAGE interaction is deemed to play a role in the pathogenesis of several disease related to oxidative stress. More other, oxidative stress has been implicated in the pathogenesis of several autoimmune disorders, including thyroid diseases. Mostly, it has been correlated to thyroid dysfunction but recently, increased levels of AGEs, have been reported in adult individuals suffering from euthyroid Hashimoto’s thyroiditis (HT) (Ruggeri et al. Thyroid 2016). Non data are available on such oxidative stress parameter in pediatric HT patients. The aim of our study was to investigate the changes in oxidative balance in euthyroid HT in pediatric age.

**Methods:** We enrolled 19 HT pediatric patients (3 M, 16 F; mean age 12.3 ± 2.4 yr) and 18 age- and sex-matched healthy controls (6 M, 12 F; mean age 12.0 ± 2.4 yr). None was on LT-4 therapy. Exclusion criteria: autoimmune, inflammatory and infection comorbidities. Patients did not differ significantly from controls with regard to lipid and glucidic profile neither for anthropometric parameters. In sera from each subject, sRAGE levels were measured by ELISA (kit sRAGE ELISA, R&D System, Minneapolis, USA; minimum detectable dose 3 pg/ml). AGEs, compounds formed by the transformation of proteins, were determined on spectrophotometric detection by ELISA (kit sRAGE ELISA, R&D System, Minneapolis, USA; minimum detectable dose 3 pg/ml).

**Results:** sRAGE levels were significantly lower in HT patients (median 307.30–850.30) than in controls (588.30–265.80–112.32; P = 0.046). These values correlated negatively with BMI (r = −0.365, p = 0.026) and anti-thyroid antibodies positivity (r = −0.364, p = 0.027), irrespective of TSH values and thyroid functional status. No differences emerged between patients and controls with regard to serum AGEs (124.25 AU/g prot, range 70.20–850.30) than in controls (588.30–265.80–112.32; p = 0.046).

**Conclusion:** sRAGE levels were decreased in HT children/adolescents, and autoimmunity per se seem to play an important role in such a reduction of sRAGE, irrespective of any functional alteration. Given the protective effects of sRAGE, children and adolescents suffering from HT may exhibit increased susceptibility to oxidative damage, even when in euthyroid status.

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**P1-01-04**

**THYROID PEROXIDASE ANTIBODIES AND ANTI-MÜLLERIAN HORMONE IN 470 WOMEN WITH UNEXPLAINED RECURRENT PREGNANCY LOSS**

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**Objectives:** Thyroid autoimmunity is common in women of reproductive age and thyroid peroxidase-antibodies (TPOAbs) have been associated with an increased risk of pregnancy loss. The mechanism is unknown, but TPOAbs have been shown to be present in ovaries of women with pregnancy loss. Anti-Müllerian Hormone (AMH) is currently debated as a marker of egg reserve (and egg quality) and low AMH has been suggested as a risk factor for pregnancy loss. However, the relationship between TPOAbs and AMH levels in women with recurrent pregnancy loss is unknown. We investigated if TPOAbs were associated with AMH levels in women with unexplained recurrent pregnancy loss (RPL).

**Methods:** Cohort study of all women with RPL attending the RPL unit at our tertiary referral center, Copenhagen University Hospital, from 2010–2015. RPL ≥3 consecutive losses. Analyses of AMH by ELISA Generation I (Beckman Coulter, Marseilles, France) and TPOAbs (automated Kryptor immuno-fluorescent assay; TPOAb-positivity >60 kU/L). Low AMH ≤5 pmol/L. Regression analyses were adjusted for age, previous losses, TPOAbs, and smoking.

**Results:** A total of 565 women with RPL had attended the unit, of which 470 (83.5%) had measurements of both TPOAbs and AMH. Of these, 72 (15.3%) were TPOAb-positive and 54 (11.5%) had AMH-levels ≤5 pmol/L. There was no difference in median AMH-levels between TPOAb-positive and TPOAb-negative women (17.0 vs. 18.0, Mann-Whitney-U, p = 0.27). Only 4 of 72 (5.6%) TPOAb-negative women had AMH-levels ≤5 pmol/L compared to 50 of 398 (12.6%) TPOAb-negative women (p = 0.11, adjusted Odds Ratio (OR) 0.4, 95% Confidence Interval (CI):0.1–1.1, p = 0.07). However, smoking was a strong predictor of AMH-levels ≤5 pmol/L (OR 4.2, 95% CI:1.5–11.9, p = 0.008) and, as expected, so was age (OR 1.2, 95% CI:1.1–1.3, p < 0.001). Among smokers, 21.4% had AMH-levels ≤5 pmol/L compared to 13.3% in non-smokers (p = 0.25). Among TPOAb-positive women, 10.8% had low levels of AMH, 14.8% had normal levels, and 19.8% had high levels if applying method- and age-specific reference ranges. Excluding all women with high AMH-levels, TPOAbs were still not significantly associated with low AMH (OR 0.4 95% CI:0.1–1.2, p = 0.11).

**Conclusion:** In 470 women with unexplained RPL, TPOAb-positivity was not associated with AMH levels. Thus, the association between TPOAbs and pregnancy loss is unlikely explained by reduced AMH levels and vice versa. However, women who smoked had a four times higher risk of having a low AMH-level. This should be confirmed in larger studies, but may serve as a clinical warning to women with RPL.

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**P1-01-05**

**PATIENTS WITH GRAVES’ DISEASE WITH NON-UNIFORM THYROID RADIO-ISOTOPE UPTAKE ARE OLDER AND HAVE LOWER THYROID HORMONE LEVELS**

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**Background:** Graves’ disease (GD) is an autoimmune condition characterised by stimulation of the TSH receptor by autoantibodies leading to hyperthyroidism. Previously, uniform uptake of radio-isotope by the thyroid gland was one of the diagnostic features of GD. However, with the advent of TSH receptor antibody (TRAb) testing a number of GD patients with non-uniform uptake are being recognized. The prevalence of GD patients with...
non-uniform uptake is unclear and their clinical characteristics and signifi-
cance is unknown.

Methods: Consecutive patients with newly diagnosed thyrotoxicosis seen in endocrinology out-patient clinics between October 2007 and March 2018 had thyroid radio-isotope uptake scanning performed with Tc99 prior to com-
men-cement of antithyroid drugs. In addition, TRAb levels were measured by Roche immunoassay. The demographic, clinical and biochemical features of GD patients (diagnosed as TRAb >1.5 U/L) with non-uniform Tc99 uptake was compared to those with uniform uptake.

Results: A total of 257 patients were included in this analysis. The pre-
vale-ence of non-uniform uptake of Tc99 was seen in 16 patients (6.2%). The patients with non-uniform uptake were older than those with uniform uptake (60.9 vs 48.2 years, p < 0.001) and tended to have lower thyroid hormone levels at diagnosis (FT4: 34.2 vs 44.7 pmol/L, p = 0.07 and FT3: 12.3 vs 18.3 pmol/L; p = 0.05) despite similar TRAb levels (9.3 vs 10.3; p = 0.35). On multivariate regression analysis, the group with non-uniform uptake had a 8.6 pmol/L lower FT4 level than those with uniform uptake independent of age, gender, smoking status and TRAb level. However, the risk of relapse was similar in both groups after 12 months of antithyroid drug cessation (25% vs 26%, respectively).

Conclusions: Non-uniform uptake of radio-isotope is seen in a small but substantial number of patients with GD and could be misdiagnosed as toxic multinodular goiter if TRAb levels are not evaluated. Furthermore, patients with non-uniform radio-isotope uptake are older, have lower thyroid hormone levels despite similar TRAb concentrations, but have similar risk of relapse as compared to those with uniform uptake.

PI-01-06
SEX LIFE IS IMPAIRED IN PATIENTS WITH BENIGN THYROID DISORDERS
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Background and Aims: Thyroid diseases may impact sexual function. The aims of this study were to describe the frequency of self-reported thyroid-related impaired sexlife in patients with thyroid diseases, to examine its clinical correlates and relationship with overall quality of life (QoL), and to investigate the effect of treatment

Methods: Two patient samples were investigated: a cross-sectional sam-
pel (759 women and 118 men) with benign thyroid diseases treated at two Danish university hospital outpatient clinics, in 2007–2008, and a longitudinal sample (358 women and 74 men) with benign thyroid diseases undergoing treatment at the abovementioned centers, during 2008–2012, evaluated before and 6 months after therapy. The thyroid-specific QoL questionnaire ThyPRO was used to identify sexlife impairment resulting from thyroid disease. Biochemical and clinical variables potentially influencing sexlife were ana-
yzed, i.e. age, education, degree of thyroid dysfunction, co-morbidity, serum thyrotropin, total thyroxine and triiodothyronine, as well as thyroperoxidase and thyrotopin receptor antibody concentrations. Medical Outcomes Study's 36-item Short Form (SF-36) was used to analyze the effect of impaired sexlife on overall quality of life

Results: In the cross-sectional sample, 36% of women and 31% of men reported impaired sexlife, attributable to their thyroid disease. Women with autoimmune thyroid diseases reported more impairment than those with non-autoimmune thyroid diseases. Shorter education in patients with Graves' disease and co-morbidities in patients with toxic nodular goiter were associated with more impaired sexlife. Overall QoL was lower in patients with thyroid-related sexlife impairment. In the longitudinal sample, 42% of women and 34% of men had impaired sexlife, which improved only in women at six months follow-up. Low education in patients with toxic nodular goiter and high plasma triiodothyronine concentrations in patients with Graves’ dis-
case were predictors of sexual dysfunction. In autoimmune hypothyroidism, younger age was associated with more sexlife impairment

Conclusion: We have found a high frequency of thyroid-related self-
reported sexlife impairment in patients with benign thyroid diseases, espe-
cially in young women with autoimmune thyroid diseases. Worsening of sexlife persisted in women treated for Graves’ disease, suggesting that normal-
ization of thyroid function was not sufficient to restore sexual function.

PI-01-07
INVESTIGATION OF NOVEL BIOMARKERS, DEFINITION OF ROLE OF MICROBIOME IN GRAVES’ ORBITOPATHY (GO (INDIGO): MICROBIOTA ANALYSIS OF PATIENTS AT RECRUITMENT
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Background: In Graves’ disease (GD) thyroid stimulating antibod-
ies (TSAB) cause hyperthyroidism; about 5% of GD patients also develop GO. Mechanisms underpinning tolerance loss are poorly understood but microorganisms, via molecular mimicry or dysbiosis, may be implicated. Dysbiosis could affect the Th17/Treg balance in the gut-associated lymphoid tissue. We tested the hypothesis that in GD/GO, bacteria inducing tolerance (Treg) are under-represented or those promoting inflammation (Th17) are over-represented.

Methods: Fecal samples were obtained from untreated patients, or within 6 weeks of commencing treatment at recruitment; GD (n = 65) with no or minimal eye signs; GO (n = 56), mild or moderate-severe (as defined by EUGOGO) and healthy controls (n = 42) from four European countries. Total DNA was extracted for microbiota analysis, using V1-V2 region primers of the 16S rRNA gene, to generate 10,000 paired-ends reads per sample (MiSeq Illumina). Data were processed using the QIIME bioinformatics pipeline for analysing microbial communities. A subset was also evaluated using tradi-
tional microbiology methodology.

Results: The within-sample alpha and between-sample beta diversity were similar in patients at recruitment and controls. However when consid-
ering phylum composition, Bacteroidetes were significantly more abundant in controls (38.5%) than in GD (24.2%) and GO (27.3%) patients, while Firmicutes were more abundant in GD (59%) and GO patients (60.5%) than controls (53.2%). Consequently the firmicutes/bacteroidetes ratio was signifi-
cantly higher in GD/GO than controls, but similar between GD and GO. In 2 GD patients who developed GO there was a decrease in the genus Bacteroides (BH adjusted p < 0.0001), confirmed using traditional microbiology tech-
niques. Furthermore, Enterococcus gallinarum counts, a pathobiont reported to be involved in triggering autoimmunity, though low overall were signifi-
cantly higher in GD and GO than controls.

Conclusions: Our preliminary data illustrate substantial perturbation of the gut microbiota composition in GD/GO, which may be driven by hyperthy-
roidism. Future analyses will explore associations between taxonomic profiles and TSAB, thyroid function and GO disease severity and whether they are affected by treatment.
**P1-01-08**

**PREVALENCE OF THE TYPE 3 MULTIPLE AUTOIMMUNE SYNDROME (MAS) IN A PROSPECTIVE SERIES OF PATIENTS WITH GRAVES' DISEASE**

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**Introduction:** Autoimmune diseases tend to cluster in the same subject or in the same family. Based on their association four types of MAS can be distinguished: type 1 (at least two of the following diseases: chronic pancreatitis, chronic hypoparathyroidism, Addison disease); type 2 (Addison disease with autoimmune thyroid disease and/or type 1 diabetes mellitus); type 3 (autoimmune thyroid disease with other autoimmune diseases but Addison disease); type 4 (association of diseases not included in the previous MAS).

In the natural history of autoimmune diseases there are three different stages: a) potential (presence of circulating autoantibodies), b) subclinical (subclinical hypofunction of the target organ) and c) clinical (signs and symptoms of the disease).

**Aim:** The aims of our study were: 1) to determine the prevalence of the organ-specific autoantibodies [anti-adrenal Ab (ACA), anti-ovary Ab (StCA), anti-thyrotrophin receptor Ab (AP), anti-thyroglobin Ab (tTGAb), anti-glutamic acid decarboxylase Ab (GADA), anti-muscle nicotinic receptor Ab (ARAB) in patients with Graves disease and 2) to define the stage of the disease in the patients with one or more positive autoantibodies.

**Materials and Methods.** One hundred and eight patients [89 F/19 M; aged 46.2 ± 12.8 (m ± SD) years] with Graves disease were prospectively enrolled from 2015 to 2017. ACA, StCA, APA, and PCA were measured by indirect immunofluorescence assay, tTGAb/GADA by immunoassay and ARAB by radioimmunoassay.

**Results:** PCA were positive in 10/108 (9.2%) patients, GADA in 7/108 (6.5%), ACA in 1/108 (0.9%) and StCA in 1/89 (1.1%). APA, tTGAb, ARAB were negative in all subjects. In patients with positive autoantibodies the most common was the potential stage.

**Conclusions:** As well as in the chronic autoimmune thyroiditis, type 3B is the most prevalent form of MAS, and particularly the association between Graves disease and chronic atrophic gastritis. The potential stage is the most frequent allowing to schedule an appropriate follow-up in order to make an early diagnosis and initiate a prompt treatment of the disease.

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**P1-01-09**

**ANEMIA AS AN EARLY ESPRESSION OF AUTOIMMUNE THYROIDITIS**

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**Objectives:** The objective of our study is to identify the linkage between anemia and Autoimmune thyroiditis.

**Methods:** The study had 54 participants (30 women aged 30 ± 5 and 24 men aged 30 ± 5) who had anemia with iron deficiency and were treated with iron medicines. Their HGB level became normal, but decreased after 2–3 months. A consultation with endocrinologist was arranged, TSH, FT₄ and anti-TPO were identified.

- TSH = 2.5 ± 1.2 mIU/L (N = 0.4–4.0 mIU/L)
- FT₄ = 1.3 ± 0.4 mg / dL
- anti-TPO >100 ± 40 IU / mL among 50 patients and <35 ± IU/mL (N <35 IU / mL).

Results of ultrasound examination of thyroid gland showed that patients had diffuse changes and colloid accumulation.

These 50 patients who had autoimmune thyroiditis were divided into two groups with 25 patients in each.

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**Table 1.** (for Abstract P1-01-09)

<table>
<thead>
<tr>
<th>1st Group</th>
<th>2nd Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGB was normal (12.0–16.0 g/dL) among 25 patients. Fe²⁺ was normal among all patients.</td>
<td>HGB was normal (12.0–16.0 g/dL) among 5 patients, and below the normal level (&lt;9.0–11.8) among 20 patients. Fe²⁺ was below the normal level among 18 patients.</td>
</tr>
</tbody>
</table>

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**1st group was treated with iron medicines and Levothyroxin (25–37.5 mg/kg X 1) with duration of 2 months. 2nd group was treated only with iron medicines for a period of 2 months.**

**Results:** Two months later Fe²⁺ and HGB were identified. All had normal levels. However another two months later following double check of Fe²⁺ and HGB the following was revealed in Table 1.

**Conclusion:** 1. If there is anemia of unknown reason which is not sustainably treated, availability of Autoimmune thyroiditis should be checked.

2. Although there is autoimmune thyroiditis at the stage of normoerythrocytosis (which normally doesn’t require treatment) and anemia conditioned with abnormality in iron absorbing, it is recommended to add Levothyroxin (25–37.5 mg/kg) to the treatment.

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**P1-01-10**

**THE EFFICACY OF SELENIUM IN THE TREATMENT OF THYROID DISEASE IN THE EUTHYROID STATE OR STAGE OF SUBCLINICAL HYPOTHYROIDISM**

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**Background:** Autoimmune thyroid disease (AITD) is a chronic disease and the most common organ specific autoimmune disorder usually resulting in dysfunction (hyper function, hypofunction or both) of the thyroid gland.

Selenium is an element that plays great role in thyroid physiology and exerts an antioxidant activity.

**Objective:** The purpose of this study is to demonstrate the efficacy of the selenium at AITD.

**Methods:** 632 patients, with mean age 19–60, 41 men and 591 women with autoimmune thyroiditis were enrolled in the study: all of them were either in the euthyroid stage or in the stage of subclinical hypothyroidism, with elevated antibodies against thyroglobulin (anti TG Ab) and antibodies against Thyroid Peroxydase (anti TPO Ab). Thyroid ultrasound and laboratory examinations (TSH, T4 free, anti-Tg, anti-TPO) were done to all patients before treatment.

Selenium with a daily dose of 100 mg per os (which is registered as a bio-logically active supplement in Republic of Armenia) was administrated to 417 patients.

**Results:** In 380 patients (91.1%) out of 417 were found an absorption of colloid cysts and inflammatory infiltrates by ultrasound examination in compare with control group (p < 0.005). In the remaining 37 patients (8.82%) was found increased TSH with unchanged patterns of thyroid glands in ultrasound examination. In the 57 (26.51%) patients of control cohort the infiltrates were changed to nodes (p < 0.05).

**Conclusion:** From the above mentioned, it can be concluded that selenium as an antioxidant biologically active supplement has a positive effect on patients with autoimmune thyroid disease in the euthyroid state or in the stage of subclinical hypothyroidism.

Taking into account the above results, the administration of selenium could be an option in the scheme of treatment of autoimmune thyroid disease in the euthyroid state or in the stage of subclinical hypothyroidism.
Case Report 1

P1-02-11 WITHDRAWN

P1-02-12 THE CHALLENGES OF TREATING A PATIENT WITH SEVERE RECALCITRANT THYROTOXICOSIS WITH THIONAMIDES-INDUCED AGRANULOCYTOSIS
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Introduction: Thionamides-induced agranulocytosis is a rare and severe complication encountered in the treatment of thyrotoxicosis. Often in this group of patients, other conventional anti-thyroid medications (iodides, lithium, steroids) are required to reduce serum thyroid hormone levels. Resistance to these medications is not commonly found, yet it poses a serious problem in managing patients with severe hyperthyroidism or thyroid storm. Stabilizing these patient’s thyrometabolic state and choosing a definitive therapy in such patients can be very challenging.

Case Report: A 20-year-old pharmacy student with Graves’ disease and a prior history of thionamide-induced agranulocytosis with both Carbimazole and Propylthiouracil, presented to our institution with severe thyrotoxicosis. She had a previous history of repeated doses of outpatient Lugol’s iodine as she refused radioactive iodine (RAI) or surgery. Both iodides and steroids therapy failed to improve her abnormal thyrometabolic state, yet there was a dramatic improvement in her serum thyroid levels after 4 days of cholestyramine, with her serum free T4 levels plunging from persistent readings of >64 pmol/L to 18.14 pmol/L. Her T4 rebounded back to >64 pmol/L when Cholestyramine had to be tapered down as it was unavailable in our institution. After being adequately beta-blocked, she underwent RAI 4 weeks later with post-RAI adjuvant lithium. Her T4 levels plummeted to 24.72 pmol/L 4 weeks post-RAI with marked improvement in her thyrotoxic symptoms.

Conclusion: Cross-reactivity is common between both Carbimazole and Propylthiouracil in thionamides-induced agranulocytosis. Repeated doses of Lugol’s iodine may render the subsequent dose ineffective. Cholestyramine is an effective option for thyrotoxicosis, either as an adjuvant therapy to the conventional anti-thyroid medications, or as monotherapy. Additional of lithium post-RAI improves the treatment’s efficacy by prolonging its length of effect. RAI is safe in an adequately beta-blocked thyrotoxic patient with no comorbidities, even if the T4 levels are >64 pmol/L.

P1-02-13 SAUSAGE THYROTOXICOSIS
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Introduction: Hyperthyroidism is mostly caused by thyroid hormone excess due to Graves’ disease or hot nodules. The cause is usually easy to determine with ultrasound, TSH receptor autoantibodies and scintigraphy. However, in some cases these tools fail to reveal the underlying cause.

Case: A 75-year-old male patient had been diagnosed with isolated T3 hyperthyroidism (TSH <0.01 mU/l [0.3–3]; FT3 4.97 ng/dl [1.7–3.7]; FT4 0.88 ng/dl [0.7–1.5]). There was no history of iodine exposure, amiodarone treatment or use of thyroid supplements. The patient’s thyroid was of normal size without nodules or signs of autoimmune thyroid disease. TPO and TSH receptor antibodies were negative and on scintigraphy, Tc-uptake was low (0.18%). A whole body 123I scan excluded ectopic thyroid tissue and a pituitary MRI showed no pituitary tumor. Thyroglobulin was in the lower half of the reference range (25.5 ng/ml; 3.5–77), indicating absence of destructive thyroiditis. A therapy with carbimazole had been tried with 10 mg/d and even 30 mg/d without any effect.

Then the patient was referred to an endocrinologist. A detailed history of the patient’s dietary habits revealed daily consumption of two types of sausage (liver sausage and smoked sausage spread). Thus, contamination of one or both sausages with thyroid hormone was suspected. Analyses of the sausages consumed by the patient and sausage samples obtained as controls in a different city revealed that indeed the patient’s liver sausage contained excessive amounts of T3, about 30 times that of a control sample (433 pmol/l [patient’s liver sausage] compared to 15 pmol/l [control liver sausage]). The patient was advised to stop consumption of this sausage. He has been euthyroid since then.

Conclusion: Hyperthyroidism in this patient was caused by consumption of sausage contaminated with T3, probably because the pig’s thyroid was not removed when cervical tissue was used for sausage production. Although exogenous thyroid hormone intake by accident, due to contaminated food, is known in principle as a cause for thyrotoxicosis, it is probably considered rare and exotic and not a valid differential diagnosis in daily practice. This case demonstrates that if the cause of hyperthyroidism is unclear, such sources of thyroid hormone need to be considered to prevent unnecessary diagnostic procedures and, even more important, unnecessary treatment.

P1-02-14 STEROID-INDUCED THYROTOXIC PERIODIC PARALYSIS, A CASE REPORT
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Introduction: Thyrotoxic periodic paralysis (TPP) is a disease characterized by recurrent episodes of muscle weakness due to a shift of potassium into cells in the presence of high levels of thyroid hormone. It occurs more commonly amongst young Asian men. Attacks are precipitated by ingestion of carbohydrate-rich meals, alcohol, or strenuous exercise. In this report, we describe a young man suffering from a TPP attack after receiving dexamethasone injection.

Case Report: A previously healthy 36-year-old Thai man presented to the emergency department complaining of weakness in both the lower extremities. Three hours prior, his general practitioner prescribed him an 8 mg of dexamethasone injection to control his tendinitis. Thereafter, he developed myalgia which progressed to paralysis predominantly of both legs. On examination, the patient appeared obese and alert. He was afebrile, normal blood pressure and pulse rate of 85 beats/min. His diffusely enlarged thyroid gland was approximately twice the normal size. No exophthalmos or thyroid bruit was noted. Neurological examinations revealed flaccid paralysis and absent deep tendon reflexes in both lower extremities. Sensory function was normal. Laboratory data revealed a serum potassium of 2.0 mEq/L (3.5–5.1), hypophosphatemia (2.0 mg/dL, 2.7–4.5), and normal serum creatine kinase (300 U/L, 24–195). Electrocardiogram showed normal sinus rhythm and a prolonged QTc interval, 0.5 sec. The patient did not have prior hypokalemia, polyuria, diarrhea or excessive perspiration. He denied history of similar weakness as well as his family members. His muscle strength and serum potassium (K+ 3.9 mEq/L) were fully restored within 6 hours after administration of 80 mEq of oral liquid potassium. Graves’ disease was confirmed with elevated free thyroxine (1.97 ng/dL, 0.8–1.8), free triiodothyronine (5.37 pg/mL, 1.6–4.0), low TSH (<0.005 μU/mL, 0.3–4.1), and a positive for TSHR Ab. Methimazole and propanolol were administered. After discharge, subtotal thyroidectomy was pursued and the patient was still in euthyroid state and has not experienced paralysis.

Conclusions: We reported an unusual case of TPP precipitated by the use of high-dose steroid. Clinicians should beware of the attacks when administer steroids in the thyrotoxic patients, especially of Asian descent.
P1-02-15
TREATMENT OF GRAVES’ORBITOPATHY DEVELOPING DURING PREGNANCY: TWO CASE REPORTS
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The development of Graves’orbitopathy (GO) is rarely observed in pregnant women and the treatment is challenging. We describe two cases of pregnant women with GO.

Case 1: A 36-year-old woman had new Graves’ disease (GD) with major hyperthyroidism, high T4Ab and goitre diagnosed at week 23 of pregnancy. Carbimazole led to euthyroid state for the mother. A fetal goitre was diagnosed by ultrasound at week 29 of pregnancy. Antithyroid drugs were rapidly stopped as euthyroid state was maintained. The patient developed eye pain and diplopia at week 24 of pregnancy. Examination revealed normal VA, eyelid retraction, proptosis, restriction of upgaze. Clinical activity score (CAS) was 4/7. Dysthyroid optic neuropathy (DON) was diagnosed. CT scanning of the orbits demonstrated left apical optic nerve compression. Three consecutive daily doses of 500 mg of methylprednisolone IV were given followed by oral steroids. The improvement was temporary. Within 2 weeks AV deteriorated (0.3) and left eye decompression was performed at week 29 of pregnancy. Left eye VA improved (0.6) but right eye VA deteriorated (0.7) despite oral steroids. At week 31, gestational diabetes developed requiring insulin therapy. At week 34 of gestation a caesarean section was performed. The newborn (2250 g) had hyperthyroidism and needed treatment. Orbital decompression of the right eye was performed 2 weeks after delivery. After the slow withdrawal of oral steroids the VA normalized.

Case 2: A 29-year-old woman had new GD diagnosed at week 20 of pregnancy. Antithyroid drugs were rapidly stopped as euthyroid state was maintained. The patient developed eye pain and diplopia at week 24 of pregnancy. Examination revealed normal VA, eyelid retraction, proptosis, restriction of upgaze. CAS was 3/7. RMN of the orbits demonstrated unilateral inflammatory enlargement of the right ventral rectus. Six weekly doses of 500 mg IV methylprednisolone were given with a reduction of the diplopia from constant to intermittent. During the treatment gestational diabetes developed and insulin therapy was necessary. At delivery (week 39) the newborn (3450 g) was euthyroid.

The treatment of choice for moderate to severe active GO and for DON is IV pulses methylprednisolone. It is not contraindicated during pregnancy but there is a risk of diabetes. If a surgical orbital wall decompression is necessary to restore visual acuity, the risk of adverse birth outcomes need to be discussed with a multidisciplinary team and the patient.

A close coordination between endocrinologists, ophthalmologists and obstetricians in required for GO treatment during pregnancy.

P1-02-16
A CASE OF HYPOTHYROIDISM AND SEVERE WEIGHT LOSS – A REMINDER OF POLYAUTOIMMUNITY AS A LIFE-THREATENING PHENOMENON
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Introduction: Thyroid autoimmunity is the most common autoimmune disease and often observed in other autoimmune diseases (polyautoimmunity). The presentation of autoimmune thyroid disease with uncharacteristic symptoms can be a sign of additional underlying severe disease.

Case Report: A 33-year-old previously healthy male was referred to a tertiary referral center due to severe fatigue and 20 kg unintended weight loss during three months. The patient had since infancy suffered from vitiligo, and had in recent years had two children without need of assisted reproductive technology. Due to complaints of increasing tiredness, loss of appetite, dizziness, he was diagnosed by his general practitioner with hypothyroidism (TSH of 44 mIU/L). Due to the severe weight loss, he was referred to a diagnostic center on suspicion of malignancy which was rejected by diagnostic imaging. The possibility of polyautoimmunity was explored. A gastroscopy showed signs of gastritis later confirmed by biopsies. The patient subsequently reported of having been unable to get out of bed in the following days, being extremely tired, nauseous and unable to eat or drink at home. Three days later he was brought by his wife to our endocrine out-patient clinic, where a syndrome test revealed a critically low 30-minute p-cortisol of 33 nmol/L (reference ≥420). He was immediately admitted to our hospital clinic for Addison’s crisis. Physical examination showed poor general appearance, universal white skin elements, hyperpigmentation in remaining skin areas, and slight activity-related dyspnoea. Blood pressure upon admission 74/69 mm Hg, P-sodium 124 mmol/l (reference 137–144), ACTH 280 pmol/L (2–11), TSH 62 mIU/L (0.4–4.8), total T4 68 nmol/L (70–140), free T4, 8.2 pmol/L (12–22), haemoglobin 7.1 mmol/l (8.3–10.5), vitamin B12 98 pmol/L (200–200), HbA1c 35 mmol/mol (<48). There were high concentrations of autoantibodies towards thyroperoxidase, the adrenal cortex, gastric parietal cells and glutamate decarboxylase 65. The patient was markedly improved on treatment with hydrocortisone, fludrocortisone, hydroxycoobalamin, and levothyroxine substitution. He will attend further follow-up in our out-patient clinic.

Conclusion: In this case of severe polyautoimmunity, the patient was diagnosed with autoimmune Hashimoto’s thyroiditis, Addison’s disease, vitiligo and pernicous anaemia (and high-level glutamate decarboxylase 65 autoantibodies) consistent with autoimmune polyglandular syndrome type 2; likely caused by an underlying breach of immunological tolerance most often due to mutations in the autoimmune regulator or forkhead box protein 3 genes. Clinical awareness of the possibility of polyautoimmunity in patients with autoimmune thyroid disease can be life-saving as seen in the present case.

P1-02-17
AN UNUSUAL CASE OF THYROIDITIS IN A YOUNG ORTHOPAEDIC PATIENT
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Introduction: Serotonin syndrome is a serious condition associated with increased serotonergic activity in the central nervous system. It is a clinical diagnosis, and may present with a range of clinical findings including autonomic instability, mental state changes and neuromuscular hyperactivity. It is associated with the use of serotonergic agents, in particular the selective serotonin reuptake inhibitors. The co-administration of other serotonergic agents, including the analsgesic tramadol hydrochloride, increases the risk of developing serotonin toxicity.

The thyroid physiology may have a modulating effect on the brain serotonergic system. Studies in humans and animals suggest hypothyroidism reduces serotonin levels, which may partly explain mood changes associated with thyroid dysfunction.

We present a rare case of a young man with serotonin syndrome secondary to sertraline and tramadol co-prescription who subsequently developed thyroiditis.

Case Report: A 29 year old man was admitted under Orthopaedics following surgical fixation of a shoulder fracture dislocation following a fall whilst jogging. His past medical history was notable for anxiety and depression, with fluoxetine switched to 50 mg sertraline 5 days prior to admission by his psychiatrist due to a deterioration in his symptoms. Post-operatively, he received tramadol at a dose of 100 mg qds as analgesia. He became anxious and agitated the following night which appeared to settle by the morning. He was discharged, and readmitted on the same day with a recurrence of agitation. On examination, he was tachycardic and pyrexial. Inflammatory causes were excluded, and a diagnosis of serotonin syndrome was made. Tramadol and sertraline were discontinued. He was subsequently found to be hyperthyroid, with thyroid stimulating hormone (TSH) 0.07 mU/L (0.27–4.2 mU/L) and free thyroxine 44 pmol/L (12–22 pmol/L), with negative thyroid receptor and antiperoxidase antibodies. He was commenced on propranolol for symptom control with hyperthyroidism and behavioural changes resolving over the following 2 weeks. Repeat TSH was 1.07 mU/L with free T4 of 20 pmol/L at two months follow-up.

Conclusion: This is the second case in the literature of a patient developing thyrotoxicosis in the context of serotonin syndrome. A possibility of non-thyroidal illness syndrome causing abnormal thyroid function in context of serotonin toxicity cannot be excluded. This case highlights the importance of measuring thyroid function tests in serotonin syndrome, and supports a link between thyroid hormones and serotonin. Close outpatient follow-up of thyroid function is mandatory in such cases.
A CASE OF AGRANULO CYTOSIS INDUCED BY SEVERE HYPERTHYROIDISM IN A PATIENT WITH TOXIC MULTINODULAR GOITER

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Introduction: A previous study reported a prevalence of neutropenia, defined as a neutrophil count lower than 2000/mm3, in 14.1% of patients with Graves disease, especially not caucasian, and a significant increase of white blood cells (WBC) after anti-thyroid therapy, significantly correlated to FT3 reduction. It is, also, known that anti-thyroid drugs may cause agranulocytosis, although very rarely. In this regard, the recent American Thyroid Association guidelines suggest caution in the prescription of anti-thyroid drugs if the neutrophil count is lower than 1000/mm3; this recommendation is, however, weak and with low quality evidences. Moreover, other studies identified single nucleotide polymorphisms (SNPs), in the HLA region of the chromosome 6, associated with agranulocytosis in patients with Graves disease, although the SNPs were different in Asian subjects compared to those from Western Europe.

Case Report: On February 2018, a 68-year old caucasian woman, affected by multinodular goiter, was admitted to the Emergency Room because of symptoms suggestive of thyrotoxicosis. An overt hyperthyroidism (TSH 0.01 mU/mL, FT3 13.9 pg/mL, FT4 46.2 pg/mL; anti-TSH receptor antibodies were positive) and agranulocytosis [WBC 2.84 thous/mm3, neutrophils (N) 13%] were detected with normal hemoglobin and platelet values. The patient was known to be affected by a mild idiopathic neutropenia and periodically monitored at the Hematology Unit without a specific treatment. In the hypothesis of a marked reduction of neutrophils induced by the severe hyperthyroidism, anti-thyroid therapy with methimazole (20 mg/day) was started. Three days after the beginning of the treatment, both the free thyroid hormones (FT3 7.4 pg/mL, FT4 30.5 pg/mL) and the WBC (2.72 thous/mm3, N 28.7%) improved and a further improvement was observed after 14 days (FT3 4.2 pg/mL, FT4 12.2 pg/mL; WBC 3.89 thous/mm3, N 50.2%) and 35 days (FT3 3 pg/mL, FT4 5.9 pg/mL; WBC 3.47 thous/mm3, N 32.5%). The patient has, recently, been scheduled to be treated with thyroectomy.

Conclusions: Since a SNP profile, that can differentiate patients with neutropenia who will worsen and develop agranulocytosis, is lacking, it is mandatory, in these cases, to use a multidisciplinary approach, involving endocrinologists and hematologists, and to strictly monitor the count blood cells to better evaluate the response to therapy and the natural history of the disease.

HYPERFUNCTIONING METASTATIC THYROID CANCER: CASE REPORT

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Introduction: Thyrotoxicosis due to functional metastases in patients with thyroid cancer is extremely rare. Here we present a case of well-differentiated thyroid cancer with hyperfunctioning bone metastasis causing thyrotoxicosis.

Case Report: A 79-year-old woman presented with complaints of persistent left hip pain. CT showed a bulky bone mass in the left iliac with 9 cm. She underwent a CT guided biopsy from the mass in December 2016, which revealed metastasis with follicular cells creating a suspicion of metastatic thyroid cancer. She was referred to our department and submitted to neck ultrasound-guided fine needle aspiration cytology of right lobe nodule with 12 mm – benign and of left lobe nodule with 10 mm – FLUS. She had no thyrotoxicosis symptoms. Thyroid profile was: TSH <0.008 uUI/mL (0.4–4), fT4 2.9 ng/dL (0.8–1.9), fT3 7.8 pg/mL (1.8–4.2), Tg 14386 ng/mL, TRAb <0.3 U/L (<1), TgAbs <20 UI/mL (<40). 18F-FDG-PET/CT (February 2017) confirmed large osteolytic lesion on the left iliac wing, conditioning marked bone destruction and an associated soft tissue mass; thyroid was enlarged with calcified images and an associated soft tissue mass; thyroid was enlarged with calcified images but without significant uptake. The patient underwent total thyroidectomy (10/02/2017). Histopathology revealed widely invasive follicular carcinoma of right lobe with 13 mm. Four weeks later and after withhold levothyroxine treatment (125 mcg) during one week she had TSH <0.008 uUI/mL, fT4 2.0 ng/dL and fT3 5.0 pg/mL, Tg 15556 U/L, negative TgAbs and was submitted to radiodine treatment (50 mCi, 20/03/2017). The post-therapy whole body scan (WBS) showed iodine concentration in the known lesion. No new lesions were detected. She was under methimazole (MMI) 5 mg id. Second radiodine treatment (164 mCi) was performed (6/11/2017). Metastatic lesion remained iodine uptake in WBS. Tg decreased to 4599 (TSH <0.008 uUI/mL). As the patient was a poor candidate for surgery she was submitted to embolization (13/12/2017) and local radiotherapy (30 Gy/10 sessions, January 2018). Last analytical evaluation (27/02/2018), under MMI 5 mg, showed: TSH 2.2 uUI/mL, fT4 0.7 ng/dL, fT3 2.2 pg/mL, Tg 7085 U/L, negative TgAbs. At this time antithyroid drug was stopped.

Conclusions: This unusual thyroid carcinoma presentation presents a therapeutic challenge. Both the metastatic cancer and thyrotoxicosis need to be treated. The huge dimension of metastasis precludes surgical intervention. Although metastatic lesion retain radioiodine uptake it also has poor differentiation areas with high F18-FDG uptake. We also needed to address hyperthyroidism treatment to avoid complications due to release of excessive thyroid hormones by the hyperfunctioning metastatic lesion.
AMYLOID GOITER AND FAMILIAL MEDITERRANEAN FEVER. A RARE CASE OF HUGE GOITER IN PATIENT UNDER LONG TERM HEMODIALYSIS THERAPY

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Diagnosis 1

NEW DIAGNOSTIC TOOL FOR THYROID CANCER; ELECTROCHEMICAL IMPEDANCE SPECTROSCOPY (EIS)

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P1-02-20

INTRODUCTION: Familial Mediterranean fever is provided by the mutation in a gene located on the chromosome 16 and it is an autosomal recessive disorder. This pathology is also known as periodic disease, Armenian disease, paroxysmal polyserositis, Jewish family fever. The clinical picture is presented by periodically occurred episodes of exudative inflammation of serous membranes. Amyloidosis in Periodic disease is systemic and mostly affects the kidneys. Renal disease is the most significant clinical sign, which sequentially passes through the stages of small asymptomatic proteinuria to nephrotic syndrome and the development of renal failure.

The thyroid gland is affected by amyloidosis in 50%–80%. Amyloid goiter grows rapidly, initially is one-sided, but later the process extends to the whole gland. In amyloid goiter the levels of thyroid hormones usually are normal. In large goiters symptom of adjacent organs compression may occur. Surgical intervention is indicated in such cases.

Case Report: In presented study, the clinical and morphological analysis of the case of huge amyloid goiter in a patient with periodic disease, who is on long-term hemodialysis therapy was performed. The patient, male, born in 1976, Armenian by nationality, was admitted to the surgical department in March 2017. Patient was complaining of cervical discomfort, cough, swallowing difficulty. The last 8 years patient gets hemodialysis sessions due to terminal stage of renal failure. The patient was born of consanguineous marriages.

In inspection, a big space-occupying lesion determined which involved the whole anterior and lateral surface of the neck covering two thirds of its circumference. After preoperative preparation of patient the thyroidectomy was performed. The patient, male, born in 1976, Armenian by nationality, was admitted to the surgical department in March 2017. Patient was complaining of cervical discomfort, cough, swallowing difficulty. The last 8 years patient gets hemodialysis sessions due to terminal stage of renal failure. The patient was born of consanguineous marriages.

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Conclusion: Thus, thyroid amyloidosis is a rare disease, the diagnosis is often difficult. The presence of dense rough surface progressing in size goiter, often leads to the assumption of thyroid cancer.

P1-02-21

PRE-OPERATIVE ASSESSMENT OF PAPILLARY THYROID CARCINOMA WITH COMPUTED TOMOGRAPHY

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Ultrasound (US) is the first choice of pre-operative imaging for papillary thyroid carcinoma (PTC). The routine use of other imaging is not recommended. In advanced cases, assessment of distant metastasis and lymph node (LN) metastasis in the mediastinum or retro-/para-pharyngeal regions by computed tomography (CT) may provide valuable pre-operative information. The purpose of this study is to detect the population that pre-operative CT provided more information than US.

Materials and Methods: We retrospectively reviewed pre-operative US and neck and/or chest CT findings of 479 PTC patients that performed initial surgery. Patients were clinically classified by US findings according to 8th edition of TNM classification. Frequency of lung and LN metastasis that could only recognized by CT and not by US in each group was calculated.

Sensitivity and specificity of US and US+CT for extrathyroidal extension (T4a) and LN metastasis were also estimated. Pathological results were used as gold standards.

Results: The age was <55 years (younger patients) in 258 patients and => 55 years in 205 patients (older patients). Frequency of lung metastasis in younger patients was 0% in T1-2, N0 patients, 3.1% in T3b; N1 patients, 0% in T4a, Any N patients. Frequency of lung metastasis in older patients was 2.8% in T1-2, N0 patients, 6.7% in T1-3b, N1 patients, 33.3% in T4a, Any N patients. Sensitivity of US and US+CT for T4a was 11.7% (95% CI: 6.7–19.8) and 20.2% (95% CI: 13.3–29.4), respectively and specificity was 99.7% (95% CI: 98.5–100) and 98.4% (95% CI: 96.6–99.3), respectively. Sensitivity of US and US+CT for N1a was 35.9% (95% CI: 30.9–41.2) and 41.9% (95% CI: 36.7–47.3), respectively and specificity was 98.0% (95% CI: 94.2–99.3) and 94.6% (95% CI: 89.6–97.2), respectively. Sensitivity of US and US+CT for N1b was 84.9% (95% CI: 79.5–89.1) and 87.7% (95% CI: 82.6–91.5), respectively and specificity was 94.2% (95% CI: 94.0–99.3) and 90.7% (95% CI: 86.8–93.5), respectively. LN metastasis in the mediastinal region was found by CT in 10 cases that were all N1b.

Conclusion: Frequency of lung metastasis was high in T4a older patients. Sensitivity of US+CT was 8% superior to US for T4a. LN metastasis in the mediastinal region was found by CT only in N1b patients. CT provides additional pre-operative information beyond US in PTC patients that are T4a especially for => 55 years of age or N1b.

P1-03-22

NEW DIAGNOSTIC TOOL FOR THYROID CANCER; ELECTROCHEMICAL IMPEDANCE SPECTROSCOPY (EIS)

Kim-Hwan Hong, Yong-Tae Hong
Chonju, Korea, Rep. of South Korea

Purpose: While ultrasonography and Fine needle aspiration (FNA) remains gold standard diagnostic tool in thyroid cancer. Electrochemical impedance spectroscopy (EIS) may be also a tool for investigating the mechanisms of electrochemical reactions, for measuring the dielectric and transport properties of tissues and for exploring the properties of porous electrodes and passive surfaces. We developed a new micro-electrical impedance spectroscopy (EIS) sensor on the tip of a hypodermic needle for distinguishing between normal and cancer tissues in thyroid gland.

Subjects and Method: The patients of thyroid papillary carcinoma who underwent thyroidectomy for thyroid papillary carcinomas were selected. Ex vivo discrimination between human normal and thyroid cancer tissues was confirmed using EiO (EIS-on-a-needle, EIS: electrical impedance spectroscopy) at the frequency range from 15.9 kHz to 1 MHz. The largest differences between normal and cancer tissues in thyroid gland.

Results: The normal and cancer tissues were clearly discriminated by using EiO (EIS-on-a-needle, EIS: electrical impedance spectroscopy) at the frequency range from 15.9 kHz to 1 MHz. The largest differences between normal and cancer tissues for the magnitude, phase, real, and imaginary part of impedance were observed at 251 kHz, 631 kHz, 251 kHz, and 398 kHz, respectively.

Conclusion: From the experimental results, the impedance values of the majority of the cancer tissues were larger than those of normal tissues, which implies the electric current is more difficult to flow in cancer tissues than in normal tissues. This could be explained by the fact that infinite proliferation in cancer tissues increases cell density; thereby reducing extracellular space where electric current can flow more freely. Thus EiO can be a new diagnostic tool in thyroid cancer.
P1-03-23
PREDICTION OF FOLLICULAR THYROID CARCINOMA ASSOCIATED WITH DISTANT METASTASIS

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Background and Purpose: Predicting factors associated with metastasis in patients with follicular thyroid carcinoma (FTC) can help establish a risk stratification model. Our aim was to identify predictive factors of distant metastasis in FTC patients.

Materials and Methods: A total of 321 patients who were surgically diagnosed as having FTC greater than 10 mm from 1994 to 2016 in our institution were included. Preoperative ultrasound (US) images and clinicopathologic features of FTC patients with and without distant metastasis were compared. Associations between distant metastases of FTC and predicting factors were evaluated by using logistic regression analysis in the preoperative and postoperative models.

Results: Distant metastasis was present in 37 (11.5%) of the 321 FTC patients. Univariate analysis showed that age (≥ 55 years), larger tumor size, widely invasive histology, multiloculated appearance, non-parallel orientation, rim calcification, and hypoechogenicity on US were significant risk factors for distant metastasis of FTC. In the preoperative model, independent predictors of distant metastasis for FTC were age (odds ratio [OR], 3.728; 95% confidence interval [CI]: 1.534–9.40); multiloculated appearance (OR, 3.420; 1.419–8.24); and rim calcification (OR, 4.987; 1.798–13.83). In the postoperative model, independent predictors were age (OR, 3.204; 1.285–7.987), rim calcification (OR, 4.582; 1.601–13.115), and widely invasive histology (OR, 4.671; 1.615–30.70). Sensitivities, specificities, and the area under the curve predicted distant metastasis of FTC were 85.6%, 76.8%, and 0.868 on preoperative status and 91.9%, 71.1%, and 0.885 on postoperative status, respectively.

Conclusion: Age and US features allow preoperative and postoperative prediction of FTC associated with distant metastasis.

P1-03-24
REFINING THE EIGHTH EDITION AJCC/UIICC TNM STAGE AND PROGNOSTIC GROUPS FOR DIFFERENTIATED THYROID CARCINOMA

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Background: The eighth edition American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system for differentiated thyroid carcinoma (DTC) was recently developed. However, further refining stage and prognostic groups are warranted to facilitate personalized probabilistic prediction for individual patient.

Methods: Patients with newly diagnosed DTC treated at two tertiary referral centers from 1994 to 2005 were included. We used recursive partitioning analysis (RPA) to derive new staging classification. Performance of the RPA stage with respect to prediction of cancer-specific survival (CSS) was assessed against the current eighth edition TNM stage.

Results: The cohort comprised 6342 patients with DTC, with a median follow-up of 11.4 years. Patients in higher RPA groups were at higher risk of death (Stage IA, IB, IIA, IIB, III, and IV 10-year CSS: 99.6%, 98.1%, 93.0%, 92.4%, 75.1%, and 56.6%, respectively; P < 0.001). The proportions of variance explained (PVEs) for the ability of the RPA stage and the eighth edition TNM to predict CSS were 7.1% and 5.7%, respectively. The C-index values were 0.869 (95% CI 0.833–0.905) for the RPA stage and 0.819 (0.789–0.850) for the eighth edition TNM.

Conclusion: This study presents a RPA-based TNM stage groupings that incorporate multiple age cutoffs and essential anatomic information, which can be conveniently used to facilitate the individual prediction of long-term CSS in patients with DTC.

P1-03-25
OUTCOME PREDICTION BY 7TH AND 8TH EDITION OF THE AJCC/TNM SATGING SYSTEM FOR PAPILLARY THYROID CANCER – A 10 YEAR FOLLOW-UP STUDY IN A SINGLE INSTITUTE

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Purpose: Clinical implication of minimal extrathyroidal extension (mETE) in papillary thyroid carcinoma (PTC) has been controversial. Recently AJCC TNM classification was revised to 8th edition. Two major changes were made in age grouping and T3b definition. T3b in new edition refers to a tumor of any size with gross ETE invading only strap muscles. Age cutoff changed from 45 years to 55 years. The aim of present study is to evaluate whether 8th AJCC TNM classification is better than previous version in prognostication in PTC.

Patients and Methods: We retrospectively evaluated a total of 239 PTC patients who underwent primary surgery for PTC at our hospital from Jan. 2007 to Dec, 2008. We reviewed medical records and interviewed patients by phone call. We used IBM SPSS Statistics 24 for statistical analysis. Disease free survival (DFS) rate and overall survival (OS) rate were evaluated by Kaplan Meier method.

Results: There were 203 females and 36 males; 235 total thyroidectomy and 4 lobectomy cases; maximum tumor size of 1.3 ± 1.0 cm (131 microscopic PTCs); multiplicity in 80 patients and bilaterality in 44 patients; ETE(+) in 100 patients; lymph node metastasis (+) in 74 patients and Lateral neck dissection in 11 patients. Postoperative radioiodine ablation was done in 200 patients. A median follow-up was 113.4 months (101.9 ± 31.1 months). Duration of a median follow-up was 7th 113.4 months (101.9 ± 31.1 months). By 8th edition compared to 7th, TNM stages migrate downward in 81 patients (33.9%); 5 patients from stage II to I; 51 patients from stage III to I; 17 patients from stage III to II; 4 patients from stage IV to I; 1 patients from stage IV to II; 3 patients from stage IV to III; A 10-year disease-free survival (DFS) rate was 97.0% for stage I, 100% for stage II, 97.0% for stage III, and 64.8% for stage IV by 7th edition while that was 96.9% for stage I, 88.9% for stage II, and 66.7% for stage III by 8th edition of the AJCC/TNM staging system, respectively. There were 3 mortality cases, not related with PTC.

Conclusion: Because of limitations in present study including a small sample size, we could not evaluate mortality rates according to different staging systems. Compared to previous edition, however, 8th edition of the AJCC/TNM staging system differentiated more patients who have a low-risk of recurrence (down-staging).

P1-03-26
DYNAMIC RISK ASSESSMENT IN PATIENTS WITH DIFFERENTIATED THYROID CANCER FOR THE DECISION OF REMNANT ABLATION

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Introduction: The therapeutic approach and the follow-up of patients with differentiated thyroid cancer is currently individualized according to the risk of recurrence (RR)1. The dynamic risk assessment could modify the individual risk over time.

Objectives: To compare the response to treatment in patients with low and intermediate static RR in whom the decision for radioiodine remnant ablation (RRA) was performed immediately after surgery with those non-ablated patients with low dynamic RR. Secondary, to compare the responses to treat-
ment in ablated patients with low static RR compared with those non-ablated low dynamic RR.

**Methods:** We included adult patients treated with total thyroidectomy, and who had at least two consecutive measurements of serum thyroglobulin and thyroidroglobulin antibodies, with a minimum follow-up of 12 months. Patients were divided in two groups: Group 1 (G1): n = 309 ablated patients and Group 2 (G2): n = 103 non-ablated patients. The evaluation of the response to treatment was performed in ablated patients according to the ATA guidelines, and in non-ablated patients according to previous published definitions. Low dynamic RR was defined in those patients who had an excellent or indeterminate response to initial treatment. Those patients in G2 with Tg levels >5 ng/ml in the dynamic risk assessment, received RRA and were excluded from the analysis. 

**Results:** The baseline characteristics can be observed in Table 1. The initial structural incomplete response (SIR) was greater in G1 compared with G2 (11.3% vs 0.9%; p = <0.001). The frequency of an excellent response at the end of follow-up was similar in G2 compared with low initial RR of G1 (72.8% vs. 62.1%; p = 0.058).

**Conclusions:** Low and intermediate static RR ablated patients had a higher frequency of SIR compared with non-ablated patients in the dynamic risk assessment. In contrast, the frequency of SIR was similar when ablated patients of low static RR were compared with those non-ablated patients of low dynamic risk. These results show how the dynamic RR helps to move those intermediate RR patients on the low RR decreasing the need for RRA.


**Table 1.** (for Abstract P1-03-27)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>39-49</td>
<td>45 (19–84)</td>
<td>46 (21–90)</td>
<td>0.50</td>
</tr>
<tr>
<td>Female</td>
<td>88.3%</td>
<td>86.4%</td>
<td>0.60</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>1.7 (0.2–8)</td>
<td>0.9 (0.1–9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Papillary thyroid carcinoma classic variant</td>
<td>73.8%</td>
<td>78.6%</td>
<td>0.59</td>
</tr>
<tr>
<td>ATA Risk Stratification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>71.9%</td>
<td>87.4%</td>
<td>0.001</td>
</tr>
<tr>
<td>Intermediate</td>
<td>28.1%</td>
<td>12.6%</td>
<td></td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>83.9±53.9</td>
<td>37.9±24.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Table 2.** (for Abstract P1-03-27)

<table>
<thead>
<tr>
<th>T1a (n = 38)</th>
<th>T1b (n = 9)</th>
<th>T2 (n = 6)</th>
<th>T3 (n = 2)</th>
<th>N0 (n = 33)</th>
<th>N1a (n = 18)</th>
<th>N1b (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bCT (pg/ml)</td>
<td>≤50</td>
<td>63.1%</td>
<td>22.2%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>&gt;50–100</td>
<td>23.7%</td>
<td>11.1%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>&gt;100</td>
<td>13.1%</td>
<td>66.7%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>sCT (pg/ml)</td>
<td>≤300</td>
<td>47.4%</td>
<td>22.2%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>&gt;300</td>
<td>52.6%</td>
<td>77.8%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Poster Presentations**

Eur Thyroid J 2018;7(suppl 1):1–118

DOI: 10.1159/000491542
IDENTIFYING RISK FACTORS OF LATERAL LYMPH NODE RECURRENTCE FOR CLINICALLY NODE-NEGATIVE PAPILLARY THYROID CANCER
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Objectives: There is still debate regarding the role of routine central lymph node (LN) dissection in treating clinically node-negative papillary thyroid cancer (PTC). The aim of this study was to investigate the risk factors for lateral recurrence after total thyroidectomy and prophylactic bilateral central LN dissection in clinically node-negative PTC patients.

Methods: We retrospectively collected the medical records of 1406 PTC patients who underwent total thyroidectomy and prophylactic bilateral central LN dissection between January 2004 and December 2008. We used Cox-proportional hazards regression analyses to inspect the predictive factors for recurrence.

Results: During a median follow-up of 107 months (range, 13–164 months), 68 (4.8%) and 37 (2.6%) patients experienced recurrence in any lesion and in lateral neck LN, respectively. Male, main tumor size >1 cm, nodal pathologic N1a, positive delphian LN, lymph node ratio >0.15, lymphovascular invasion, and extrathyroidal extension (ETE) were significantly associated with lateral neck LN recurrence in univariate analysis. Multivariate analysis showed that male (hazard ratio [HR], 2.217; 95% confidence interval [CI], 1.057–4.647; p = 0.035), main tumor size >1 cm (HR, 2.257; 95% CI, 1.138–4.476; p = 0.020), pathologic N1a (HR, 5.957; 95% CI, 2.573–13.789; p < 0.002), minor ETE (vs. no ETE, HR, 3.027; 95% CI, 1.315–6.966; p = 0.009), and gross ETE (vs. no ETE, HR, 4.058; 95% CI, 1.685–7.974; p = 0.002) were independent predictive factors for lateral neck LN recurrence. Among the patients with pathologic N1a, LN ratio of more than 0.55 had worse lateral neck LN recurrence-free survival.

Conclusion: Lateral neck LN recurrence in clinically node-negative PTC patients is predicted by the factors of male sex, main tumor size >1 cm, ETE, and pathologic N1a.

VALUE OF SPECT-CT WITH IODINE-131 IN STAGING AND THERAPEUTIC MANAGEMENT OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA
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Background: In patients with differentiated thyroid carcinoma (DTC), treatment follow-up and metastasis screening can be performed with whole body scan (WBS), with or without additional SPECT/CT images. The definition of the structures that uptake iodine in the pre-RIT WBS of patients with DTC is of fundamental importance for the therapeutic decision, since it can differentiate physiological sites of uptake from those metastatic. Although the SPECT/CT images aid in the interpretation of the WBS findings, their impact on the therapeutic decision is not fully clarified in the literature.

Aims: To evaluate possible changes in staging and conduct determined by SPECT/CT images performed in complementation with WBS with 131I before radiiodine therapy (RIT) in patients with DTC.

Methods: One hundred and ninety-nine patients with DTC who performed SPECT/CT images complementary to pre-RIT WBS were selected, 167 men and 32 men, mean age 46.3 years, 187 with papillary DTC and 12 follicular DTC, 150 of them performing first WBS and 49 WBS monitoring. The images were taken 48/72 h after oral administration of 5 mCi of 131I. A nuclear physician evaluated the WBS and classified staging, risk classification and therapeutic management, which were compared to the SPECT/CT findings previously evaluated by another nuclear physician and a radiologist, and these classifications were compared.

Results: The therapeutic course changed in 20.6% (41/199) of the cases after the analysis of the SPECT/CT images. The staging changed in 22.1% (44/199) of the cases, with an increase in 36.4% (64/184) and a decrease in 63.3% (28/44). In 63.5% (26/41) there was a decrease in the 131I activity administered due to staging decrease, 34.1% (14/41) required greater activity due to staging increase and in 2.4% (1/41) surgical management was indicated due to staging change. Lymph nodal staging was statistically different between the WBS and SPECT/CT methods (41/199, p = 0.019). Positive stimulated thyrogbulin presented a correlation with metastatic SPECT/CT findings, but not the risk classification.

Conclusions: The differentiation between benign cervical structures and affected lymph nodes was the main determining factor for the reestablishment and modification of the conduct. The association of SPECT/CT to pre-RIT WBS contributed to the correct staging of DTC patients (upstaging 36.4% and downstaging 63.5%), mainly regarding lymph node involvement, modifying the therapeutic management of DTC in a significant part of the cases (20.6%), and leading to a global decrease in the 131I administered activity.

WITHDRAWN

WITHDRAWN

SONOGRAPHIC FEATURES PREDICT THE GROWTH OF PAPILLARY THYROID CARCINOMA DURING ACTIVE SURVEILLANCE
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Background: Active surveillance has been generally accepted as a management option for low-risk papillary thyroid carcinoma (PTC). However, there are no clear recommendations regarding patients suitable for undergoing active surveillance.

Methods: In this retrospective cohort study from a single tertiary referral center, we evaluated tumor size change between the initial and last ultrasonography (US). We analyzed 217 PTC patients who underwent active surveillance over 1 year rather than immediate thyroid surgery. Tumor size increase was defined as maximum diameter increase over 3 mm or volume increase over 50% change between the initial and last US findings.

Results: The mean patient age was 51.6 years and 76.0% patients were female. The initial maximum diameter and volume of PTC were 5.8 ± 1.7 mm and 76.8 ± 66.9 mm³, respectively. During the median 38.8-month follow-up, 55 patients (25.3%) experienced tumor size increase. Three features (patients younger than 45 years, taller-than-wide shape on US, and macrocalcification) were associated with increased risk of tumor size increase. A time-dependent increase in the number of these three tumor size increase-related features was significantly associated with higher risk of tumor growth (p < 0.001). The relative risk of tumor size increase with more than two suspicious features was significantly increased compared with that of tumor size increase with one or no suspicious features (hazard ratio = 2.3, p = 0.006).

Conclusions: Some PTC may grow during active surveillance. Young age and the US features of taller-than-wide shape and macrocalcification were associated with tumor size increase. Therefore, active surveillance should be carefully considered in PTC patients with these features.
Epidemiology and Clinical Features

P1-04-33
ISC: ANTI THYROID PEROXIDASE POSITIVITY PROTECTIVE AGAINST THYROID CANCER IN GRAVES DISEASE?

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1Ankara Yıldırım Beyazıt University, School of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey; 2Ankara Yıldırım Beyazıt University, School of Medicine, Endocrinology and Metabolism Diseases, Ankara, Turkey

Aim: Anti thyroid peroxidase (AntiTPO) and antithyroglobulin (AntiTg) are known to be positive in 75–90% and 35–50% of patients with Graves disease, respectively. Although studies investigating the association between thyroid cancer and Hashimoto thyroiditis (HT)- in which AntiTPO is an important hallmark of the disease- reported controversial results, studies showing higher risk in HT outweigh. However, the association between AntiTPO and thyroid cancer in patients with Graves disease was not studied. We aimed to investigate whether AntiTPO or AntiTg positivity have any effect on malignancy risk in these patients.

Methods: Graves patients operated in our center was recruited for the study retrospectively. The clinical features, operation indications and thyroid autoantibodies (AntiTPO, AntiTg and TSH receptor antibody) were recorded. Patients were grouped as benign and malignant according to histopathological diagnosis

Results: Data of 602 patients were analyzed. There were 410 (%68.1) female and 192 (%31.9) male patients with a mean age of 43.5 ± 12.69. Preoperative ultrasonography revealed no nodule in 286 (%47.5), single nodule in 286 (%47.5), and multiple nodules in 253 (%42.0) patients. There were 400 (66.4%) patients with positive AntiTPO and 279 (46.3%) with positive AntiTg. Histopathological diagnosis was benign in 512 (%85) and malignant in 90 (15%) patients. Age, sex and TSH receptor antibody positivity did not differ between benign and malignant patients. 267 (52.1%) patients in benign and 19 (21.1%) patients in malignant group had no nodule in preoperative ultrasonography (p < 0.001). There was significant difference in operation indications between benign and malignant patients (p < 0.001). AntiTg was positive in 48.2% of benign and 35.6% of malignant patients (p = 0.026). AntiTPO was positive in 356 (69.5%) of benign and 44 (48.9%) of malignant patients (p < 0.001). With multiple regression analysis, association between AntiTg positivity and benign histopathology was lost (p = 0.600), while association between AntiTPO positivity and benign histopathology remained significant (p = 0.016).

Conclusion: In accordance with the literature, the presence of nodule in Graves patients increased malignancy risk in our study. Additionally, for the first time we showed that AntiTPO positivity might play a protective role against thyroid cancer in patients with Graves disease.

P1-04-34
RESULTS OF A NATIONWIDE SURVEY ON MULTIDISCIPLINARY TEAMS OF THYROID CANCER IN SPAIN

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Background: The multidisciplinary approach of patients with thyroid cancer is a glaring necessity of healthcare shared by providers and patients. Recently the Sociedad Española de Endocrinología y Nutrición (SEEN, Spanish Society of Endocrinology) has reported a consensus statement in which the composition, requirements, structure and operation plans of multidisciplinary units of thyroid cancer are delineated. However, an important lack of knowledge persists on the functioning of these multidisciplinary units in real life. Therefore, information of the running of these units in the clinical practice in our country is imperative.

Objective: The aim of the present study has been to retrieve real data on the composition, structure, and functioning developed by the multidisciplinary units of thyroid cancer existing in Spain.

Methods: A nationwide survey was carried out through the SEEN website. The survey was distributed through the SEEN members and through direct contact with specialists of other disciplines involved in the field of thyroid cancer. The survey consisted of several questions about composition, structure and functioning of multidisciplinary teams. It was available on the SEEN website from November 15, 2017 to February 15, 2018.

Results: Seventy-five multidisciplinary units responded to our survey. Of these, 20% were exclusive of thyroid cancer, while 80% included other endocrine disorders or non-endocrine tumors. The mean (±SD) of members of the teams was 11 ± 4.0. The most frequent medical specialties in the units were: Endocrinology (100%), Surgery (97.4%), Nuclear Medicine (92.2%), Pathology (89.6%), Radiology (84.0%) and Medical Oncology (83.0%). 52% of the units had a coordinator and 61.0% had written operating regulations. Periodicity of the meetings was weekly in 14.3%, fortnightly in 23.4% and monthly in 58.4%. Apart from clinical case discussions in the meetings, 21.8% of the units included educational activities and 14.1% research subjects. The annual number of cases (median, interquartile range) studied by the teams was 40(20–69). 38.5% of the teams discuss all thyroid cancer patients who come to the hospital, while 70.5% study only cases with special difficulties. Team decisions were recorded in the patient’s medical record in 85.7% of hospitals. 60.5% of the multidisciplinary teams have elaborated clinical protocols for local use, and 22% have developed their own quality indicators.

Conclusion: These results suggest that international recommendations on the multidisciplinary approach to patients with thyroid cancer are followed in Spain. This gives us the opportunity to further studies analyzing the real impact of this high standard of care on patient outcomes.

P1-04-35
ANALYSIS OF THE FACTORS CONDITIONING THE CLINICAL COURSE OF DIFFERENTIATED THYROID CARCINOMA IN CHILDREN AND YOUNG ADULTS

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Objectives: aim of this study was to ascertain for the first time whether characteristics of differentiated thyroid carcinoma (DTC) may significantly vary according to age, even within a peculiar study population covering only young patients aged less than 30 years.

Methods: the population was composed by 64 patients (47 females) aged <30.0- yrs at diagnosis of DTC (mean age 22.9 ± 5.5 yrs). The main clinical, biochemical and pathologic data at DTC diagnosis were retrospectively recorded in 2 selected cohorts including, respectively, 19 patients aged less than 18 years (Group A) or 45 young adults aged between 20 and 29.8 years (Group B).

Results: The distribution of DTC cases in the different age ranges progressively increased with age. Both groups had a higher proportion of females, indeed the female; male ratio was 2.6:1 and 2.75:1 in Group A and B respectively. Group A exhibited at diagnosis a more severe clinical involvement and a higher rate of extra-regional metastases. Moreover, the association with autoimmune thyroid diseases (AITDs) and biochemical thyroid dysfunction was also more common in Group A (p = 0.02 and p = 0.007 respectively). The age at DTC diagnosis correlated with the tumor size at pathology evaluation (r = -0.27, p < 0.05) but not with US nodule diameter, TSH and fT4 serum levels.

Thyroid dysfunction at DTC diagnosis was associated more frequently with multifocality (p = 0.02), metastasis (p = 0.004) and recurrence (p = 0.005) and needed also more radiotherapy cycles (p = 0.006) if compared with euthyroid DTC patients. Thyroid nodules were smaller in patients with AITDs in comparison to those without AITDs (p = 0.006). Moreover, multifocality of DTC required more cycles of therapy (p = 0.02).

During the whole follow-up time, the overall survival rate was 100%, but 11.1% in Group A and 4.5% in Group B were alive with persistent residual TC.
Conclusions: In a study population younger than 30 years: a) the risk of developing DTC increases with age, achieving its zenith during the 3rd decade of life; b) clinical presentation is more severe in children and adolescents younger than 18 years than in the patients aged between 20 and 30; c) in the cohort of children and adolescents DTC is more often associated withAITDs, which might play some role in conditioning the more aggressive phenotypi
cal presentation of DTC in this patient group. A close US follow-up in chil
dren and adolescents with thyroid dysfunction, ATD and/or thyroid nodules is
needed and indicated to earlier diagnosis of a thyroid malignancy.

**P1-04-36**

**DETECTION OF EIF1AX GENE MUTATIONS IN THYROID CARCINOMAS AND BENIGN NODULES IN CZECH COHORT**

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Objectives: Thyroid carcinoma is the most often endocrine malignancy. The most frequent somatic point mutations in thyroid cancer are in genes BRAF, HRAS, NRAS and RET. Recently, The Cancer Genome Atlas (TCGA) study identified EIF1AX gene as a new causal gene in the thyroid tumour development. This gene is located on chromosome X and encodes the eukaryotic translation initiation factor 1A. The goal of this study was to analyse the EIF1AX gene in different types of thyroid carcinomas and compare the prevalence of main genes mutations associated with thyroid carcinomas.

Methods: DNAs were isolated from 275 fresh-frozen thyroid tissues of 222 patients with papillary thyroid carcinoma (PTC), 5 with anaplastic thyroid carcinoma (ATC) and 52 with MTC. All samples were prepared using Nextera XT kit and analysed by next generation sequencing technology. Mutations in the exon 15 of the EIF1AX gene were detected: P2L mutation in the exon 1 in one follicular variant of PTC, G9D mutation in the exon 2 in one benign nodule and A113 splice mutation in exon 6 in one ATC. No other classical thyroid gene mutations were found in these cases. In the PTC cohort, BRAF mutation in 37% and RAS mutations in 13% were detected. In the ATC cohort, one BRAF mutation was detected. In the RET-negative MTC cohort, only RAS mutations in 56% and no EIF1AX mutations were found. In the cohort of thyroid benign nodules, RAS mutations in 22% of cases were found.

Conclusions: Totally, the three different mutations in the EIF1AX in 3 positions of the gene in 3 cases were found – in ATC, PTC and benign nodule. All three mutations were reported in the literature, it seems that each mutation has different impact on the function of the protein and aggressiveness of tumour. The most aggressive was A113 splice mutation in accordance with the literature. Mutations in the exon 2 were reported in benign nodules as same as in our case. However, it is necessary to enlarge the studied cohorts, because the detection rate of mutations is low. This work was supported by AZV 16-32665A and MZ ČR-RVO (EU, 00023761) grants.

**P1-04-37**

**IDENTIFYING RISK FACTORS OF RECURRENT FOR PAPILLARY THYROID CANCER PATIENTS WHO UNDERWENT MODIFIED RADICAL NECK DISSECTION**

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Objectives: The papillary thyroid cancer (PTC) patients with ipsilateral neck metastatic lymph node (LN) and those with contralateral neck metastatic LN belong to N1b. Only a few studies reported the comparison with regard to laterality of metastatic lateral LN. The aim of this study is to evaluate predictive factors for contralateral neck LN metastasis and to determine prognostic factors for recurrence in PTC patients with N1b.

Methods: This retrospective study reviewed the medical records of 390 PTC patients who underwent total thyroidectomy and central LN dissection plus ipsilateral or bilateral MRND between January 2004 and December 2012.

Results: During a median follow-up of 81 (range, 6–156) months, 84 patients occurred recurrence in any lesion. Male gender, more than 2 cm of main tumour, number of metastatic central LN, number of harvested and metastatic lateral LN, total LN ratio, multifocality of tumors, bilaterality or tumors, and gross ETE had significance in the patients who underwent bilateral MRND. In multivariate analysis, the patients with LN ratio >0.44 in the central compartment (hazard ratio [HR], 1.890; 95% confidence interval [CI], 1.124–3.178; p = 0.015), LN ratio >0.29 in the lateral compartment (HR, 2.251; 95% CI, 1.477–3.743; p < 0.001), and multifocality (HR, 1.583; 95% CI, 1.030–2.431; p = 0.036) were associated with worse RFS. However, bilateral MRND had statistically significance only in univariate analysis.

Conclusions: Recurrence in N1b patients is predicted by central neck LN ratio >0.44, lateral neck LN ratio >0.29, and multifocality or tumors. We suggest that patients with mentioned factors should receive short-term follow-up and appropriate management.

**P1-04-38**

**FUNCTIONING BONE METASTASES OF FOLLICULAR THYROID CARCINOMA IN TOXIC NODULE**

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Background: Functioning metastasis occur rarely in differentiated thy
roid carcinoma, mainly as a complication of a malign toxic nodule. In this case report, we described a patient with a follicular thyroid carcinoma in a toxic nodule who developed thyrotoxicosis due extensive metastatic disease.

Case Report: A 45 year-old man diagnosed with a Toxic Adenoma (4 cm lesion in the right lobe) in 1997. He presented complete resolution of thyrotoxicosis and Tg = 28 ng/mL. He required levothyroxine withdrawal, developing thyrotoxicosis (FT4 = 7.24 ng/dl, RV = 0.9–1.8) successfully controlled by Methimazole. (2010) He underwent guided surgery for resection of left rib and half of right femur with prosthesis placement. Histopathology confirmed Follicular Thyroid Carcinoma Metastases. He presented complete resolution of thyrotoxicosis and Tg = 28 ng/mL. Levothyroxine was restarted to keep TSH suppression. (2012) He developed thyrotoxicosis again (FT4 = 5.29 ng/dl) and Tg increase (3420
ng/mL). During this time, the patient did not present clinical conditions for another surgery. Tyrosine Kinase Inhibitors are not available at our hospital. After 14 years from initial diagnosis, still under methimazole, the patient died of respiratory failure secondary to H1N1 infection.

**Conclusions:** Functioning metastasis are rare in differentiated thyroid carcinoma, however the thyrotoxic state in these cases have to be promptly recognized and treated. Methimazole was an effective drug for such. Unfortunately, the prognosis of these tumors is very poor, and thyrotoxicosis is an aggravating factor that can worsen the general condition of the patient and increase the chances of cardiovascular complications.

**P1-04-39**
THE CLINICO-PATHOLOGIC FACTORS FOR THE PATTERN OF LYMPHATIC METASTASIS IN PAPILLARY CARCINOMA OF THE THROYD: A PROSPECTIVE STUDY

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**Introduction:** Papillary thyroid carcinoma (PTC) is the most common form of thyroid gland malignancy with a tendency for lymphatic spread. Lymph node (LN) metastasis in differentiated thyroid carcinomas are related to the high recurrence rate, low disease-specific survival rate, and overall survival rate. The ideal treatment for regional LN metastasis has remained a subject of debate. Determining the extent of neck dissection should be mainly based on the predictable pattern of spread of regional LN metastasis from PTC. If we can identify the predictive clinic-pathologic factors of regional LN metastasis, we can make the proper preoperative plans.

**Method:** We prospectively evaluated the pattern and predictive factors of LN metastasis of 397 patients with PTC who underwent total thyroidectomy and bilateral central LN dissection with or without therapeutic lateral LN dissection.

**Result:** The incidence of ipsilateral central LN metastasis was (133/397) 33.5%, and that of contralateral central LN metastasis was (29/397) 7.3%. Only male sex was statistically significantly related to central LN metastasis (p = 0.03), and ipsilateral central LN metastasis was significantly related to contralateral central LN metastasis (p < 0.01). About metastasis to lateral LN, the incidence of ipsilateral lateral LN metastasis was (100/397) 25.2% and that of contralateral lateral LN metastasis was (48/397) 12.1%. Extracapsular spread (ECS) were statistically significant (p = 0.01), and central LN metastasis was significantly related to lateral LN metastasis (p = 0.01).

**Conclusion:** Ipsilateral central neck dissection is recommended for all PTC patients. With ipsilateral central LN metastasis, the possibility of contralateral central LN involvement is high. Therefore, complete bilateral central LN dissection would be a proper option. Lateral cervical metastasis frequently occurs with extracapsular invasion and ipsilateral central LN metastasis. More precise pre-operative evaluation should be needed in those patients for lateral LN metastasis.

**P1-04-40**
10-YEAR REVIEW OF 683 THYROID CANCER CASES IN AN IRISH TERTIARY REFERRAL CENTRE

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1St James’s Hospital, Dublin, Ireland; 2School of Medicine, Trinity College, Dublin, Ireland

**Objective:** The histopathologic classification of differentiated thyroid cancer (DTC) informs staging, risk-stratification, treatment choice. This study set out to set out to review:

- Histological subtypes of DTC recorded over a 10-year period.
- Temporal trends, if any of each subtype over the 10-year period.
- Treatment choices made based on the application of current guidelines and risk-stratification at the time of diagnosis

**Response to treatment by applying current (American Thyroid Association-ATA-2015) response to therapy reclassification**

- Final patient status: alive with active disease, alive and disease free, dead with disease, dead from another cause.

**Methods:** Patients who underwent thyroidectomy for thyroid cancer over a 10-year period (2005–2016) at a tertiary hospital were identified. 683 histology reports were reviewed and classified into papillary thyroid cancer (PTC), follicular, medullary and anaplastic subtypes as well as subtypes associated with higher risk (tall cell, diffuse sclerosing as the WHO classification guidelines.

Patient samples collected with disease recurrence or non-primary tumours were excluded from the dataset. The incidence of each histological sub-type was examined on a year-to-year basis.

All DTC were reviewed on treatment choice and response. Thyroglobulin (TG), and TSH-stimulated TG together with neck imaging was assessed at 1-year post and 5-year post-surgery. Patient treated with further surgical intervention and/or RAI were identified over the 10-year period.

Response to RAI was classified as excellent response, biochemical incomplete response, structural incomplete response and indeterminate response as per the ATA guidelines.

Current patient status was documented as dead from disease, dead from other cause, alive with active disease, alive disease-free.

33% of differentiated thyroid cancer cases received RAI as per current guidelines. At year one 20% structural incomplete response (SIR) and 12% achieving a biochemical incomplete response (BIR) and 12% had an indeterminate response. At year 5, 24% a SIR and 14% a BIR. Of those with an incomplete response, 6.9% required further RAI treatment.

98.1% of those with DTC are alive at the time of analysis.

**Conclusion:** Within our cohort of 683 patient, 639 presented with DTC, of which 33% underwent RAI. 98.1% of those with DTC are alive at submission.

**P1-04-41**
PAPILLARY THYROID MICROCARCINOMAS. WHAT MAKE THE DIFFERENCE

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Efterpi Margaritidou1, Eriini Poimenidou1,
Constantinos Toulis Pantelitsa Rakitzi2, Alexandra Chrisoulidou2,
Maria Boudina2, Kalliopi Pazaitou-Panayiotou2
1Theagenio Anticancer Hospital of Thessaloniki, Thessaloniki, Greece; 2Department of Endocrinology-Endocrine Oncology, Theagenio Cancer Hospital, Thessaloniki, Greece

Papillary thyroid microcarcinomas (PTMs) are the most commonly diagnosed thyroid cancers in individuals who are older than 45 years which often are found incidentally after thyroidectomy or during thyroid ultrasound. Sometimes, PTMs may have a more aggressive behaviour with extrathyroidal extension and cervical lymph node metastases.

**Aim:** Identify factors that may be related to aggressive behaviour of PTMs

**Material and Methods:** The medical records of patients with thyroid cancer followed at the Theagenio cancer Hospital were retrospectively reviewed.

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Table 1. (for Abstract P1-04-38)

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<tr>
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<tbody>
<tr>
<td>Thyroid bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left rib and right femur</td>
<td>6.7</td>
<td>74.9</td>
<td>31.7</td>
<td>27.3</td>
</tr>
<tr>
<td>Left rib and right femur</td>
<td>100</td>
<td>300</td>
<td>300</td>
<td>300</td>
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Poster Presentations

Eur Thyroid J 2018;7(suppl 1):1–118
DOI: 10.1159/000491542

53
Hypothyroidism 1

P1-05-42
DIFFERENCES IN LEVOTHYROXINE DOSAGES FOR REPLACEMENT IN CHILDREN WITH DISTINCT CAUSES OF PERMANENT HYPOTHYROIDISM
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Objectives: L-thyroxine (L-T4) is considered the treatment of choice in hypothyroidism, either congenital (CoH), autoimmune (AH) or central (CH). The study objective was to find the mean L-T4 doses for CoH, AH and CH in pediatric age to maintain optimal hormone replacement.

Methods: In this one center, cross-sectional and retrospective study, 67 of 267 evaluated patients, aged <18.0 yrs, with overt and permanent hypothyroidism, followed at the Outpatient Pediatric Endocrinology Clinic of University of Messina, were enrolled on the basis of the following inclusion criteria: a) age <14.0 years at hypothyroidism diagnosis; b) follow-up at least 3 yrs under L-T4 therapy; c) normal value of fT4 and/or TSH for at least six months under unchanged L-T4 therapy. Our study population consisted of: 22 children affected by CoH (14 by thyroid dysgenesis- CoH1, 8 by dyshormonogenesis- CoH2), 23 by AH and 22 by CH (13 by idiopathic hypopituitarism- CH1, 9 secondary to pituitary tumors- CH2). Serum fT4 and TSH levels were measured by commercial kits at mean age of 14.9 ± 2.3 yrs.

Results: In AH children, mean L-T4 maintenance euthyroid doses were significantly lower than in the CoH and CH groups (p = 0.02 and p = 0.008 respectively), while no differences were found between CoH and CH groups (p = 0.1) (Table1). Mean L-T4 doses to maintain euthyroidism were similar in patients with a hyperthyroidism vs dyshormonogenesis (p = 0.1) and in those with idiopathic and secondary CH (p = 0.4). Moreover, there was no statistically significant correlation between LT4 dosage and serum FT4 levels or chronological age in all forms of permanent hypothyroidism in our study population. In all groups mean FT4 levels were not different, and in AH and CH mean TSH values were similar.

Conclusions: In our experience CH children need (weight-based daily) L-T4 dosages similar to CoH ones, while significantly lower doses are sufficient to maintain clinical and biochemical euthyroid status in those with AH. These findings are agreeing with the hypothesis that LT4 replacement dose is inversely correlated with the functionally of thyroid tissue.

Table 1. Average L-T4 doses and serum concentrations of TSH and free T4 (mean and SD) at the follow-up visit (for Abstract P1-05-42)

<table>
<thead>
<tr>
<th></th>
<th>AH</th>
<th>CoH</th>
<th>CoH1</th>
<th>CoH2</th>
<th>CH</th>
<th>CH1</th>
<th>CH2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>15±2.1</td>
<td>14.3±2.5</td>
<td>14.6±2.6</td>
<td>13.7±2.3</td>
<td>15.6±2.2</td>
<td>16.1±1.8</td>
<td>14.8±2.5</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>1.5±1.2</td>
<td>1.8±1.2</td>
<td>2.0±1.4</td>
<td>1.3±0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>16.7±4.2</td>
<td>17.1±2.4</td>
<td>17.5±2.1</td>
<td>16.5±3.1</td>
<td>15.0±5.1</td>
<td>16.9±4.5</td>
<td>13.7±4.3</td>
</tr>
<tr>
<td>LT4 (μg/kg/die)</td>
<td>1.4±0.4</td>
<td>1.7±0.4</td>
<td>1.8±0.2</td>
<td>1.5±0.5</td>
<td>1.8±0.7</td>
<td>1.8±0.8</td>
<td>1.9±0.5</td>
</tr>
</tbody>
</table>

Table 1. Distribution of patients with different thyroid function depending on eGFR (for Abstract P1-05-43)

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>eGFR</th>
<th>Normal TSH level (TSH 0.5-2.5 mIU/L)</th>
<th>Subclinical hypothyroidism (TSH 4-10 mIU/L)</th>
<th>Overt hypothyroidism (TSH &gt;10 mIU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>CKD 3B-5</td>
<td>484</td>
<td>7.3% (n = 35)</td>
<td>14.63% (n = 61)</td>
<td>14.29% (n = 7)</td>
</tr>
<tr>
<td>CKD 2-3A</td>
<td>471</td>
<td>47.11% (n = 228)</td>
<td>70.74% (n = 295)</td>
<td>59.18% (n = 29)</td>
</tr>
<tr>
<td>CKD 1</td>
<td>441</td>
<td>45.66% (n = 221)</td>
<td>46.3% (n = 61)</td>
<td>26.53% (n = 13)</td>
</tr>
</tbody>
</table>

Correlation between eGFR and free T3 (r = 0.34) and weak relationship between eGFR and free T4 (r = −0.1) were found.
Conclusions: Patients with hypothyroidism were older. There were more women in the group with hypothyroidism compared with euthyroid patients. In hypothyroid patients, severe CKD, low T3 syndrome were often detected in comparison with euthyroid patients. TSH level did not significantly differ in patients with different eGFR values.

P1-05-44
METHODOLOGICAL ASPECTS OF INTERPRETATION OF THYROID-STIMULATING HORMONE REFERENCE INTERVALS IN THE NORTH-WEST REGION MEGAPOLIS HOSPITAL

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The prevalence of subclinical hypothyroidism (SH) is large and according to various studies is from 3 to 21%. There are no major epidemiological studies assessing thyroid function in the Russian Federation.

Objectives: to study TSH level in patients who turned to the clinical units of a large hospital in the North-West region to determine the prevalence of thyroid dysfunction in patients of different sex and age

Methods: 5,303 patients were examined, who applied to the I.P. Pavlov SPbSMU clinics for 2017. In all patients TSH level and free T4 was determined. SH was considered to increase the level of TSH more than 4.0 mIU/l at a normal level of free T4. Patients were divided into groups by age and TSH level in accordance with existing recommendations.

Results: There were 29.26% of men and 70.73% of women. The mean age was 55.08 ± 17.07 years. TSH level had an abnormal distribution and averaged 2.77 mIU/l (TSH median 1.73 mIU/l). The prevalence of SH was 10.1%. Significant differences were found between TSH level and the age of the examined patients (p = 0.003). In young group and in senile group age, the median TSH was 1.64 mIU/l (mean 2.4 mIU/l) and 1.75 mIU/l (mean 2.8 mIU/l), respectively (p = 0.018). Middle age group and senile group also significantly differed in TSH level (median TSH was 1.66 mIU/l (mean 2.7 mIU/l) and 1.75 mIU/l (mean 2.8 mIU/l), respectively (p = 0.009). Elderly patients group significantly differed from young group and middle age group in accordance with TSH level. In women TSH level was significantly higher in all studied groups of patients (p = 0.0001). Among women, there were significant differences in TSH level between the elderly and young patients (p = 0.015). The prevalence of SH was 7.3% in men and 11.3% in women.

Conclusions: TSH level has abnormal distribution. Increased TSH levels were associated with female sex and older age. In the elderly group, the incidence of subclinical hypothyroidism in women was 2 times higher than in men. In most cases (77.4%) in patients with SH, TSH level was in the range of 4.0–6.9 mIU/l.

P1-05-45
TAILORING THYROXINE TREATMENT: USEFULNESS OF SOFTGEL PREPARATION IN PATIENTS WITH IMPAIRED GASTRIC PH

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Background: Patients with gastric disorders (H.Pylori related gastritis, gastric atrophy, using proton pump inhibitors) require high dose of thyroxine (T4). Gastric pH has been suggested as critical factor for both dissolution and bioavailability of thyroxine. Softgel thyroxine preparation showed a better in vitro dissolution profile at increasing pH as compared to tablet T4 preparation. Clinical studies suggest a better performance of softgel T4 preparation in treat patients with or without T4 malabsorption.

Aim: To analyze whether, in vivo, the better efficacy of softgel preparation may be related to the pH variations of gastric juice.

Methods: We enrolled 28 hypothyroid patients (24F/4M; median age = 48 years) treated, for at least 2 years, with a stable dose of tablet T4 (median = 1.65 μg/kg/day) showing a consistent and stable TSH values (<0.8–2.5 mIU/l). All patients warranted to take T4 in fasting conditions waiting at least one hour before eating or drinking. All of these patients underwent endoscopy for either dyspepsia or follow up of gastric disorders. Gastric juice has been sampled during endoscopy to measure gastric pH. These patients switched to softgel T4 preparation, titrated to obtain individual serum TSH values as above.

Results: Mean gastric juice pH in the whole sample was 2.87 and, based on this value, patients were subdivided in two groups: Group A (n = 20) with a mean pH of 1.69 and Group B (n = 8) showing a mean pH of 5.81, that mirrors a defined reduced gastric acid production. The pH values well correlated with the dose of T4 in both groups (p = 0.0329 and 0.0023). Following the switch to softgel, T4 requirement was the same in 19 out of 20 (95%) of patients with normal pH. On the contrary in 7 out of 8 (88%, p < 0.0001; PPV 95%), Likelihood ratio = 7.6) patients with high gastric pH the requirement of T4 in softgel formulation was significantly reduced. The median reduction in these latter patients was from 1.98 to 1.67 μg/kg/day (~19%).

Conclusions: These data indicate that the dose of both tablet and softgel thyroxine correlates with gastric pH and, in hypothyroid patients with disorders or conditions impairing gastric acid secretion, softgel T4 preparation should be the preferred therapeutic choice.

P1-05-46
HYPOTHYROID PATIENTS HARBORING POLYMORPHISMS IN THE DIO2 AND MCT10 GENES DID NOT PRESENT HIGHER DISEASE BURDEN AT DISEASE ONSET

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Objectives: A few studies have shown better treatment effects in patients harbouring specific single nucleotide polymorphisms (SNPs) in genes responsible for end target concentrations of T3. However, no study has provided information on how the SNP distribution may affect symptom presentation when hypothyroidism is diagnosed.

Methods: We investigated the clinical presentation of 132 patients newly diagnosed with autoimmune overt hypothyroidism. All patients diagnosed at hospital but also in primary care were included. Thus, patients were recruited without referral bias. We characterized the distribution of SNPs for the following: the DIO2 gene (rs225014 = Thr92Ala, rs12885300 = ORFa-Gly3Asp, and rs225015) responsible for the conversion of T4 to T3 within the target cell, and the MCT10 gene (rs17606253) responsible for the thyroid hormone influx. We analyzed whether the SNP presence had any impact on the disease presentation. Primary end-point was symptom score = number of hypothyroid symptoms (range: 0–13). Secondary end-points were: Co-morbidity, well-being, self-judged health, TSH-T3-T4 concentrations, thyroid auto-antibodies, blood pressure, GP and hospital visits, and sick days) when hypothyroidism was diagnosed. We have previously shown that the symptom presentation is highly age-dependant. Thus, analyses were dichotomized by age (young, age <50 y. vs. elderly, age ≥50 y.).

Results: Younger patients harbouring the rs225014 (Thr92Ala) wild type gene (TT) had borderline higher symptom-score (7.4 vs. 5.5, p = 0.01) and longer duration of symptoms (22 vs. 8 months, p = 0.007) compared to SNP carriers (CC or CT). This was not reproduced among patients aged 50 years or above. We found no evidence of higher disease burden at disease onset in patients harbouring any of the other SNPs investigated, neither among young or elderly patients. In addition, we could not demonstrate any association between SNP presence and the other patient characteristics studied.

Conclusions: Hypothyroid patients harbouring the DIO2 and MCT10 SNPs did not present higher disease burden compared to wild type patients at disease

Poster Presentations
onset. This is somewhat surprising, as some studies have shown worse symptoms during treatment if the patients harboured the CC or CT variant (vs. wild type TT) of the rs225014 (The92Ala) gene. Based on our findings, analysis of gene polymorphisms seems not to be warranted at the time of diagnosis.

**P1-05-47**

**THE EFFECT OF SAMPLE TIMING ON THE DIAGNOSIS OF SUBCLINICAL THYROID DISEASES IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: THE THYRAMI 1 STUDY**

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Honey Thomas⁵, Shahid Junejo⁶, Petra Bijsterveld⁷, Salman Razvi⁸

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**Background:** Observational studies have reported an association between subclinical thyroid disease (SCTD) with adverse cardiovascular outcomes in cardiac patients. In health TSH secretion follows a circadian pattern with peak levels observed between 02:00–04:00 and a nadir between 16:00–20:00. However, it is unknown whether this diurnal variation in TSH is retained in acute myocardial infarction (AMI) and if it impacts on the diagnosis of SCTDs.

**Aim:** To determine whether a diurnal pattern exists in the serum levels of TSH, fT4 and fT3 levels in the context of AMI, and if present, to evaluate its effect on the diagnosis of SCTD.

**Methods:** The multicentre THYRoxine in Acute Myocardial Infarction (THYRAMI) study prospectively recruited patients aged >18 years presenting with AMI (n = 1569). Serum TSH, fT4 and fT3 samples were obtained at admission. Patients with pre-existing thyroid disease or on medications affecting thyroid function were excluded. Cosinor and logistic regression analyses were performed to describe the pattern of serum TSH, fT4 and fT3 levels and to analyse predictors of SCTD, respectively.

**Results:** Serum TSH maintained its diurnal rhythm with a peak in the early hours of the morning (02:40 am) and nadir in the afternoon. Serum fT4 also exhibited a diurnal rhythm with a peak approximately 2½ hours after TSH (05:09 am). Serum fT3 had no significant diurnal variation (Table 1).

Corresponding to the TSH diurnal rhythm, the prevalence of subclinical hypothyroidism (SCH) was more than double in the period of 00:00–05:59 than during 12:00–17:59 (23.9% vs 10.6%). Conversely, subclinical hyperthyroidism (SHyper) was more prevalent between 12:00–17:59 than in the 00:00–05:59 period (2.6% vs 1.4%). Female gender, serum creatinine levels and early morning sampling time period were independent predictors of SCH in AMI patients.

**Conclusions:** Serum TSH levels in AMI patients follow a diurnal pattern with the timing of acrophase and nadir similar to the published data for healthy individuals. This results in almost one quarter of AMI patients meeting the criteria for SCH in the early hours of the morning compared to a tenth of healthy individuals. This results in almost one quarter of AMI patients meeting the criteria for SCH in the early hours of the morning compared to a tenth of healthy individuals. This results in almost one quarter of AMI patients meeting the criteria for SCH in the early hours of the morning compared to a tenth of healthy individuals. This results in almost one quarter of AMI patients meeting the criteria for SCH in the early hours of the morning compared to a tenth of healthy individuals.

**Table 0.** (for Abstract P1-05-47)

<table>
<thead>
<tr>
<th>Assay</th>
<th>MESOR (IU/L)</th>
<th>Amplitude (IU/L)</th>
<th>Acrophase</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum TSH (mU/L)</td>
<td>2.50</td>
<td>0.47</td>
<td>02:40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum fT4 (pmol/L)</td>
<td>14.46</td>
<td>1.71</td>
<td>05:09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum fT3 (pmol/L)</td>
<td>4.77</td>
<td>0.123</td>
<td>00:47</td>
<td>0.432</td>
</tr>
</tbody>
</table>

**Objective:** Since few data are present in literature regarding the effectiveness of Levothyroxine (L-T4) liquid formulation in patients recently undergone to total thyroidectomy (with no malabsorption), we aimed to study the effectiveness of this liquid formulation with respect to L-T4 tablets, in totally thyroidectomized patients for thyroid cancer (without malabsorption or drug interference).

**Methods:** We have enrolled 114 patients of which 57 received liquid L-T4 formulation, while 57 took L-T4 tablets using the same dosage (1.5 mcg/kg/day). Patients began the treatments the day after surgery, and were administered with the drugs 30 min before breakfast. Serum levels of thyroidotropic hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were assessed in both groups at week 6 (1st control), and then at week 12 (2nd control).

**Results:** Significantly lower TSH values were observed in the liquid L-T4 group, than in the tablet L-T4 group, at the first (P < 0.05) and at the second control (P < 0.01), meanwhile FT4 and FT3 levels were not significantly different. In the L-T4 tablet group there is a higher prevalence of patients in the hypothyroid range (TSH >3.6 mcU/ml).

**Conclusions:** Our findings suggest a better efficacy of liquid L-T4 with respect to L-T4 tablets in controlling L-T4 levels in patients previously undergone to total thyroidectomy for thyroid cancer not having malabsorption, gastoric disorders, or drug interference.

**P1-05-49**

**DIFFERENT TSH LEVELS DO NOT AFFECT LIPID PROFILES OF PATIENT IN EUTHYROID STATE**

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¹Ankara University, Faculty of Medicine, Department of Endocrinology and Metabolic Diseases; Faculty of Medicine, Ankara, Turkey.

**Objective:** Thyroid dysfunction and hyperlipidemia are common disorders with the prevalence rates 1–10% and 30–39%, respectively. Relationship between thyroid dysfunction and dislipidemia is well-established, especially for hypothyroidism. But effect of thyroid hormones within normal reference ranges to lipid levels in still controversial. In this study we aimed to demonstrate any correlation between serum lipid levels and thyroid hormones in euthyroid state.

**Material and Method:** Serum lipid levels of 606 euthyroid patients who admitted our out-patient clinic were analyzed retrospectively, after excluding patients with familial hyperlipidemia and diabetic mellitus. Patients on antilipidemic treatment were also excluded. Patients were divided into three groups according to their serum TSH (muU/mL) levels; Group 1 with TSH levels between 0.3–1.0, Group 2 with TSH levels between 1.0–2.49, and Group 3 with TSH levels between 2.5–4.5.

**Results:** Basic characteristics of patients are as follows: 466/606 (76.9%) of our patients were male and the rest 23.1% were female with the mean age of 43.115.1 years for the whole group. Median body mass index was 27 kg/m². Mean TSH level was found to be 2.05 ± 1.17 mU/mL. Mean lipid levels were as follows: 202 ± 44.6 mg/dL for total cholesterol, 126.7 ± 37.9 mg/dL.
for LDL cholesterol, 52.3 ± 14.1 mg/dL for HDL-cholesterol, and 119.9 ± 83.2 mg/dL for triglyceride. Table 1 shows the comparison of lipid profiles according to their TSH levels.

Neither of the lipid fraction was positively or negatively correlated with TSH levels in euthyroid patients. Lipid profiles of three groups were similar. Multivariate analysis of the groups according to male/female ratio, mean age, TSH levels in euthyroid patients. Lipid profiles of three groups were similar. Results: The mean age of the study population was 42.3 ± 10.5 years, and the mean BMI was 43.93 ± 5.54 kg/m². The prevalence of hypothyroidism treated with levothyroxine was 9.0%. The mean weight loss in patients without known hypothyroidism was 35.1 ± 15.0 kg and in patients with treated hypothyroidism was 34.0 ± 13.7 kg (p = 0.39), corresponding to a BMI decrease of 13.24 ± 5.31 kg/m² and 13.54 ± 5.35 kg/m², respectively (p = 0.85). The variation of BMI 1 year after surgery was not significantly different even after adjustment for age, sex, BMI, type of surgery, diabetes and preoperative TSH levels (+0.39 [–1.20 to +0.42] mg/kg decrease of BMI decrease in the group treated with levothyroxine; p = 0.35). In the propensity score analysis (n = 134 in each group), the variation of BMI 1 year after surgery was not significantly different between patients with hypothyroidism treated with levothyroxine and patients without known hypothyroidism (13.39 ± 5.30 vs 13.66 ± 4.87 kg/m², p = 0.65).

Conclusions: The weight loss after bariatric surgery is not significantly affected by the presence of hypothyroidism treated with levothyroxine. Patients with hypothyroidism treated with levothyroxine present a benefit from bariatric surgery similar to euthyroid patients.

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### Table 1. Comparison of lipid profiles of patients in different groups (mean±SD) (for Abstract P1-05-49)

<table>
<thead>
<tr>
<th>Group</th>
<th>TSH</th>
<th>Group 2</th>
<th>TSH</th>
<th>Group 3</th>
<th>TSH</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mIU/L)</td>
<td>(mIU/L)</td>
<td>(mIU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>92</td>
<td>328</td>
<td>186</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>204.3±47.2</td>
<td>199.7±43.6</td>
<td>202.3±45.7</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>128.2±40.2</td>
<td>125.6±36.3</td>
<td>126.7±39.6</td>
<td>0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>51.8±13.5</td>
<td>52.6±15.7</td>
<td>52.3±15.0</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>117.7±68.0</td>
<td>111.2±62.1</td>
<td>136.6±115.0</td>
<td>0.096</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**P1-05-50**

**EFFECTS OF HYPOTHYROIDISM TREATED WITH LEVOTHYROXINE ON WEIGHT LOSS AFTER BARIATRIC SURGERY**

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**Introduction:** Thyroid hormones have a central role in the regulation of energy expenditure and body weight. Bariatric surgery is currently the most effective strategy to treat morbid obesity. These surgeries may interfere with levothyroxine absorption. Whether the weight loss after bariatric surgery is different in patients with hypothyroidism treated with levothyroxine remains unknown. Therefore, our aim was to compare the weight loss in patients with morbid obesity and hypothyroidism treated with levothyroxine, with euthyroid patients with morbid obesity.

**Methods:** We evaluated 1547 patients (85.8% women) with morbid obesity who underwent bariatric surgery. We compared the weight loss (assessed by the variation of BMI 1 year after surgery) between patients with hypothyroidism treated with levothyroxine and euthyroid patients, using t-test and multiple linear regression model adjusted for potential confounders. We also performed a propensity score matched analysis comparing patients with hypothyroidism treated with levothyroxine, with patients without known hypothyroidism. Patients were matched for age, sex, TSH, BMI, diagnosis of diabetes and type of surgery (adjustable gastric band, roux-en-Y gastric bypass or sleeve gastrectomy). The weight loss of the matched groups was compared using student’s t-test. A P-value of <0.05 was considered statistically significant.

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**P1-05-51**

**FEATURES OF SECONDARY AND MIXED HYPOTHYROIDISM IN A COHORT OF PATIENTS PRESENTING WITH HYponATREMIA**

Raluca-Alexandra Trifanescu1, Corin Badiu2, Mariana Purice3, Catalina Poiana2

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**Objectives:** To present characteristics of secondary hypothyroidism in a lot of patients presenting with hyponatremia due to pituitary failure.

**Patients and Methods:** 34 patients (16 M/18 F), aged 60.5 ± 14.2 years, with multiple pituitary insufficiencies, including secondary hypothyroidism, presenting with moderate or severe hyponatremia (serum Na <130 mEq/L) were retrospectively reviewed. Baseline serum sodium (measured by sodium-selective membrane electrode), potassium, urea, glucose levels, serum & urine osmolality were assessed. TSH and FT4 measured by chemiluminescence were used for diagnosis of secondary hypothyroidism. ECG and cardiac ultrasound were performed when appropriate.

**Results:** Serum sodium levels at presentation was 114.6 ± 8.4 mEq/L (range 97–128), while potassium levels were normal (4.2 ± 0.8 mEq/L). All patients but two showed severe hyponatremia (<125 mEq/L). Plasma osmolality was 269.6 ± 26.3 mosm/kg and urine osmolality was 456 ± 145.5 mosm/kg. Acute hyponatremia occurred in 27 patients and chronic hyponatremia in 7 patients. 31 patients showed secondary hypothyroidism (TSH = 1.1 ± 1 mUI/L, FT4 = 8.9 ± 4.9 pmol/l), while 3 patients showed mixed primary and secondary hypothyroidism (TSH 13 ± 2 mUI/L, FT4 = 9.0 ± 8.2 pmol/l). One patient associated chronic autoimmune thyroiditis. All patients showed secondary adrenal insufficiency (median plasma cortisol = 2.56 μg/dL, 25th percentile 1.42 μg/dL, 75th percentile 5.5 μg/dL; median plasma ACTH = 15.2 pg/ml, 25th percentile 4.5 pg/ml, 75th percentile 28.5 pg/ml), gonadotroph insufficiency (median serum FSH = 1.4 mIU/mL, 25th percentile 0.66 mIU/mL, 75th percentile 4.5 mIU/mL), somatotroph insufficiency (median serum IGF1 = 20.8 ng/ml, 25th percentile 11.3 ng/ml, 75th percentile 0.2 mUI/ml, 75th percentile 0.7 mUI/ml) and somatotroph insufficiency (median serum IGF1 = 20.8 ng/ml, 25th percentile 11.3 ng/ml, 75th percentile 0.2 mUI/ml, 75th percentile 0.7 mUI/ml).

**Conclusion:** In cases of hyponatremia, a screening for secondary hypothyroidism due to Sheehan syndrome showed large amount of pericardial effusion with both clinical and echocardiographic signs of tamponade, who required pericardioscintesis.

**Conclusions:** In cases of hyponatremia, a screening for secondary hypothyroidism and secondary adrenal insufficiency have to be performed. In very rare cases, cardiac tamponade associated with hypothyroidism could be the revealing signs.
**P1-05-52**

**EFFECTS OF LEVOTHYROXINE TREATMENT ON INSULIN RESISTANCE MARKERS IN PATIENTS WITH AUTOIMMUNE THYROIDITIS**

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**Introduction:** Autoimmune thyroiditis (AIT) and subclinical hypothyroidism (SCH) are associated with insulin resistance. Our aim was to evaluate the effects of L-thyroxine therapy in markers of insulin resistance.

**Methods:** One hundred and twenty patients caused by AIT, without any prior treatment for thyroid or cardiovascular were selected. Patients followed up in our ambulatory department were diagnosed with autoimmune thyroiditis if anti-peroxidase (anti-TPO) serum antibodies were positive and a typical ultrasound pattern was present. Patients only entered the study if they had maintained a stable state of SCH (as demonstrated by two thyroid hormone profiles). Patients were evaluated regarding insulin resistance markers including HOMA-IR (Homeostasis Model Assessment for insulin resistance), QUICKI (Quantitative Insulin Sensitivity Check Index), HISI (Hepatic Insulin Sensitivity Index), and IGI (Insulinogenic Index), before and after treatment with levothyroxine. The correlation between markers of insulin resistance and thyroid function tests [TSH, free T3 (fT3) and free T4 (fT4)] and levels of antithyroid antibodies (anti-TPO and anti-Tg) were also evaluated. Statistical analysis was performed with Mann-Whitney test and spearman correlations. Patients gave their informal consent to participate and the study was approved by the Ethical Committee of our institution.

**Results:** The mean age of the study population was 45.7 ± 12.2 years, 80 patients (66.7%) were women and the mean BMI was 28.4 ± 0.8 Kg/m². After treatment of SCH patients with L-thyroxine, TSH significantly decreased from 6.43 ± 0.53 mUI/mL to 1.23 ± 0.42 UI/mL (p = 0.03). Treatment with levothyroxine significantly reduced insulin levels (67.6 ± 41.0 vs 51.1 ± 24.0 mU/mL, p = 0.01), C-peptide (9.4 ± 3.1 vs 8.2 ± 2.4 ng/ml, p = 0.02), HOMA-IR (0.24 ± 0.17 vs 0.17 ± 0.10, p = 0.03), and HISI (334.9 ± 703.8 vs 92.9 ± 97.1, p = 0.01). Before treatment with levothyroxine, TSH levels were positively correlated with IGI levels (r = 0.217, P = 0.05). After treatment, there was no significant correlation between thyroid function and insulin resistance markers.

**Conclusions:** We have found a significantly decrease in insulin levels, C-peptide and insulin resistance markers after treatment with levothyroxine. Our results suggest that treatment of SCH with levothyroxine significantly improves hyperinsulinism and insulin resistance.

**P1-06-53**

**WITHDRAWN**

**P1-06-54**

**ANALYSIS OF INCIDENTALLY DETECTED THYROID LESIONS ON SPINE MRI**

Jung Kyu Ryu¹

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**Objectives:** To evaluate the results following US-guided fine needle aspiration (FNA) of incidental thyroid nodules detected on spine MRI

**Methods:** From January 2007 to May 2017, a total of 32,293 patients underwent spine MRI in our hospital. Among these, 162 patients had incidentally detected thyroid lesions on spine MRI and were recommended to perform thyroid US according to radiology reports. Only 44 patients who had undergone thyroid US were retrospectively evaluated and included in this study. Spine MRIs were variously examined as follows; C-spine (n = 20), L-S spine MR (n = 21), and T/L-spine MRI (n = 1), T-spine MRI (n = 1) and whole spine MR (n = 1). These spine MRIs routinely included whole spine T2 sagittal MRI which extended from brainstem to coccyx, covering near entire thyroid gland. Of 44 patients, 2 patients with diffuse thyroid enlargement, 3 patients with multiple spongiform nodules and 3 patients with cysts were excluded. Among 36 patients, 23 had a single dominant nodule, 10 patients had two solid nodules and 3 patients had more than three nodules. Finally, 36 patients had 53 solid nodules. Among these 53 thyroid nodules, FNAs were performed for 44 thyroid nodules whereas 9 nodules were excluded (3 nodules were coexisting with malignant nodules and 6 nodules were lost during follow up).

**Results:** In FNA result of 44 thyroid nodules, 2 nodules were papillary carcinoma, 2 nodules were suspicious for papillary carcinoma, 1 nodule had both papillary carcinoma and follicular neoplasm. 27 nodules were benign and 12 were non-diagnostic on FNA. On surgery, 3 nodules were proven as papillary carcinoma and 2 nodules were follicular carcinoma. The pathology of 27 benign nodules on FNA were benign follicular nodules whereas 9 nodules were excluded (3 nodules were coexisting with malignant nodules and 6 nodules were lost during follow up).

**Conclusions:** Our results suggest that the spine MRI has limited value for the detection of thyroid lesions and the presence of such lesions cannot be excluded based only on MR imaging of the spine. However, asymptomatic thyroid lesions, including thyroid cancer, can be detected on spine MRI, we recommend reporting all thyroid nodules detected on MR, considering possibility of further work-up with thyroid ultrasound for the patient.
**P1-06-55**


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**Purpose:** To compare the diagnostic performance of ultrasound (US)-based risk stratification systems for thyroid nodules in the 2015 ATA guidelines with those of the 2016 KTA/KSTHR and 2017 ACR guidelines.

**Materials and Methods:** From June 2013 to May 2015, a total of 902 consecutive thyroid nodules were enrolled in four institutions and their US features retrospectively reviewed and classified using the categories defined by the three guidelines. We calculated the malignancy risk of each category, as defined by all three risk-stratification systems, and compared the diagnostic performance of the fine-needle aspiration (FNA) indications of the ATA guidelines with those of the KTA/KSTHR and ACR guidelines.

**Results:** Of all nodules, 636 (70.5%) were benign and 266 (29.5%) malignant. The calculated malignancy risks for ATA categories 5, 4, 3, 2, and 1 were 71.9, 21.3, 2.6, 3.9, and 0%, respectively. Of all nodules, 5.0% (45/902) did not meet the ATA pattern criteria but the malignancy risk was calculated to be 13.3% (6/45). The ATA guidelines afforded significantly higher diagnostic sensitivity (93.1%) than the ACR guidelines (74.3%), but a lower specificity (44.1% vs. 77.1%) (both p < 0.001). The unnecessary FNA rate was the lowest when the ACR guidelines were used (18.9%), followed by the ATA (46.2%), and KTA/KSTHR (59.4%) guidelines.

**Conclusion:** The 2015 ATA guidelines afford relatively moderate sensitivity and unnecessary FNA rate for thyroid cancer detection, compared to the 2016 KTA/KSTHR and 2017 ACR guidelines. US practitioners require a deep understanding of the benefits and risks of the US-based FNA criteria of different guidelines.

**P1-06-56**

**MODIFIABLE RISK FACTORS ASSOCIATED WITH DIFFERENTIATED THYROID CANCER**

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**Background:** Differentiated thyroid cancer (DTC) is the most common endocrine neoplasia and its prevalence has followed an upward trend over the last decades. On the other hand, obesity has also undergone a doubling of its prevalence over the last 30–40 years and the metabolic syndrome affects up to 25% of the adult population. The aim of this study is to analyze the relationship between obesity, metabolic syndrome and DTC, regarding cancer presentation and aggressiveness at diagnosis.

**Methods:** We retrospectively analyzed the files of 493 patients who underwent, between January 2012- September 2015, total thyroidectomy or lobectomy in our surgery department. Anthropometric, biologic and imagistic data, indications of thyroid surgery, surgical procedures and pathology results were recorded.

**Results:** The study population included 86 subjects with DTC (mean age 53.99 ± 13.91 years, 83.7% women) and 66 age and gender matched control subjects with benign thyroid pathology. We found no significant differences between patients with DTC compared to patients in the control group regarding: weight (p = 0.647), body mass index (p = 0.890), body surface area (p = 0.560), glycemia (p = 0.429) and the lipid profile: total cholesterol (p = 0.293), triglycerides (p = 0.542), HDL-cholesterol (p = 0.684), LDL-cholesterol (p = 0.300), obesity (p = 0.882) and metabolic syndrome prevalence (p = 0.665). Systolic blood pressure was significantly higher in DTC group compared to the control group (median = 130, IQR = 20 vs median = 125, IQR = 30 mm Hg, p = 0.025). In obese patients, the prevalence of diabetes was significantly lower in patients with DTC compared to controls (3.3% vs 34.8%, p = 0.004). Weight (68.57 ± 18.23 vs. 79.64 ± 15.05 kg, p = 0.022) and BMI (25.51 ± 5.15 vs. 29.43 ± 5.90 kg/m², p = 0.035) were significantly lower in DTC patients with vascular invasion than in those without. T1 stage was more common in hypertensive patients (48.3% vs 14.8%, p = 0.004), while T2 stage was more common among patients with normal blood pressure levels (25.9% vs 6.9%, p = 0.004). Capsular invasion was more frequent in normotensive patients (59.3% vs 36.2%, p = 0.046) and vascular invasion was more common among those without metabolic syndrome compared to those with this syndrome present (32.4% vs 7.1%, p = 0.046).

**Conclusion:** Our data showed that the prevalence of obesity and metabolic syndrome were not different in patients with DTC compared to patients with benign thyroid disorders. Furthermore, aggressive DTC seemed to be associated to nonobese patients without metabolic syndrome.

**P1-06-57**

**COMPARISON OF ULTRASONOGRAPHY (US) AND COMPUTED TOMOGRAPHY (CT) FEATURES OF CALCIFIED THYROID NODULES (CTNs): HISTOPATHOLOGIC CORRELATION**

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**Objectives:** This study aimed to compare the patterns and types of CTNs examined by preoperative neck US and CT.

**Methods:** From January to June 2011, 224 patients who underwent neck US and CT before thyroid surgery were included. Of the 224 patients, 165 had a CTN showing a clear match on US and CT. The CTN patterns were classified as follows: peripheral, central, and combined. The CTN types were classified as follows: micro-, nodular, eggshell, curvilinear, pure, and mixed. The patterns and types of CTNs examined by preoperative neck US and CT were compared and correlated with histopathologic findings.

**Results:** Of the 165 CTNs in 165 patients, 143 were papillary thyroid carcinomas, 2 follicular thyroid carcinomas, 7 follicular adenomas, and 13 nodular hyperplasias. The most common CTN pattern on US and CT was combined and central, respectively, and a statistical difference was observed in the CTN patterns between US and CT (p < 0.0001). In the type of CTNs, the most common type of US was microcalcification (64.2%, 106/165), whereas the prevalence rate of punctate calcification on CT was only 9.1% (15/165). A statistical difference was observed in the type of CTNs between US and CT (p < 0.0001). In addition, eggshell calcification on US and CT showed a low malignancy rate (37.5% and 28.6%), whereas nodular and pure calcifications on CT showed a high malignancy rate (77.6% and 87.5%).

**Conclusions:** US is superior to CT in the evaluation of microcalcifications, whereas macrocalcifications showed the different features between US and CT. Recognizing the different features of CTNs on US and CT may be helpful in the evaluation of thyroid nodules.
P1-06-58
APPLICATION OF ELASTOGRAPHY IN THE ASSESSMENT OF VARIOUS BENIGN LESION IN CHILDREN AND ADOLESCENTS
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Introduction: Elastography is a noninvasive imaging technique based on estimation of the tissue flexibility. There are two methods of elastography: Static Elastography and Shear Wave Elastography. Scale of deformation under pressure is presented as a colourful map – elastogram, where red colour signifies soft tissues, green colour signify middle tough tissues and blue colour signify tough tissues. Analysis of elastograms enable us to present results as ROI1/ROI2 index.

Results: In a prospective study between February 2013 and December 2017 112 patients with lesions in thyroid were examined. We compared ROI1/ROI2 index with results of fine needle aspiration cytology (FNAC) to determine any correlations. Elastography parameters were acquired with Toshiba Apio MX SSA-780A system and analyzed while comparing of ROI1/ROI2 index with results of fine needle aspiration cytology and December 2017 112 patients with lesions in thyroid were examined. We

Conclusion: All 112 patients were benign in cytological examination. In 34 patients with lymphatic thyroiditis ROI1/ROI2 index was 2.47 with SD 1.42. In 78 patients with nodular goiter, colloid nodular goiter, nodular goiter with oxyphilic metaplasia, partially cystic nodular goiter, lymph node, lymphatic tissue with single Hodgkin like cells, lesion resembling hamartomatos cysts ROI1/ROI2 index was 3.55 with SD 2.99 and it was statistically significant higher than in patients with lymphocytic inflammation (p = 0.048).

P1-06-59
THE IMPACT OF ESOPHAGEAL COMPRESSION ON GOITER SYMPTOMS IN PATIENTS WITH BENIGN NODULAR GOITER, A PROSPECTIVE COHORT STUDY
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Introduction: Benign nodular goiter is associated with swallowing difficulties, but insight into the associated pathophysiology is limited. Uncomplicated thyroidectomy significantly improves both symptoms related to swallowing and quality of life. The aim of this study was to investigate the effect of surgery on the degree of esophageal compression, and its correlation to swallowing difficulties.

Methods: Esophageal compression and deviation were evaluated blindly on magnetic resonance images (MRI) of the neck, prior to and six months after thyroid surgery for symptomatic benign goiter. Goiter symptoms and swallowing difficulties were measured by the Goiter Symptom Scale of the Thyroid-Specific Patient-Reported Outcome (ThyPRO) questionnaire. Cohen’s d was used for evaluating effect sizes (ES) with ES of 0.2–0.5 being a small change, 0.5–0.8 a moderate change, and values >0.8 as a large change.

Results: Sixty-four patients completed the study. Eighty-five percent of patients were females, and the mean age of patients was 54 ± 13 years compared to 55 ± 16 years for non-participants (p = 0.80). Before surgery, median goiter volume was 57 mL (range: 14–642 mL). Median esophageal horizontal dimensions (medial-to-lateral) increased from median 15 mm (range: 10–21 mm) to 17 mm (range: 12–24 mm) [ES = 0.94, p < 0.001] after surgery, while no statistically significant change was observed for the sagittal dimension (anterior-to-posterior), thus reflecting an increasingly ellipsoid esophageal shape. The smallest cross-sectional area of the esophagus (SCAE) increased from median 95 mm² (47–147 mm²) to 137 mm² (72–286 mm²) [ES = 1.31, p < 0.001]. Esophageal deviation decreased moderately after surgery from median 4 mm (0–23 mm) to 3 mm (0–10 mm) [ES = 0.54, p = 0.05] using multiple regression analyses the preoperative volume of the thyroid and SCAE was significantly correlated, with a reduction in SCAE of 0.35 mm² for every 10% increase in goiter volume (p = 0.01). However, no correlation was found between changes in goiter volume and changes in SCAE following surgery.

The goiter symptom score improved profoundly from 40 ± 21 points to 10 ± 10 points [ES = 1.5, p < 0.001] after surgery. There were no statistically significant correlations between goiter symptoms and any of the MRI variables.

Conclusion: Six months after thyroid surgery, patients with symptomatic benign nodular goiter showed large increases in SCAE and esophageal horizontal dimensions, and reduction in esophageal deviation. However, these changes were not significantly correlated with improvements in goiter symptoms. The evaluation and understanding of esophageal compression therefore continues to rely on patient reported outcomes.

P1-06-60
DIAGNOSTIC EFFICACY OF CORE NEEDLE BIOPSY AS A FIRST LINE DIAGNOSTIC TOOL FOR LOW OR INTERMEDIATE SUSPICION THYROID NODULES: COMPARISON WITH FINE NEEDLE ASPIRATION USING PROPENSITY SCORE ANALYSIS
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Purpose: To retrospectively compare the diagnostic efficacy of fine needle aspiration (FNA) and core-needle biopsy (CNB) as a first-line diagnostic tool for low or intermediate suspicion thyroid nodules.

Material and Methods: From January, 2010 to May 2015, consecutive 408 thyroid nodules (≥ 1 cm) with low or intermediate suspicion US patterns were selected from a database of patients who initially underwent CNB at one institution. For the comparison of CNB, another dataset of consecutive 433 thyroid nodules (≥ 1 cm) were included from patients who initially underwent FNA at two institutions. Adjustments for significant differences in patients’ characteristics were facilitated via propensity score matching (PSM). The rate of inconclusive results including nondiagnostic or atypia/follicular lesion of undetermined significance (AUS/FLUS) was compared. Diagnostic values for malignancy and the complication rate of FNA and CNB were evaluated.

Results: A 1:1 matching of 299 patients via PSM yield no significant differences between two groups for any covariate. After PSM, CNB showed lower rates of nondiagnostic result (1.0% vs. 7.0%, P < 0.001), AUS/FLUS (9.7% vs. 29.4%, P < 0.001), and inconclusive result (10.7% vs. 36.5%, P < 0.001) than FNA. A total of 208 FNA and 253 CNB nodules were finally diagnosed. With the criteria of Bethesda category 4, 5, and 6, CNB showed a significantly higher sensitivity (100% vs. 48.0%, P = 0.001) for malignancy than FNA, while the specificities of those were similar (99.2% vs. 98.4%, P = 0.450). There were only several cases of mild hemorrhage in both groups. However, the complication rate showed no statistical difference (CNB: 1.47% vs. FNA: 0.23%, P = 0.065).

Conclusion: CNB may be more effective for the diagnosis of malignancy than FNA as a first-line diagnostic tool in low or intermediate suspicion thyroid nodules.
P1-06-61
PAPILLARY THYROID CARCINOMA: THE SIZE OF RISK
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Objectives: Papillary thyroid carcinoma ≤1 cm is recognized as a separate entity by the World Health Organization: papillary microcarcinoma (microPTC). Biological behavior and clinical outcomes are heterogeneous and conflicting findings are reported in the literature. The aim of this study was to describe the disease status after 6–18 months from primary treatment of microPTC patients.

Methods: A prospective cohort of consecutive cases were collected from the Italian Thyroid Cancer Observatory database according to the following inclusion criteria: microPTC with histologic confirmation; complete data about initial treatment and histology; a 6–18 months disease assessment including serum thyroglobulin and anti-thyroglobulin antibodies measurement, and imaging studies (neck ultrasound and other imaging if clinically indicated). Risk of recurrence was defined as: very low (pT1aN0), low (pT1a multifocal, N0), low-intermediate (pT3 or N1a with <5 metastatic lymph nodes), intermediate-high (N1a ≥5 metastatic lymph nodes, N1b, aggressive histology), high (T4, metastatic lymph node of >2 cm, gross incomplete resection of tumor, M1). Response to treatment was classified according to the 2015 American Thyroid Association guidelines.

Results: 826 subjects were enrolled (77% females, median age 49 years). Initial treatment consisted in total thyroidectomy in 807 (98%) and hemithyroidectomy in 19 (2%) patients. Radioiodine remnant ablation was performed in 358 (43%). The risk of recurrence was very low in 379 (46%), low in 167 (20%), low-intermediate in 155 (19%), intermediate-high in 109 (13%) and high in 16 (2%) cases. Response to treatment at 6–18 months from primary treatment was: excellent in 518 (63%), biochemical incomplete in 55 (7%), biochemical complete in 57 (7%), indeterminate in 219 (27%), and structural incomplete in 34 (7%) patients. The rate of structural persistent disease was 2%, 4%, 5%, 8% e 19% in patients with very low, low, low-intermediate, intermediate-high and high risk of recurrence respectively.

Conclusion: microPTC is a heterogeneous group of tumors in terms of risk of recurrence and response to treatment. Treatment and surveillance should be adapted to initial and dynamic risk stratification rather than to tumor size.

P1-06-62
GROWTH RATE AND SIZE OF LARGE THYROID NODULES OF 2 CM OR LARGER: BE USEFUL TO DIFFERENTIATE MALIGNANCY FROM BENIGNITY?
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Purpose: To clarify whether or not the growth rate and size are the useful measures for distinguishing malignancy from benignity in large thyroid nodules.

Materials and Methods: From 2012 to 2015, fine needle aspiration (FNA) or core needle biopsy (CNB) was done for 1856 nodules with longest diameter over the 2 cm in our institute. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of the FNA and CNB were evaluated in benign and malign tumor confirmed by surgical pathology. Among them, nodules with previous ultrasonography with at least 12 months of time interval and accurate 3 dimension measurement were identified for calculation of growth rate of nodule. The rate of tumor growth was defined as increase of the longest diameter and volume per follow up period.

Result: 342 nodules (169 benign and 173 malignant) were confirmed by surgical pathology. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value are 0.77, 0.73, 0.75, 0.77, 0.73 and 0.84, 0.37, 0.60, 0.55, 0.72 in FNA and CNB, respectively. Among them, calculation of growth rate was available in 81 nodules (47 benign, 34 malignant). Growth rates of the largest diameters were 0.2 ± 0.4 mm/month and 0.3 ± 0.6 mm/month in benign and malignant tumors, respectively. Those of the volumes are 0.4 ± 0.6 ml/month and 1.8 ± 0.7 ml/month in benign and malignant tumors, respectively. Difference of growth rates of both largest diameter and volume between benign and malignant tumors are not statistically significant (p = 0.560 and 0.235, respectively). Longest diameter and volume of the nodules are not significantly different between benign and malignant tumors (p = 0.085 and 0.063, respectively).

Conclusion: The growth rate and size of thyroid nodule may not be the useful measures for distinguishing malignancy from benignity in large thyroid nodules.

P1-06-63
CHANGE IN SIZE OF SMALL THYROID NODULES OF 2 CM OR LARGER: BE USEFUL TO DIFFERENTIATE MALIGNANCY FROM BENIGNITY?
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Objectives: There is still scarce data on natural course of small (<1 cm) thyroid nodules; therefore different guidelines about follow-up of such nodules are inconsistent. Our aim was to evaluate if there is any significant change in size of small thyroid nodules in euthyrotic patients without autoimmune disease in an iodine-sufficient area.

Methods: 187 patients evaluated at our outpatient clinic in 2010–2012, that were diagnosed with one or more unsuspicous thyroid nodules and in which autoimmune disease or thyroid dysfunction were excluded, were invited for re-evaluation by mail after five years. 146 (132 female, 14 male) patients with median age 51 years (range, 18–77) responded and thyroid ultrasound was performed. Thyroid nodules were measured in three axes and nodule volume was calculated. TSH (normal value, 0.55–4.78 mU/L) and Tg level (normal value, 2–68 μg/L) at baseline were recorded. For analysis of significance of change in nodule size, Wilcoxon signed-rank test was used. To determine the correlation, Spearman rho test was calculated.

Results: Out of 245 nodules identified at baseline, only nodules with largest diameter smaller than 10 mm at baseline (N = 101) and nodules with baseline volume below 0.523 mL (N = 79) were included in the analysis.

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We found a significant increase in largest diameter of the nodules – presented as median (range) – from 6 (2–10) mm to 7 (2–26) mm, p < 0.001, as well as a significant increase in nodule volume from 0.08 (0.00–0.45) mL to 0.11 (0.00–16.55) mL, p < 0.001, respectively.

Median baseline TSH value was 1.50 (range, 0.405–4.657) mU/L; no correlation between baseline TSH and nodule diameter change (rho = 0.07; p = 0.4) or between baseline TSH and nodule volume change (rho = –0.07; p = 0.4) was found. Median baseline thyroglobulin value was 14 (range, 2–1910) μg/L; a significant positive correlation between baseline thyroglobulin and nodule diameter change (rho = 0.16, p < 0.05) and nodule volume change (rho = 0.24, p < 0.05) was found.

Conclusions: Our results suggest that even small thyroid nodules increase in size with time; the change in size is correlated to baseline thyroglobulin but not to baseline TSH in euthyrotic patients without autoimmune disease. Further studies should explore the clinical significance of growth of small thyroid nodules.

**Thyroid Cancer**

**P1-07-64**

**THE PROLIFERATION AND RECOVERY EFFECTS OF PHOTOBIOMODULATION ON RADIATION INDUCED IN THE THYROID FOLLICULAR CELLS**

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Low-level light therapy (LLLT) is a non-thermal phototherapy used in several medical applications for modulating wound, pain reduction and amelioration of oral mucositis. Despite of diverse application photobiomodulation (PBM) to medical therapy, there was no evidence of thyroid function involvement. Radiation therapy is well known to destroy residual normal thyroid tissue due to inhibited the cell cycle and induce apoptosis. The aim of this study is to investigate the cell cycle and signal transduction mechanism of normal thyroid follicular cells damaged by gamma-radiation, and how PBM using 850 nm LLLT recovered the thyroid function in vitro and in vivo.

Human normal thyroid cell line (N-Thy-3.1) was used for the in vitro study. In a clonogenic assay, a lethal dose of N-Thy-3.1 was revealed 66Gy. To find out the PBM recovery effect to gamma-radiated cells, 850 nm light emission diode (LED) array at 10, 30 and 50 J/cm2 was used. In Proliferation assay, PBM at 10 J/cm2 was most effective and cell cycle analysis using flow cytometry supported this result. G2/M accumulation and apoptotic portion by gamma-radiation were reduced after PBM. Enzyme-linked immunosorbent analysis (ELISA) also revealed that PBM enhanced the cyclic adenosine mono-phosphate (cAMP), not thyroglobulin. Western blot analysis showed that PBM regulated the phosphorylation of p53 and retinoblastoma (Rb) which had been concerned the cell cycle arrest by gamma-radiation. For in vivo study, 30 Gy gamma-radiation and 60 J/cm2 of PBM were used to C57BL6 mice. PBM recovered the expression of cAMP, thyroglobulin, and thyroid function maker such as thyroid stimulating hormone (TSH) and thyroid hormone (T4). Furthermore, results showed that PBM could restore the proliferation by regulation of Rb and p53 in histological observation of gamma-radiated thyroid follicular tissues.

Taken together, PBM had an effect on the function recovery of gamma-radiation-induced thyroid follicular cell by increasing the proliferation and the expression of cAMP in vitro and in vivo.

In conclusion, PBM is effective for gamma-radiation induced hypothyroidism by complementing the cell proliferation and cAMP, and is good clinical application with novelty.

**P1-07-65**

**SYNERGISTIC ANTI-CANCER EFFECT OF SYNERGISTIC ANTI-CANCER ACTIVITY OF HISTONE DEACETYLASE INHIBITION AND POLYMERASE OF THE GLYCOPTIC PATHWAY**

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Background: Advanced cancer has been shown to have a higher percentage of epigenetic changes are more often events than genetic mutations. Preclinical models have shown that combination of the HNHA (N-hydroxy-7-(2-naphthylthio) heptanamide) and 2DG (2-Deoxy-D-glucose) is a play crucial role in ATC (cancer stem-like cell, anaplastic thyroid cancer). The aim of this research is to study that caspase cleavage dependent apoptosis by combination therapy of HNHA and 2DG in ATC.

Methods: ATC cell lines were exposed to HNHA and 2DG alone or combined, and cell viability was determined by MTT assay. Synergistic anti-cancer effects of the combination therapy on cell cycle and intracellular signaling pathways were estimated by flow cytometry and immuno blot analysis. The ATC cell lines xenograft model was used to examine the anti-tumor activity in vivo.

Results: Consequently, our results are suggest that combination therapy of HNHA and 2DG is synergistically decreased cell viability in ATC cell, and also significantly induced apoptotic cell death in these cells, as showed by the cleavage of caspase-3. HNHA and 2DG combination was reduced anti-apoptotic factor in these cells. Thus, combination therapy with HNHA and 2DG most significantly reduced tumor volume in ATC cell xenografts.

Conclusions: The current study suggests that HNHA and 2DG combination treatment was more effective than treatment with the HNHA or 2DG alone. These findings may offer a new therapeutic approach to ATC include the cancer stem-like cells.

**P1-07-66**

**SYNERGISTIC ANTI-CANCER ACTIVITY OF TYROSINE KINASE INHIBITORS AND PACLITAXEL WITH RADIATION ON ANAPLASTIC THYROID CANCER IN VITRO AND IN VIVO**

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Introduction: Anaplastic thyroid carcinoma (ATC) although rare is the most deadly form of thyroid cancer. The goal of this study was to investigate the anti-tumor activities of paclitaxel with radiation and in combination with tyrosine kinase inhibitors (TKI) in anaplastic thyroid cancer cells in vitro and in vivo.

Material and Methods: Three ATC cell lines were exposed to TKI in the presence or absence of paclitaxel with radiation and cell viability was determined by MTT assay. Effects of combined treatment on cell cycle and intracellular signaling pathways were assessed by flow cytometry and western blot analysis. The ATC cell lines xenograft model was used to examine the anti-tumor activity in vivo.

Results: Our data showed that paclitaxel with radiation and TKIs synergistically decreased cell viability in ATC cells, and also significantly increased apoptotic cell death in these cells, as proved by the cleavage of caspase-3 and DNA fragmentation. Paclitaxel and TKI with radiation combination reduced anti-apoptotic factor in ATC. Thus, TKI that targeted the vascular endothelial growth factor receptor family (PDGFR-beta and Kit), which play key roles in tumor progression and angiogenesis. Combination therapy with paclitaxel and TKI with radiation significantly decreased vessel density, and most significantly reduced tumor volume and increased survival in ATC xenografts.
Conclusions: These results propose that paclitaxel and TKI with radiation has significant anti-cancer activity in preclinical models, potentially suggesting a new clinical approach for patients of advanced thyroid cancer type.

P1-07-67
DIFFERENTIAL EXPRESSION LEVELS OF RET9 AND RET51 ISOFORMS IN NORMAL THYROID AND IN MEDULLARY THYROID CARCINOMA TISSUES
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Object: Medullary thyroid cancer (MTC) is a tumor arising from the parafollicular C cells of the thyroid gland. C-cells express RET, however its expression in follicular cell is still controversial. RET gene is alternatively spliced in the 3’ region and encodes for three different isoforms: RET9, RET51 and RET43, with the latter very little expressed. RET isoforms are generally co-expressed but have distinct molecular and functional properties; in particular, several studies have shown that RET51 and RET9 may differently regulate processes such as cell proliferation and cell motility.

Our study was to investigate differences in the expression levels of RET9 and RET51 isoforms, in normal thyroid and MTC tissues, in order to evaluate if a differential expression of these isoforms could play a role in MTC pathogenesis.

Materials and Methods: Total RNA was extracted from 14 normal thyroid samples and from 6 MTC samples. cDNA was prepared using the SuperScript™ IV Vilo™ and quantitative real-time PCR was used to analyze the expression levels of RET isoforms using the Syber Green PCR kit (Bio-Rad). Primers were specifically designed to distinguish the two isoforms; G6PDH gene was used as housekeeping and relative quantification of RET expression was obtained with the ΔΔCt and 2-ΔΔCt method. TT cell line, obtained from MTC, was used as positive control while adipose tissue was used as negative control.

Results: RET9 and RET51 isoforms were both and similarly expressed in the TT cell line with a ΔCt of 0.35 and –0.35 respectively while no RET amplification was detected in the adipose tissue.

Fourteen/14 (100%) normal thyroid samples expressed the RET9 with a mean ΔCt value of 6.91 while 11/14 (78.6%) expressed the RET51 isoforms with a mean ΔCt value 9.37; both RET9 and RET51 isoforms were expressed in 6/6 MTC samples with a mean ΔCt value of 7.29 and 3.96 respectively. No statistically significant difference was observed between RET9 expression in MTC and normal thyroid while RET51 was significantly more expressed in MTC (p = 0.02). The ratio between the two isoforms RET9 and RET51 isoform expression was 3.23 in MTC and 0.13 in normal thyroid.

Conclusions: Our results indicate that thyroid follicular cells express both RET isoforms with RET9 expression levels similar to those observed in MTC. At variance RET51 expression is higher in MTC than in normal thyroid. Finally, we showed that while in MTC RET51 is expressed more than RET9, the opposite was observed in normal thyroid.

P1-07-68
DIFFERENT LONG NON-CODING RNAs AND THYROID MASTER GENES
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The transcription factors Nkx2-1, Pax8, Hhex and FoxE1 govern thyroid development and differentiation. Few causative mutations in these genes have been found in patients with thyroid dysgenesis, suggesting the involvement of other mechanisms. Non-protein-coding genes for micro-RNAs and long non-coding RNAs (lncRNA) might contribute to the modulation of transcription factor genes. Divergent lncRNAs are often located next to transcription factor genes and might fine tune their expression. In a global transcriptomic characterization we previously identified the UniGene ID Mm.389547, later replaced by Gmi12246, as one of the most enriched transcripts of the early mouse thyroid primordium. The Gmi12446 gene is located immediately next to FoxE1 and is transcribed in the opposite direction, making it a putative divergent lncRNA regulator of FoxE1, that is involved in the migration of the early thyroid primordium. Whereas FoxE1 is broadly expressed in the foregut, it is differently regulated in the thyroid placode and in the adjacent endoderm by unknown mechanisms.

Objectives: To define putative divergent lncRNAs located next to thyroid master genes and investigate their expression in normal mouse tissues and in a murine model of thyroid cancer.

Methods: Bioinformatic analysis of genomic regions surrounding FoxE1, Nkx2-1, Pax8 and Hhex. qPCR analysis of normal mouse tissues and thyroid tumors (Tgα-c-Myc murine model of papillary thyroid cancer).

Results: Gmi12446 is located next to FoxE1 and produces two transcripts of 798 and 713 nucleotides that are both expressed in the mouse thyroid. Neither transcript contains a meaningful open reading frame, thus defining them as divergent lncRNAs. The expression of Gmi12446 correlates to that of FoxE1 as both genes are expressed in the thyroid, esophagus and skin whereas neither transcript is detected in the lung or kidney. We found that potential divergent lncRNAs also located nearby two other thyroid master genes: Gmi13415 close to Pax8 and Gm26973 close to Nkx2.1. Whereas no expression of Gmi13415 could be detected, the expression of Gm26973 paralleled that of Nkx2-1. In a mouse model of papillary thyroid cancer, the decreased expression of FoxE1 and Nkx2-1 was accompanied by similar changes of their contiguous lncRNAs.

Conclusions: We identify divergent lncRNAs located next to thyroid master genes that constitute a new potential regulatory layer of gene expression that might modulate these transcription factors during normal development and tumor progression. Ongoing work aims at further exploring their mode of action by unbiased search for interacting proteins and more detailed characterization by RNA sequencing.

P1-07-69
NEXT GENERATION SEQUENCING REVEALED RET OR RAS MUTATIONS IN MEDULLARY THYROID CANCER THAT WERE NEGATIVE AT SANGER SEQUENCING
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We sequenced 114 medullary thyroid cancer samples for RET and RAS mutations by Sanger sequencing (SS). Forty three /114 (37.7%) resulted to be RET/RAS negative. These samples were reanalyzed with a next generation sequencing system (ION SS) using a custom panel. Twenty-nine cases were confirmed to be RET/RAS negative and also negative for any other analysed oncogene. Fourteen cases became either RET or RAS positive. Three cases were positive for H-RAS (2 G12R, 1 Q61R) with a mean allelic frequency (AF) of 34.91%. These mutations were reanalyzed by SS and still considered as negative. Eight cases were positive for RET (4 M918T, 1 C634W, 1 C620R, 1 p.Asp898, Gln901del, 1 S1024F, 1 Q762K) with a mean AF of 13.66%. These mutations were reanalysed by SS that showed the presence of a very low peak for the mutated allele, that would not be considered as positive without the NGS information. The 3 other cases were also positive for RET but the discrepancy was due to technical problems: 1 case had a germline M918T RET mutation not revealed by SS for the presence of a single nucleotide polymorphism (SNP) at the 5’ end of one primer in the mutated allele that caused the amplification of the wild type allele only; 1 case had a mutation L56M in exon 2 that is not usually investigated with the routine SS; 1 case had a somatic M918T mutations revealed by SS only following an increase in the MgCl2 in the amplification mix. We also compared the AF of mutations found by NGS with the ratio between the height of the SS peak of the mutated and wild type allele. With this analysis we demonstrated that the ratio of the SS peaks likely a quantitative method the ratio of the peak heights of the two alleles likely indicates the relative amount of the mutated allele.

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P1-07-70
MITOCHONDRIAL HOMEOSTASIS IN A CELLULAR MODEL OF ONCOCYTIC THYROID TUMOUR
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Background: The PGC-1 (Peroxisome proliferator-activated receptor Gamma Coactivator-1) family of coactivators (PGC-1α, PGC-1β, and PRC) plays a central role in the translational control of mitochondrial biogenesis and oxidative phosphorylation (OXPHOS) processes. The XTC.UCl cell line is a mitochondria-rich model of thyroid tumors whose biogenesis is almost exclusively dependent on PRC.

Objective: To propose an integrative view of the mitochondrial homeostasis regulated by PRC

Methods: XTC.UCl cells invalidated for PRC were tested on cDNA and miRNA microarrays. Chromatin-immunoprecipitation of six factors either transcription factors (Estrogen Related Receptor alpha, ERR1; Nuclear Respiratory Factors, NRF1 and NRF2; CAMP Response Element Binding, CREB; and Ying Yang, YY1) and PRC obtained from XTC.UCl cells were tested on promoter arrays. Combined bioinformatics analyses were applied to propose the metabolic pathway controlled by PRC.

Results: PRC induces a complex network of cellular functions interacting with at least one to five of the studied transcription factors. We confirmed that ERR1 is a key partner of PRC in the regulation of mitochondrial functions and suggest a potential role of this complex in RNA processing. PRC is also involved in transcriptional regulatory complexes targeting 12 miRNAs, five of which are involved in the control of the OXPHOS process.

Conclusion: Our findings demonstrate that the PRC coactivator can act in complex with several transcription factors and regulate miRNA expression to control the fine regulation of main metabolic functions in the cell. These results are discussed in the context of therapeutic targets for oncocytic thyroid tumours.

P1-07-71
STUDY OF THE MITOGENIC EFFECT OF RECOMBINANT HUMAN THYROID STIMULATING HORMONE (RH-TSH) IN NORMAL AND PAPILLARY CANCER THYROID FOLLICULAR CELLS
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Objectives: L-thyroxine suppression therapy is recommended in the treatment of patients with advanced differentiated thyroid cancer (DTC). No randomized prospective clinical trials have been done to prove the benefits of this iatrogenic subclinical hyperthyroidism. Older in vitro studies, which examined the effect of bovine TSH on human normal and cancerous thyroid follicular cells replication, had contradicting results. To this end, we sought to carefully investigate for the first time the effect of recombinant human thyroid stimulating hormone (rh-TSH) on human thyroid cell replication using cell lines of normal and papillary cancer thyroid cells.

Methods: The cell lines Nthy-Ori 3.1 and K1 were used as models of normal and papillary thyroid cancer cells respectively. These lines were initially incubated with increasing concentrations of fetal bovine serum (FBS), namely 2.5%, 5% and 10%, so as to determine the minimum required concentration in which cells can normally survive and replicate and use it as control. Using the control FBS concentration cells were incubated with 1, 5, 10, 20, 50, 100 mU/L and a “megados” of 1000 mU/L rh-TSH for 48 hours and the cell number was evaluated. The experiments were performed three times each and no other growth factors were added in the cell cultures. Data were analyzed by one-way ANOVA with Tukey’s post-hoc test.

Results: A concentration of 2.5% FBS (control) was enough to preserve the cells of both lines in a healthy proliferative state and this concentration was employed in the subsequent experiments with rh-TSH. Two days after incubation with the studied concentrations of rhTSH (1, 5, 10, 20, 50,100 and 1000 mU/L), the number of cells was increased in both cell lines. In Nthy-Ori 3.1 cells the increment was similar between the control and the different rh-TSH concentrations whereas in K1 cells it seems that the increment was gradually increased compared to the control and reached a plateau with rh-TSH concentration ≥20 mU/L (one-way, ANOVA, ns).

Conclusions: In this preliminary in vitro study, we show for the first time that, the enrichment of cell cultures of normal and papillary cancer thyroid cells with rh-TSH, was not adequate to further increase cell proliferation. We chose several rh-TSH concentrations to approach the serum TSH values observed in routine practice in DTC patients.
P2-01-73
ULTRASOUND CHARACTERISTICS (EU-TIRADS) AS MOST IMPORTANT FACTOR IN THE EVALUATION OF THYROID NODULES
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Background: The characterisation of thyroid nodules is still an ongoing dilemma. Due to new technical tools as elastography, MIBI scintigraphy etc the clinical growth of the importance of the new diagnostic procedures must be ruled out. These findings are summed using reporting systems (EU-TIRADS). Thus we analysed the features in our group of patients that were sent to thyroid surgery in 2016 and 2017 and compared to the histological findings.

Methods: The patients of our department, that is spread over the region Fulda, Rotenburg, Lauterbach and Gießen (central Hessia), were registered and characterized after histological determination. The parameters sex, age, TNM stage, time to surgery, ultrasound characteristics, EU-TIRADS, scintigraphy, volume of the total thyroid gland, volume of the nodule, elastographic characterisation, TSH-level, fT4 level, TPO-antibody, hTG (each BRAHMS), and calcitonine (IBL) were documented and ultrasound and scintigraphic findings were analyzed by two different experienced investigators.

The statistical analysis was performed using Statistica 10 with a significance level of p < 0.05.

Results: 105 patients were sent to surgery, 55 patients suffered from thyroid carcinoma (10 medullary, 39 papillary and 6 follicular thyroid carcinoma). The mean age was 47.4 ± 17.4 years. In the MANOVA evaluation the following p values could be measured sex p < 0.1, age p < 0.39, echogenicity of the nodule p < 0.000, interior perfusion p < 0.009, halo p < 0.006, margins p < 0.01, total thyroid volume p < 0.08, nodule volume p < 0.29, scintigraphic finding as cold nodule p < 0.09, TSH p < 0.009, fT4 p < 0.06, TPO p < 0.06, hTG p < 0.07, calcitonine 0.03. The statistical analysis itself reached significance levels p < 0.000, R² 0.998. 89% of the nodules histologically proven as malignant were found within 2 months between first investigation and surgery.

Conclusion: The statistical analysis revealed that the ultrasound characterisation using EU-TIRADS is not the only but the most relevant evaluation factor to divide between a benign and malignant thyroid nodule in our system.

The new reporting system therefore plays a prominent role in the evaluation of thyroid nodules.

Reference

P2-01-74
THE VALUE OF COLOR DOPPLER ULTRASONOGRAPHY WITH B-MODE MALIGNANT ULTRASOUND FEATURES FOR EVALUATION OF CYSTIC THYROID MASSES
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Purpose: To investigate the value of color Doppler ultrasonography (US) with B-mode Malignant Ultrasound features for evaluation of predominantly cystic thyroid masses.

Material and Method: This retrospective study included 138 predominantly cystic masses who had undergone Fine needle aspiration biopsy (FNAB) between Jan 2016 to December 2017 with Color Doppler US. We defined central color flow positive when flow was detected in solid papillary protruding portion and none when the flow was not visualized with in the cystic mass. We measured the diagnostic accuracy of color Doppler study compared with B-mode US accuracy alone. Sensitivity and specificity were calculated among with US features such as papillary protrusion and internal calcifications with and without color Doppler study to diagnose the malignancy in predominantly cystic thyroid nodule.

Results: Among 138 thyroid cystic masses mean size was 2.41 cm (range,1.0 cm-5.4 cm). FNAB confirmed 5 patients malignant and 2 patients AUS. Color flow present specifically within the solid papillary protruding portion showed the highest specificity of 99.2% (95% CI:95.8%–100%) but low sensitivity 42.9% (95% CI:9.9%–81.6%) whereas B-mode US malignant features alone showed specificity of 76.8% (95% CI:70.6%–85.3) with sensitivity of 71.4% (95% CI: 29%–96.3%). US B-mode malignant feature alone shows higher sensitivity compare to US B-mode and central Color Doppler flow (57.1% vs 42.9%) but without statistical significance (p > 0.3173) Higher specificity was noted in comparison of these two groups (92.4% vs 99.2%) with statistically significant p value of 0.0027.

Conclusion: Color flow present in center of solid papillary portions is a highly specific finding of malignancy when compared to B-mode US malignant features such as papillary protrusion with microcalcifications alone in diagnosing predominantly cystic mass. This specific finding can be used adjunct to malignant US features of cystic mass in deciding candidates of sclerotherapy in thyroid nodule.

P2-01-75
DIAGNOSIS OF MELLULAR THYROID CARCINOMA THROUGH AN APPENDECTOMY
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Introduction: A case of medullar carcinoma with atypical diagnostic course

Case Report: In December 2014, a female patient aged 44, was sent to endocrinologist to evaluate a tumorous formation on the right side of the neck. On ultrasound the nodus appeared inhomogenous, 22x10 mm, accompanied by enlarged lymph nodes. TSH, free thyroid hormones, anti TPO antibodies, and inflammatory parameters were in reference range.

Fine needle punction was not informative, so operation was indicated. Ex tempore pathohistology reported papillary type of malignancy, but definitive change to invasive follicular carcinoma. Radiojodine therapy was applied twice. In October 2015 patient underwent urgent appendectomy. As procalcitonin remained constantly high after surgery, and CT showed nodular formations in the lung, revious investigations related to malignancy has been performed. Octreoscan gave significant accumulation zones in the projection of the thyroid gland and central mediastinum. Calcitonin analysis for the first time above 2000. Reasonable suspicion in previously diagnosed cancer type justified complete revision of intraoperative pathohystology samples. In futher course tumor treated and controlled by NET specialist as infiltrative medullar carcinoma. January 2016 CT and octreoscan visualises pathologic focuses in the lung, revisory investigations related to malignancy has been performances in the lung, revisory investigations related to malignancy has been performances in the lung, revisory investigations related to malignancy has been performances in the lung, revisory investigations related to malignancy has been performances in the lung, revisory investigations related to malignancy has been performances in the lung.
ROLE OF FROZEN SECTIONS IN THE SURGICAL MANAGEMENT OF THYROID NODULES WITH INDETERMINATE CYTOLOGY

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The role of frozen sections in the surgical management of thyroid nodules with indeterminate cytology is controversial; current guidelines suggest lobectomy as first-line approach, followed by completion thyroidectomy when malignancy is diagnosed on postoperative histology.

Intraoperative frozen sections has often been used at our Institution; we retrospectively compared intraoperative to definitive histological diagnosis, to assess the usefulness of frozen sections as a guide to a correct surgical approach to indeterminate thyroid nodules (that is, to prevent a second surgical procedure).

From 2000 to 2017, frozen sections were performed in 1721 patients undergoing total thyroidectomy (51.5%) or lobectomy (49.5%). Cytological specimens were available in 1103 nodules.

In the whole series, malignancies were 21.5%. The sensitivity of the intraoperative histology was 68%, the specificity was 99.7%, PPV and NPV were 98.9% and 91%, respectively.

A concordance between intraoperative and definitive histological diagnosis was observed in 92.5% of cases, the mismatches accounting for 7.5%. Indeed, the Cohen test showed a satisfactory agreement between intraoperative and definitive histological diagnosis ($k = 0.76$) ($p = 0.05$).

The discrepancies between intraoperative and definitive histological diagnosis were mainly due to follicular lesions classified as benign intraoperatively and malignant at the final histology.

436 nodules out of 1103 for which cytology was available encompassed the indeterminate cytological class TIR 3 (according to the Italian SIAPEC classification). The “TIR 3A” (low-risk) were 105: 2 out of 8 cancers were correctly diagnosed intraoperatively; the sensitivity of frozen sections was 25%, the specificity 100%.

The “TIR 3B” (high-risk) were 321: in 49 cases out of 115 malignant nodules at definitive histology, frozen sections identified a carcinoma, addressing the surgeon towards an immediate total thyroidectomy. False positive intraoperative diagnosis were 2 in out 205 benign nodules (0.9%). The sensitivity and specificity of intraoperative exam were 42.6% and 99% respectively.

In the whole series, the intraoperative histological examination was highly specific, showing only few false positive cases, due to follicular lesions.

Regarding the nodules with indeterminate cytology, the intraoperative test enabled us to diagnose a malignancy in 49 cases, which correctly addressed surgical procedure (total thyroidectomy) and allowed to prevent second surgeries in 42.3% of the patients harboring cancer, thus reducing the time of treatment and saving money for the National Health System. Thanks to very small number of false positive cases, the risk of overtreatment is almost negligible.

In conclusion, frozen section may be a useful tool in surgical management of thyroid nodules with indeterminate cytology.
at diagnosis, size of the nodule and levels of basal CT. A weak correlation was found between basal CT levels and nodule size (P = 0.042). According to EU-TIRADS guidelines, we found that 55% of nodules were in EU-TIRADS 5 class (high risk of malignancy) while 39% were EU-TIRADS 4 (intermediate risk of malignancy). Around 6% were equally distributed within EU-TIRADS 2 (benign) and EU-TIRADS 3 (low risk of malignancy) classes. Tumor size showed tendential positive correlation with nodule size, even though it did not reach statistical significance (P = 0.093). In conclusion, preoperative neck ultrasound showed features of “high and intermediate risk of malignancy” in 94% of patients, with the highest rate of hypoechoc and solid nodules. The US characteristics found in our patients are not exclusively pertaining to MTC, but can be found in other thyroid malignant tumors. It remains to be cleared whether their associations with CT plasma values may be a particular feature of MTC.

P2-01-79
THE INFLUENCE OF THYROGLOBULIN ANTIBODIES TO THE OUTCOME THYROGLOBULIN MONITORING BY HIGHT-SENSITIVITY TESTS AFTER TREATMENT OF WELL-DIFFERENTIATED THYROID CANCER
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Aim: To optimize the approach to postoperative monitoring of serum thyroglobulin (Tg) in patients with well-differentiated thyroid cancer (WDTC). Design: 50 patients with WDTC underwent the combined treatment (a total thyroidectomy and radioiodine therapy) were included in the study during the period from 2010 to 2012. All patients were at low-to-intermediate risk (disease advanced was T1N0M0).

To exclude the persistence of the disease and regional and/or distant metastasis, initial examination of patients included: TSH, FT4, basal Tg, TgAb, neck ultrasonography, radiography of the lungs; TSH stimulation test (withdrawal of levothyroxine for a period of 4–5 weeks), at the end of which the stimulated Tg level was determined and a diagnostic whole-body scan with radioiodine (WBS-I131) was carried out.

Serum samplings of Tg were measured by immunometric method with functional sensitivity (FS) 0.9 ng/mL (Hoffmann la Roche, France) and by high-sensitive assays with FS ≤0.2 ng/mL (EIASON GmbH, Germany).

Treatment outcomes were estimated based on recurrence quantity and on number of the lethal outcomes causes by WDTC (2012–2018, the observation period is not less than 5 years).

Results: The research included 50 patients: average age 42.3 ± 7.2 years; women – 88% (n = 44); the papillary carcinoma prevailed in 94% cases. During suppressive therapy Tg values below 0.5 ng/mL were defined at 72%, between 0.7–0.9 ng/mL – at 28%. Prevalence of TgAb carrier was 36%. High-sensitivity Tg tests demonstrated low reproducibility for all TgAb-positive patients (in 100% there was a low reliability of results), while in TgAb-negative patients (n = 32, 64%) all results were reliable. TSH stimulation test detected disease recurrence in 5 patients, all cases were paratracheal lymph node metastases of papillary carcinoma (stimulated Tg in the range of 2.95–4.58 ng/mL). Retrospective analysis of the treatment outcomes after subsequent complex examination demonstrated a disease-free five-year survival in all TgAb-negative patients (n = 32) with absence of both stimulated Tg (Tg <2.0 ng/mL) and basal Tg levels increase for the moment of the initial examination.

Conclusions: Stimulated Tg is a reliable marker of disease recurrence. Presence of TgAb reduces the clinical value of Tg measurements by high-sensitivity test (FS ≤0.2 ng/mL), therefore can’t replace completely stimulating test.

However, it was justified for low-to-intermediate-risk patients without TgAb; this approach allows tailoring follow-up intensity on an individual basis, considerably reducing the need for detection of stimulated Tg further.

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cally confirmed. Other only 2 patient of 16 patient were thyroidectomied and histopathology was benign.

Conclusion: BRAF test is approved as determinative method in addition to FNAB.

P2-01-82
DIAGNOSTIC BENEFIT OF REPEATED FINE-NEEDLE ASPIRATION ACCORDING TO ULTRASOUND PATTERNS IN THYROID NODULES INITIALLY DIAGNOSED AS ATYPIA/FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE

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Purpose: To determine the diagnostic benefit of repeated fine-needle aspiration (RFNA), according to the US patterns in thyroid nodules initially diagnosed as atypia/follicular lesion of undetermined significance (AUS/FLUS).

Materials and Methods: This study included 273 consecutive nodules in which follow-up RFNA was performed among 502 thyroid nodules (≥1 cm) initially diagnosed as AUS/FLUS from January 2010 to December 2014. The diagnostic benefit of obviating unnecessary diagnostic surgery was determined when the RFNA cytology result was benign. We assessed the rate of diagnostic benefit, surgery decision (RFNA result of category 2, 4, 5, 6), and conclusive diagnostic result (RFNA result of category 2, 4, 5, 6) on RFNA according to US patterns of nodules defined by Korean Thyroid Imaging Reporting and Data System (K-TIRADS).

Results: The diagnostic benefit of benign RFNA result was found in 49% in K-TIRADS 3, 37.8% in K-TIRADS 4, and 28% in K-TIRADS 5 nodules, and there was a decreasing trend of the diagnostic benefit rate on RFNA with increasing K-TIRADS score (P = 0.034). The surgery decision was made in 3.4% in K-TIRADS 3, 11.2% in K-TIRADS 4, and 28% in K-TIRADS 5 nodules (P < 0.001). There was no difference of conclusive RFNA results among US patterns of nodules defined by K-TIRADS (P = 0.895).

Conclusion: The diagnostic benefit of RFNA to obviate unnecessary surgery was found at least 28% in the initially diagnosed AUS/FLUS nodules. Therefore, repeated biopsy may be helpful to reduce the unnecessary diagnostic surgery in AUS/FLUS nodules with high suspicion (K-TIRADS 5) US pattern.

Graves’ Orbitopathy

P2-02-84
SERUM HIGH CHOLESTEROL IS A NOVEL RISK FACTOR FOR GRAVES’ ORBITOPATHY (GO): RESULTS OF A CROSS-SECTIONAL STUDY

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Objectives: Limited data suggest that treatment with statins is associated with a reduced risk of GO in patients with Graves’ disease (GD), attributed to the anti-inflammatory rather than to the hypolipemic effects of these medications. Here we investigated whether there is an association between high cholesterol and GO. The primary outcome was the relation between GO and LDL-cholesterol. The secondary outcomes were the relations between severity or activity [the clinical activity score (CAS)] of GO and LDL-cholesterol.

Methods: We conducted a cross-sectional investigation in consecutive patients with GD who came to our observation to undergo radioiodine treatment, a stratification aimed at forming two distinct groups of patients under the same conditions. We enrolled 250 patients, 133 with and 117 without GO. Ophthalmological assessments and serum lipids measurements were performed.

Results: In multivariate analyses with correction for the duration of hyperthyroidism, a variable that differed between patients with respect to the presence or absence of GO, a correlation between the presence of GO and both total (P = 0.01) and LDL-cholesterol (P = 0.02) was observed. In patients with hyperthyroidism lasting <44 months, total and LDL-cholesterol were higher (P = 0.01 and P = 0.008, respectively) among GO patients. In this subgroup, based on the presence/absence of GO, we established cut-off values for total (191 mg/dl) and LDL-cholesterol (118.4 mg/dl), above which an increased risk of GO was observed (total cholesterol RR: 1.47; P = 0.03; LDL-cholesterol RR: 1.28; P = 0.03). GO severity and CAS did not correlate with serum lipids. However, CAS was found to be higher (P = 0.02) in patients with high total cholesterol. When the analysis was restricted to untreated GO patients, we found a correlation between CAS and both total (P = 0.04) and LDL-cholesterol (P = 0.03), after adjustment for GO duration.

Conclusions: In patients with a short duration of hyperthyroidism, total and LDL-cholesterol correlate with the presence of GO, suggesting a role of cholesterol in the development of GO. Depending on GO duration, total and LDL-cholesterol correlate with GO activity, suggesting a role of cholesterol in the clinical expression of GO.
CONCOMITANT VS SEQUENTIAL GLUCOCORTICOIDS AND RADIATION THERAPY FOR MODERATE-TO-SEVERE GRAVES ORBITOPATHY

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Background: Glucocorticoids (GCs) and external orbital radiotherapy (RT) are used alone or in combination in the treatment of moderate-to-severe forms of Graves’ orbitopathy (GO), but some uncertainties remain about the optimal treatment schedule.

Methods and Materials: 73 patients with moderate to severe GO were treated with a combination of i.v. GCs and RT, according to two different protocols, in which RT was delivered with concomitant schedule (Group A, 53 patients) or subsequently to the first GCs course (Group B, 20 patients), respectively. Clinical outcomes were assessed by Clinical activity score (CAS) and NOSPECS classification. The aim of this retrospective analysis was to check if one schedule was superior to the other in controlling GO.

Results: At baseline, CAS (median 4.0) and the percentage of patients encompassing the various grades of the classes 2, 3 and 4 of the NOSPECS score were similar in both groups. Six months after the end of RT, CAS significantly improved (p = 0.0003 vs baseline), without significant difference between the two groups (2.0 in both), as well as the extraocular muscle dysfunction NOSPECS class 4, (p < 0.001 vs baseline). The improvement in soft tissue involvement (NOSPECS class 2) at 6 months was significantly greater in group A than in group B (p = 0.016). Furthermore, the median cumulative dose of GCs was significantly lower in group A than in group B (median 4.500 vs 6000 mg, p < 0.007); the overall length of therapy was shorter in group A than in group B (68 ± 33 days vs 106 ± 49, mean± SD, p < 0.001). Proposis (NOSPECS class 3) was unchanged in both treatment groups. In the long-term follow-up, CAS and NOSPECS classes 2, 3 and 4 further improved, without significant difference between the two groups.

Conclusion: Our data show a favorable effect of concomitant GCs and RT schedule in moderate to severe GO, thus suggesting that RT should be carried out early during steroid therapy, when clinical symptoms do not improve or deteriorate after the first i.v. administrations of GCs.

TEAMED-5: A PRACTICAL APPROACH FOR USE BY ENDOCRINOLOGISTS TO IMPROVE OUTCOMES IN THYROID EYE DISEASE

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Thyroid eye disease (TED) is the commonest and most distressing complication of Graves’ disease (GD). TED can have a significant and negative impact upon the quality of patients’ lives and visual function. Delays in making a diagnosis of TED and initiating treatment are common. TEAMeD (Thyroid Eye Disease Amsterdam Declaration Implementation Group UK) has developed a process to improve care for people with TED and prevent TED in those at risk by a system of 5 care steps to be used by all endocrinologists managing Graves’ Disease – “TEAMeD-5”. (1) DIAGNOSE: TEAMeD recommends that an accurate diagnosis of the cause is made in all cases of thyroidosis to identify those at the risk of TED e.g. using TRAβ. (2) SCREEN: A systematic assessment should be performed for early signs/ symptoms of TED in all patients with an established diagnosis of GD to allow prompt and timely referral to appropriate ophthalmic care. DiaGO was developed as a clinical assessment tool to screen all patients with GD for signs and symptoms of TED. DiaGO has been tested and was found to be highly sensitive in picking up TED with a low false positive rate (<3%). (3) ALERT: All patients with GD should be informed about the risk of TED and given an early warning card. TEAMeD has developed “GO early warning cards” which can be given to all patients with an established diagnosis of GD to raise awareness of TED and to facilitate earlier diagnosis. The warning card describes early symptoms of TED and smoking advice. In a pilot study of 160 patients issued TEAMeD early warning cards, 6% of patients contacted their endocrine service about new eye symptoms. Nine calls resulted in an additional clinic review and four diagnoses of TED were made. (4) PREVENT: Current smokers should be referred to smoking cessation services. In all patients with GD, euthyroidism should be achieved promptly and maintained avoiding periods of hypothyroidism. Patients receiving 131I should be closely monitored and treated early with thyroxine to avoid a period of hypothyroidism. In active TED, 131I therapy should either be deferred or steroid cover given. (5) REFER: Patients with mild TED can be managed by an endocrinologist with an interest in TED. Patients with moderate or severe TED, or TED which affects their quality of life, should be referred to a specialist multidisciplinary joint thyroid eye clinic. The detailed recommendations and tools are available at http://www.btf-thyroid.org/projects/teamed/332-teamed-5.

CLINICAL MANIFESTATIONS AND ORBITAL MSCT PARAMETERS OF GRAVES’ ORBITOPATHY

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Objectives: To investigate the relationship between clinical manifestations of GO in patients with Graves’ disease (GD) and the multispiral computed tomographic (MSCT) parameters of orbital tissues.

Methods: 102 patients (204 eyes / orbits) with GO symptoms were examined. 72 of them were women (70.6%) and 30 men (29.4%), control group included 9 patients (18 eyes / orbits) without eye diseases. All patients underwent the standard ophthalmological examination. The activity and severity of GO were defined with CAS scale and EUGO protocol, respectively. All patients were performed a three-dimensional orbital MSCT. The extracocular muscles (EOM) and orbital fat tissue (OFT) density were examined in coronal and axial projections, stepping 1–2 mm from the contours of the muscle. The follow-up period was from 6 to 12 months.

Results: Increase of EOM density and orbital fat tissue density was observed in patients with severe GO. The above changes were not pronounced in eyes with mild GO. Our data show a favorable effect of concomitant GCs and RT in reducing the activity of GO, but without significant difference between the two groups.

Conclusions: The analysis of clinical and tomographic parameters allowed to distinguish 3 variants of GO. The isolated independence clinical variants of GO with features of clinical symptoms and different tomographic characteristics testifies different pathogenetic mechanisms of GO development and determines personalized approaches of treatment.
P2-02-88

ORBITAL RADIOTHERAPY AS A FIRST-CHOICE TREATMENT IN SELECTED CASES OF THYROID-ASSOCIATED OPHTHALMOPATHY

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Objectives: To assess the therapeutic potential of orbital radiotherapy (OR) used as a treatment of first choice in patients with moderate-to-severe thyroid-associated ophthalmopathy (TAO) and severe co-morbidities.

Methods: 5 out of 40 patients with untreated moderate-to-severe TAO referred to our clinical center in the last year, had severe co-morbidities. In these cases, the long-term high-dose glucocorticoid pulse therapy seemed to have an unfavorable benefit/risk ratio. Instead, low-dose fractionated OR was performed combined with low-dose oral glucocorticoids.

The patients were examined before OR and at the 2nd week, 3rd month and 6th month after the end of the therapy. Changes in ocular symptoms and status, as well as side effects, if any, were recorded. Quality of life was assessed at baseline and at the 6th month follow-up by a disease-specific questionnaire.

Results: OR lead to a significant improvement of subjective symptoms, periorbital congestion, partial or complete resolution of preexisting diplopia and motility deficits in 4 out of the 5 patients. One of these patients experienced an improvement of visual acuity as well. The initial effect was observed as early as 2 weeks after OR. During the follow-up there was a gradual decrease in the clinical activity score. The quality of life improved in parallel with the clinical amelioration of TAO. The only patient whose ocular manifestations did not significantly change after OR had the longest history of TAO with the lowest clinical activity score at baseline compared with the others.

As side effects, an acceleration of cataract formation was found in one patient, who was previously diagnosed with incipient cataract. A slight increase in body weight was observed in all patients most likely due to the concomitant intake of oral glucocorticoids.

Conclusions: OR is effective and safe when used as a first-choice treatment of TAO in patients who cannot tolerate an optimal-dose intravenous glucocorticoid treatment. The early application of OR in the disease course seems to give better results.

P2-02-89

CLINICAL MANIFESTATIONS AND ORBITAL MSCT PARAMETERS OF GRAVE'S ORBITOPATHY (GO)

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Objectives: To investigate the relationship between clinical manifestations of GO in patients with Graves’ disease (GD) and the multispectral computed tomographic (MSCT) parameters of orbital tissues.

Methods: 102 patients (204 eyes / orbits) with GO symptoms were examined. 72 of them were women (70.6%) and 30 men (29.4%), control group included 9 patients (18 eyes / orbits) without eye diseases. All patients underwent the standard ophthalmological examination. The activity and severity of GO were defined with CAS scale and EUGOGO protocol, respectively. All patients were performed a three-dimensional orbital MSCT. The extraocular muscles (EOM) and orbital fat tissue (OFT) density were examined in coronal and axial projections, stepping 1–2 mm from the contours of the muscle. The follow-up period was from 6 to 12 months.

Results: Increase OFT in the absence of enlargement EOM, observed in 20% of patients with GO (group 1), increase EOM without increasing OFT – in 11% (group 2). In 69% of the cases GO had a typical character with involvement in the process of both EOM and OFT (group 3). In the group 1 course of GO was more benign. Despite the expressed exophthalmos, EOM movements were preserved in full, there was no optic neuropathy and decreased eyesight. EOM x-ray density evaluation revealed areas corresponding to the density of the fat tissue (from 0 to minus 36 HU). In the group 2 there was a violation of the function of EOM with the development of diplopia, strabismus, but without pronounced exophthalmos. Fibrosis developed rapidly – in 4–6 months after first clinical manifestations. The presence of fibrosis was evidenced by an increase in EOM density (plus 50 – plus 98 HU).

Conclusions: The analysis of clinical and tomographic parameters allowed to distinguish 3 variants of GO. The isolation of independent clinical variants of GO with features of clinical symptoms and different tomographic characteristics testifies different pathogenetic mechanisms of GO development and determines personalized approaches of treatment.

P2-02-90

CENTRAL CORNEAL AND CENTRAL RETINAL THICKNESSES, INTRAOCULAR PRESSURE AND THICKNESSES OF CORIORETINAL LAYERS IN GRAVES’ DISEASE PATIENTS WITH OR WITHOUT ORBITOPATHY

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Objectives: Graves’ disease is an autoimmune disease that may consist of hyperthyroidism, goiter, eye disease (orbitopathy), and occasionally dermopathy. Graves’ orbitopathy (GO) is an autoimmune disease of the retroocular tissues. At initial presentation, the majority (approximately 75 percent) of patients had no ocular involvement, whereas mild, moderate-to-severe, and sight-threatening orbitopathy were present in approximately 20, 6, and 0.5 percent of patients, respectively. We aimed to compare central corneal (CCT) and central retinal thicknesses (RT), intraocular pressure (IOP) and thicknesses of chorioretinal layers in Graves’ Disease patients with or without Orbitopathy.

Methods: We enrolled 98 patients with Graves’ disease (71 females, 27 males and mean age: 45.04 ± 14.35 years). Sixteen (16.3%) of the patients had GO while 82 (83.7%) of the patients didn’t have. Patients with or without GO had similar age and gender. All participants underwent ophthalmological examination including measurement of central corneal thickness (CCT), retinal thickness (RT), intraocular pressure (IOP) and thicknesses of chorioretinal layers. The seven chorioretinal layers were retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE). Additionally, we calculated the mean thickness of two combined layers: inner retinal layer (IRL) and photoreceptor layer (PL). The results of patients with GO were compared with the patients without GO.

Results: There were no statistically significant differences in median right-left and mean RNFL, GCL, IPL, INL, OPL, ONL, RPE IRL and PL measurements between patients with Graves’ disease with or without GO (p > 0.05 for each). Median right-left CCT, mean CCT, median right and mean IOP was higher in patients with GO (p = 0.043, p = 0.011, p = 0.048, p = 0.032, p = 0.02, respectively). Left IOP was similar in two groups (p = 0.062).

Conclusion: To our knowledge, this is the first study that evaluates thicknesses of chorioretinal layers in patients with Graves’ disease. Thicknesses of chorioretinal layers were similar in patients with or without GO, while CCT and IOP was higher in patients with GO.
P2-02-91

THYROID OPHTALMOPATHY THERAPY IN GRAVES DISEASE WITH METHYLPPREDNISOLONE – EXPERIENCE OF THE EYE CLINIC AT OUR INSTITUTION

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Introduction: Graves’ Thyroid Ophthalmopathy (GO) occurs in this disease in about 20 to 25% of cases. The measurement of its activity and severity, through validated scores, is essential for the appropriate treatment. Most cases of GO are classified as mild and self-limited, in which conservative measures are appropriate. In moderate to severe GO, the need for more aggressive therapy is mandatory, with the use of methylprednisolone.

The Thyroid Eye clinic establishes a close articulation between Ophthalmology and Endocrinology, using defined protocols for the referral of these patients.

Objectives: To characterize the group of patients with GO who underwent methylprednisolone (PMP) vs group of patients not submitted to methylprednisolone (nPMP) and identify statistically significant correlations.

Material and Methods: retrospective evaluation of the patients observed at the Thyroid Ophthalmopathy clinic between 2007 and March 2018. The methylprednisolone group was submitted to 0.5 g methylprednisolone, intravenously; weekly for 6 weeks, followed by 0.25 g methylprednisolone weekly for 6 weeks. The GO activity was assessed using the Clinical Activity Score (CAS) at the first appointment and subsequent visits. Statistical analysis was performed using the SPSS program (version 21). The threshold of statistical significance (p) considered was 0.05.

Results: From a total of 380 patients, 38 (10%) were submitted to PMP, 30 women and 8 men, the nPMP group consisting of 276 women and 66 men. There were no differences in smoking habits in the groups. In the PMP group the mean age was higher (57.09 vs 48.60, p < 0.001), as was the initial activity (p < 0.001). The time interval between onset of symptoms and referral to Ophthalmology was 1.09 years on average in PMP patients and 4.24 years on average in nPMP patients, and this difference was statistically significant (p = 0.001). There was a more favorable evolution of CAS over time in PMP vs nPMP patients (p < 0.001). In the PMP group, 20 cases reduced TRAb (54%) after therapy, and the measured activity decreased in 77%.

Conclusion: The PMP group is older and has higher disease activity than the nPMP group. The time interval between the symptoms and the appointment was significantly lower in the PMP group, which meant a faster reference to Ophthalmology. The creation of the specialized Eye-thyroid clinic facilitated the referral processes and consequently of GO therapy, as a multi-disciplinary approach is required.

P2-02-92

VERY LOW DOSE RITUXIMAB FOR THE TREATMENT OF ACTIVE MODERATE TO SEVERE GRAVES’ ORBITOPATHY

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Previous studies have shown that Rituximab (RTX) is effective as a disease modifying drug at doses of 500 mg or 1000 x2 mg in active GO. We have conducted a pilot study (EUDRACT 2012-001980-53) in which patients with active moderate-severe GO were treated with a very low dose of RTX (100 mg) in a single administration.

Patients and Methods: Sixteen patients with 0.5–10.1 months disease duration were enrolled and completed the study at 76 weeks. Eight patients were unresponsive to i.v. steroids, eight had newly diagnosed GO. Disease activity was assessed with the clinical activity score (CAS) and severity with NOSPECS score. The primary endpoint was the decrease of the CAS of 2 points or CAS ≤ 3 at 12 and 24 weeks.

Results: All patients were B cell depleted and some had minor infusion-related reactions. Fifteen out sixteen of them had inactive disease at 12 weeks (ANOVA P = 0.01), whether the disease duration was less or more than median duration of disease (4.2 months) (P = NS). One patient, inactive at 8 weeks, underwent surgical orbital decompression because of signs of consecutive disease at 11 weeks. At 16 weeks two patients underwent surgical orbital decompression because of suspected subclinical optic neuropathy. One patient who had transient disease reactivation at 12 weeks became inactive at 32 weeks, without any further treatment. None of the patients showed relapse of GO through follow-up until 76 weeks. The inactivation incidence cumulative rate showed that 50% of patients was already inactive at 4 weeks with a further increase up to 94% at 12 weeks.

Conclusion: very low dose of RTX leads to a rapid disease inactivation in active moderate to severe GO with no long term relapse of the disease. While we confirm that 100 mg RTX is effective for GO inactivation in most patients, we do not recommend its use in patients with suspected subclinical optic neuropathy, also according to the recently published EUGOGO guidelines.

P2-02-93

EYE THYROID CLINIC- RESULTS OF A TERTIARY HOSPITAL

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Introduction: 20 to 25% of Graves’ Disease (GD) patients with hyperthyroidism have orbitopathy (GO). Activity assessment (Clinical Activity Score CAS) is essential for therapeutic decision. Early referral for Ophthalmology clinic avoids the progression of the inflammatory process. Eye-Thyroid Clinic allows to define strategies.

Material and Methods: Retrospective evaluation of GO appointment data from 2007 to March 2018 of a tertiary Hospital Ophthalmology Clinic. A Thyroid-Eye Clinic was implemented in 2013 with referral protocols. GO activity was assessed using CAS score. Statistical analysis is performed with SPSS (version 21).

Objectives: Characterize the population and analyze the effect of the implementation of an Eye – Thyroid Clinic.
Hypothyroidism 2

P2-03-94
THYROID FUNCTION AND CARDIO-ANKLE VASCULAR INDEX
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Background: The cardio-ankle vascular index (CAVI) is independent of blood pressure, and hypothyroidism is known to cause arteriosclerosis. We aimed to determine the relationship between thyroid function and arteriosclerosis using CAVI.

Patients and Methods: We enrolled 413 patients with untreated thyroid dysfunction who presented at an outpatient clinic between April 2015 and March 2017 and provided informed consent. We excluded patients with hyperthyroidism and those under treatment for hypercholesterolemia. We divided the patients into groups A, B, and C based on thyroid stimulating hormone (TSH) levels of 0.2–2.5 (n = 235), 2.51–4.5 (n = 67), and >4.5 (n = 39), respectively. Multiple regression analysis included CAVI as the target variable and age, body mass index (BMI), C-reactive protein (CRP), low density lipoprotein cholesterol (LDL-C), hemoglobin A1c, free thyroxine (FT4), and TSH as explanatory variables.

Results: CAVI did not significantly differ among the groups (p = 0.1125). The median (range) CAVI in groups A, B, and C was 6.9 (3.7–10.2), 7.2 (4.7–10.5), and 7.1 (5.3–11.3), respectively, and FT4 levels did not significantly correlate with CAVI. Multiple regression analysis selected CAVI as the target variable and age, BMI, CRP, and TSH values as being significantly associated with CAVI.

Conclusion: Thyroid function has little effect on CAVI.

P2-03-95
SELENIUM AS A REASON FOR THYROID HYPOFUNCTION
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Objectives: The objective of our study is to identify whether Selenium deficit leads to dysfunction of thyroid gland.

Methods: The study had 100 female participants aged 35 ± 7, who had Subclinical hypothyroidism, but not as a result of Autoimmune thyroiditis. These patients were divided into 2 groups with 50 patients in each. TSH of all patients was 5–10 mIU/L (N = 0.4–4.0 mIU/L), FT4=0.8–1.3 mg/dl (N = 0.7–1.9 mg/dl); anti-TPO was less than 35 IU / ml. The 1st group was treated with the Supplement of Iodine (200 mkg). The 2nd group was treated with 200 mkg of the Supplement of Iodine and 100 mg of Selenium (as a preventive measure and with the allowable dosage without checking the level of Selenium as it’s not done in our country).

Results: After 6 months (See Table 1).

Table 1. (for Abstract P2-03-95)

<table>
<thead>
<tr>
<th>1st Group</th>
<th>2nd Group</th>
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</thead>
<tbody>
<tr>
<td>TSH</td>
<td>TSH</td>
</tr>
<tr>
<td>30%&lt;5 mIU/L</td>
<td>74%&lt;5 mIU/L</td>
</tr>
<tr>
<td>48%&lt;5–7 mIU/L</td>
<td>18%&lt;5–7 mIU/L</td>
</tr>
<tr>
<td>22%&lt;8–10 mIU/L</td>
<td>8%&lt;8–10 mIU/L</td>
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As you can see the group that in the group treated with Selenium the compensation percent is higher than in the 2nd group for 44%.

Conclusion: 1. Not in all cases thyroid hypofunction is conditioned with Iodine deficit. 2. The treatment of hypothyroidism and Subclinical hypothyroidism requires adding Selenium to the treatment.

P2-03-96
RELATION OF THYROID FUNCTION WITH TROPONIN T LEVELS IN ACUTE MYOCARDIAL INFARCTION – THE THYRAMI 1 STUDY
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Background: Both troponin levels and thyroid dysfunction at the time of an acute myocardial infarction (AMI) are important adverse predictors of cardiovascular outcomes.

Objective: To analyse the relationship between troponin T levels and thyroid function in AMI patients.

Methods: The ThyrAMI 1 study is a prospective multicentre study that assessed thyroid function on admission to hospital in consecutive AMI patients (both ST-elevation [STEMI] and non-ST-elevation [NSTEMI]) between January 2015 and December 2016. Multiple linear regression analyses were performed to evaluate the relationship of thyroid status and thyroid function with 6-hour troponin T levels after AMI, taking into account relevant demographic and clinical factors.

Results: Of the 1407 patients analysed, the majority of participants were euthyroid (72.1%). The prevalence of subclinical hypothyroidism (SCH) was 19.5%, subclinical hyperthyroidism was 0.8%, levothyroxine-treated hypothyroidism was 6.2% and isolated low T3 state was 1.0%. Individuals with SCH had higher median (interquartile range) troponin T levels than those with euthyroidism: 581 (147–2594) vs 334 (101–1483), p = 0.002, which remained 22.6% (95% confidence interval, 4–51%) higher after adjustment for con-
founders. In the euthyroid group, serum free triiodothyronine (FT3) had an independent quadratic (‘U’-shaped) relationship with tripronin T levels [FT3: p < 0.001 and (FT3): p = 0.001], which was not observed with free thyroxine or thyrotropin (TSH).

**Conclusions:** SCH at the time of AMI is related to higher 6-hour tropo- nin T levels. Studies with appropriate doses of thyroid hormone treatment are required to evaluate cardiovascular outcomes in SCH patients with AMI.

**P2-03-97**

**ULCERATIVE COLITIS: A NOVEL CAUSE OF INCREASED NEED FOR THYROXINE**

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Ulcerative colitis (UC) is a chronic inflammatory disorder of the large bowel whose incidence is 10 to 200 cases/100000 inhabitants and the prevalence of about 0.01% in the general population. Data on the association with thyroid disorders are scarce and whether this disease may interfere with thyroxine (T4) treatment efficacy is not known. The aim of this study has been to analyze the presence of UC and its possible role in the oral thyroxine mal-absorption in a large cohort of consecutively examined patients with thyroid disorders.

The records of 8537 patients were retrospectively analyzed and a total of 43 patients bearing an inflammatory bowel disease were recruited (0.005%). Among them, 32 patients had UC (28F/4M; median age = 59 years), and 15 of them (F/M; median age = 60 years) were in need for T4 treatment. All patients have pledged to take thyroxine in fasting conditions, abstaining from eating or drinking for at least one hour. According with the policy of our Centre, T4 was prescribed in an increasing fashion until the target serum TSH (<0.8–2.5 mIU/L) has been attained and maintained in at least 2 controls. To calculate the possible excess of T4 required in our patients, the individual requirement of T4 was compared to the one observed in 115 similarly treated age- and BMI-matched patients, clearly devoid from gastrointestinal and/or pharmacological interference.

The dose required was higher than in the reference group in 13/15 patients (87%) and the median thyroxine dose needed was 1.72 μg/kg/day. A median dose excess of 22% has been observed as compared to the minimal effective dose in control group. Since half of these were senior patients, we divided the sample in two groups: under 60 years (7 patients; median age = 53 years) and over 60 years (8 patients; median age = 73 years). In adult patients a dose excess has been detected in 5 out of 7 patients (median T4 increase=+26%). The median T4 requirement in younger patients was 1.78 μg/kg/day with a significant increase as compared to reference patients (1.31 μg/kg/day; p = 0.003). In elderly patients an increased T4 dose was seen in all 8 patients (median T4 increase=+21%). The median T4 requirement was significantly higher than in the age-matched reference group (p = 0.019). The increased need for thyroxine was therefore similar independently from the age of patients. In conclusion, these data support the hypothesis that ulcerative colitis may represent a novel cause of increased need for thyroxine.

**P2-03-98**

**NON-IMMUNE RELATED HYPOTHYROIDISM AND ITS RELATIONSHIP WITH EXCESS IODINE: A MAJOR CAUSE OF HYPOTHYROIDISM IN IODINE SUFFICIENT AREAS**

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**Background:** Autoimmune hypothyroidism has been regarded as the main cause of hypothyroidism in iodine-sufficient areas and only susceptible subjects such as those with positive thyroid peroxidase antibody (TPO Ab) is related to hypothyroidism induced by excess iodine. However, the proportion of non-immune related hypothyroidism and its relationship with excess iodine have been rarely evaluated.

**P2-03-99**

**THYROID DISEASES IN ELDERLY TURKISH PATIENTS**

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**Objectives:** The population of aging people is increasing worldwide. It is supposed that the increase in population over 70 years will double in 2030. Like many other chronic diseases, thyroid diseases increase with age. Changes in thyroid function tests and increased nodularity of thyroid paranchyme are also common in aging people. The region neighbouring capital city of Turkey is characterized with mild to moderate iodine deficiency. We aimed to evaluate functional and structural thyroid diseases in people over 70 years of age in Eskisehir.

**Methods:** We evaluated 730 patients (150 male, 580 female) aged between 70–79, who were admitted to the outpatient clinic of endocrinology due to thyroid disease in years between 2013 and 2018. Electronic records regarding anamnestic data, thyroid antibodies, ultrasound reports, and thyroid function tests were reviewed. Four hundred fifty three of them had previously known thyroid disease, while 277 (69 male, 208 female) had new diagnosis.

**Results:** Mean age was 75.29 ± 3.83. Among the patients with previously known thyroid disease, 239 were using levothyroxine (TSH 4.04 ± 9.34 mIU/L) and 81 were either on propylthiouracil or methimazole therapy (TSH 1.81 ± 8.35 mIU/L). Eight patients had previously established diagnosis of thyroid cancer (one medullary thyroid cancer, 7 differentiated thyroid cancer). One patient had previously established diagnosis of Graves’ disease.

**Conclusions:** Our study is the largest study in Turkey evaluating thyroid diseases in elderly patients. Since many patients were referred to endocrinol-
ogy clinics due to suspicion of thyroid disease or abnormal thyroid function tests, our study does not reflect the actual prevalence of thyroid diseases in elderly people. Nodular thyroid disease takes the lead both in patients with previous diagnosis and new diagnosis. Surgery was a common cause of hypothyroidism in our patients. Hyperthyroidism was much more common than hypothyroidism in patients with new diagnosis of thyroid disease. It may be due to increased autonomy of nodules with aging. Another contributing factor to the high prevalence of nodular thyroid diseases in elderly patients may be longer exposure to iodine deficiency before national iodisation programme.

**P2-03-100**

**THYROID DYSFUNCTION IN HEAD AND NECK CARCINOMA AFTER EXTERNAL RADIOTHERAPY: METASTASES AND TYPE 2 DIABETES AS RISK FACTORS**

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**Aims:** To evaluate the presence of thyroid dysfunction among patients submitted to external radiotherapy for the treatment of head and neck neoplasia, with serial evaluation of thyroid function. Besides that, the evaluation of variables related to the development of thyroid dysfunction, as well as the time to its occurrence and the association with the final outcome of the patient’s evolution until the end of follow-up, should be highlighted.

**Methods:** This is a retrospective longitudinal study of the follow-up of thyroid function in patients submitted to external radiotherapy for the treatment of head and neck neoplasia. Patients were classified as having overt primary hypothyroidism, subclinical hypothyroidism, central hypothyroidism and subclinical thyrotoxicosis.

**Results:** 53.8% of 340 patients presented thyroid dysfunction, 45.2% of them maintained persistent dysfunction. The most common dysfunction was subclinical hypothyroidism (n = 125). Of these, 68.8% remained with subclinical hypothyroidism, 20.8% evolved to overt hypothyroidism, 0.8% presented central hypothyroidism and 9.6% returned to the euthyroid state. The mean time after radiotherapy for the occurrence of subclinical dysfunction was 16.8 months, whereas for overt evolution it was 23.8 months. Regarding the risk of progression of subclinical hypothyroidism, a direct correlation with TSH level was observed: all patients with TSH ≥7.5 mIU/mL evolved to primary hypothyroidism or remained in subclinical hypothyroidism, whereas among those with TSH <7.5 mIU/mL, 19.6% were euthyroid at the end of follow-up. Type 2 Diabetes Mellitus was a risk factor for thyroid dysfunction and a development at an earlier age as were the existence of distant metastases and patients not undergoing surgery for primary tumor.

**Conclusions:** Fifty percent of our patients presented some degree of hypothyroidism in 23.8 months on average and 4.8% developed subclinical thyrotoxicosis, in an average time of 3.8 months. These data indicate the need for frequent monitoring of thyroid function in these patients, with early and long-term onset. Special attention should be given to the population at greater risk, such as those with distant metastatic disease, extensive lymph node disease (N3) and type 2 diabetes mellitus.

**P2-03-101**

**REPORT OF A LARGE SERIES OF PATIENTS WITH AUTOIMMUNE ATROPHIC GASTRITIS WHO OBTAINED A SERUM TSH LEVELS NORMALISATION AFTER SWITCHING FROM ORAL L-T4 IN TABLET FORM TO L-T4 IN LIQUID FORMULATION**

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**Objectives:** Patients with autoimmune atrophic gastritis could report several issues in L-thyroxine (L-T4) absorption.

**Methods:** Thirty-two patients with autoimmune atrophic gastritis and showing high serum thyrotropin (TSH) levels (in the hypothyroid range), while following a therapy with L-T4 in tablet formulation, were enrolled. All patients were switched to receive an oral L-T4 liquid formulation maintaining the same dosage.

**Results:** We have observed a circulating TSH levels normalisation/reduction in all the patients who had been switched from L-T4 in tablet formulation to an oral liquid one with the same L-T4 dosage. TSH levels worsened again, reaching levels in the hypothyroid range, in eleven patients who were switched back again to receive L-T4 in tablets maintaining the dosage.

**Conclusion:** Considering that the change from tablets to oral liquid formulation normalised serum TSH levels, and that switching back to tablets caused TSH levels to worsen, it has been hypothesized that absorption of L-T4 is greater with oral liquid formulations in these patients. We can suppose that the oral L-T4 liquid formulation could circumvent the pH alteration resulting from atrophic gastritis.

**P2-03-102**

**IMPACT OF METFORMIN ON THYROID-STIMULATING HORMONE LEVELS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS**

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**Objective:** Metformin is widely prescribed medication with favorable safety profile in patients with type 2 diabetes mellitus (T2DM). Several studies have previously reported that metformin can affect levels of thyroid-stimulating hormone (TSH) in diabetes with hypothyroidism, but levels of TSH in euthyroid population remain unaltered. The aim of the study was to establish a relationship between metformin and TSH levels in hypothyroid and euthyroid patients with T2DM.

**Methods:** A cross sectional population based study included patients with T2DM that have been examined in Clinical center of Montenegro during one day. Demographic data were collected, along with a type of treatment for T2DM. The patients were divided in two groups: the first with pre-existing hypothyroidism (on treatment with L-thyroxine) and the second with normal thyroid function. Statistical analysis was performed using descriptive statistics and Student t-test.

**Results:** Study included 89 subjects, 48 were female and 41 were male, mean age 66.78 ± 9.67 years. All of them were treated with metformin, solely or in a combination with insulin or other oral glucose-lowering agents. Out of 89 patients, 26 (29.2%) were hypothyroid, with mean TSH level of 1.3 ± 0.83 mIU/L. Other 63 (70.8%) had TSH levels in reference range (mean 3.9 ± 1.24 mIU/L). Between two groups, we found statistically significant difference (p < 0.01).

**Conclusion:** Our study demonstrated that metformin have significant influence on TSH levels in patients with T2DM and hypothyroidism.
BODY MASS INDEX AND WAIST CIRCUMFERENCE CORRELATION WITH TSH LEVELS AMONG THE EUTHYROID PATIENTS

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Introduction: Thyroid dysfunction and obesity are common disorders with the prevalence rates 1–10% and 30–60%, in population based studies, respectively. Relationship between thyroid dysfunction and obesity is well-established, especially for hypothyroidism. Although weight gain in hypothyroidism usually modest, serum TSH concentrations within the normal range have also been associated with mild increase in body fat composition.

Aim: In this study we aimed to demonstrate any correlation between body mass index (BMI) and waist circumference (WC) and thyroid hormone levels in euthyroid state.

Material and Method: Serum TSH levels of 487 euthyroid patients who admitted our out-patient clinic were analyzed retrospectively, after excluding patients with diabetes mellitus and other forms of obesity syndromes. Patients were divided into two groups according to their serum TSH (mIU/mL) levels; Group 1 with TSH levels were between 0.3–1.99, Group 2 with TSH levels were between 2.0–2.5.

Results: 373 patients were female (76.5%) and 144 (23.5%) were male, mean age was 43.0 ± 15.1, 358 (73.5%) patients had underlying thyroid disorders. Patients with diabetes mellitus and other forms of obesity syndromes. Patients admitted our out-patient clinic were analyzed retrospectively, after excluding patients with diabetes mellitus and other forms of obesity syndromes. Patients were divided into two groups according to their serum TSH (mIU/mL) levels; Group 1 with TSH levels were between 0.3–1.99, Group 2 with TSH levels were between 2.0–2.5.

Results: 373 patients were female (76.5%) and 144 (23.5%) were male, mean age was 43.0 ± 15.1, 358 (73.5%) patients had underlying thyroid disorders, mean TSH level was 2.0 ± 1.14 mIU/mL and serum free levothroxine level was 11.9 ± 3.63 pmol/L, mean BMI was 27.7 ± 6.0 kg/m² and WC was 90.4 ± 13.8 cm.

Body mass index / waist circumference and TSH levels does not seem to be correlate in euthyroid patients. Obesity parameters of two groups were similar. Multivariate analysis of the groups according to male/female ratio, mean age, and underlying thyroid disorders did not make any change in our results.

In conclusion, in euthyroid state, high-normal and low-normal TSH levels within normal ranges, does not seem to be releated to increase in body mass index and waist circumference.

Table 1. Comparison of lipid profiles of patients in different groups (for Abstract P2-03-103)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (TSH: 0.3–1.99 mgU/mL)</th>
<th>Group 2 (TSH: 2.0–4.5 mgU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>260</td>
<td>227</td>
</tr>
<tr>
<td>Body mass index (kg/m²) (mean)</td>
<td>27.4±5.7</td>
<td>28.1±6.3</td>
</tr>
<tr>
<td>Waist circumference (cm) (mean)</td>
<td>90.1±13.3</td>
<td>90.8±14.3</td>
</tr>
<tr>
<td></td>
<td>0.34</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Conclusion: Frozen section plus immunohistochemical staining is of value for determining the extent of thyroidectomy in patients with follicular neoplasm.

P2-04-106
COMPUTER-AIDED DIAGNOSTIC TECHNIQUE IN FDG POSITIVE THYROID NODULES
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Aim: The aim of this study was to apply a computer-aided diagnosis (CAD) technique to assist ultrasonography (US) diagnosis of 18-FDG-avid thyroid incidentalomas.

Patients: A total of 82 18-FDG-avid thyroid nodules found in 74 non-thyroid cancer patients during August 2008 to October 2016 at Chang-Gung Memorial Hospital (CGMH) were retrospectively analyzed by US and the CAD software (AmCAD-UT; AmCad BioMed, Taiwan); which were compared to another 36 non-18-FDG-avid nodules found in the same patient group after US examination. The CAD parameters included anechoic area, hyper- and hypo-echogenicity, heterogeneity, margin, taller than wide, eccentric area and the lesion size. Fine needle aspiration cytology (FNAC) was done simultaneously and 13 of these patients received surgical intervention. Eventually, 46 benign, 5 indeterminate and 19 (8 thyroid originated, 10 metastatic, 1 indeterminate) malignant lesions were reported in 70 FDG avid nodules in contrast to 16 benign, 1 indeterminate and 1 thyroid cancer in 18 non-FDG-avid nodules.

Result: No significant difference of mean size or individual CAD parameters was found among benign, indeterminate and malignant groups in FDG-avid nodules. A taller than wide cancer character was found significantly different between thyroid originated and metastatic cancers (0.30 vs 0.16, P < 0.05). In patients co-existing FDG-avid and non-avid nodules, higher eccentric area CAD value was found in benign nodules with FDG uptake. Nevertheless, neither a single nor the sum-up (from 1–7) scores of the CAD parameter predicts malignancy of the incidentaloma. However, a discrimination point of 4 with a sensitivity of 75% and a specificity of 79% predicts malignancy of the incidentaloma when combining the CAD parameters and PET/CT (0–4) scores. The area under the ROC curve (AUC) was 0.750 with 95% confidence interval (95% CI) within 0.601–0.890; p = 0.001.

Conclusion: We conclude that benign thyroid nodules with irregular shape of solid component and greater than 15% cystic part may be correlated with FDG uptake. Furthermore, a total of CAD and PET score less than 4 may predict benignity of thyroid incidentaloma.

P2-04-107
WITHDRAWN

P2-04-108
INITIAL EXPERIENCE OF TRANSORAL ENDOSCOPIC THYROIDECTOMY VESTIBULAR APPROACH FOR THYROID NODULE BY SINGLE Surgeon
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¹Taipei, Taiwan; ²Taoyuan City, Taiwan

Objectives: Transoral endoscopic thyroidectomy vestibular approach (TOETVA) is a kind of thyroid natural orifice surgery using three port technique through oral vestibular approach. The scarfless surgery have excellent cosmetic result. This study reports the surgical outcome of TOETVA surgery by a single surgeon.

Methods: From June 2017 to February 2018, 34 consecutive patients underwent transoral endoscopic thyroidectomy vestibular approach (TOETVA) surgery for benign and malignant thyroid diseases. Three port technique through vestibular approach was used. The main indications are Graves’ disease, symptomatic benign thyroid nodules <10 cm and malignant thyroid nodule <3 cm. The surgical outcomes are retrospectively reviewed.

Results: Thirty-four patients (31 females, 3 males; mean age 48.4 ± 15.8 (range, 19–78) years) underwent TOETVA surgery. Among them, twenty-six patients received unilateral thyroid lobectomy with or without central neck lymph node dissection, seven patients received bilateral total thyroidectomy, and one patient received unilateral lobectomy followed by completed total thyroidectomy at two weeks after the first operation. The final diagnosis is as follows: Twenty-six patients with benign thyroid nodules (mean size: 3.7 ± 1.8 cm, range, 1.4–8.8 cm), four patients with Graves’ disease, four patients with papillary carcinoma (mean size: 1.5 ± 0.8 cm, range, 0.8–2.7 cm). The surgical margin of the malignant cases were free. The mean surgical time was 242 ± 58 minutes with or without intraoperative frozen section. The mean hospital stay was 2.5 ± 0.8 days. The VAS pain score were 2.3 ± 1.0 at immediate post-operation, 2.0 ± 0.9 on postoperative day 1, 1.7 ± 0.9 on postoperative day 2, and 1.7 ± 0.7 on postoperative day 3. Two patients reported transient vocal cord palsy. Two patients experienced transient paresthesia of the lower lip less than 0.5 cm width which resolved within 4 weeks. None of the surgical complications including seroma, hematomata, or surgical site infection was reported.

Conclusion: Transoral endoscopic thyroidectomy vestibular approach (TOETVA) is a feasible natural orifice thyroid surgery with few minor complications and excellent cosmetic results.

P2-04-109
ACTIVE SURVEILLANCE: A NEW ALTERNATIVE IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA
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¹Hospital de Clínicas – University of Buenos Aires, Buenos Aires, Argentina

Introduction: The recent dramatic increase in the incidence of papillary thyroid carcinoma (PTC) is largely due to a rise in the diagnosis of small (<1 cm) PTC, also known as papillary microcarcinomas (PMCs). If never diagnosed and treated, most (estimated as 50%–90%) of these PTC would not go on to cause symptoms or death. This situation has been characterized as an “epidemic of diagnosis” rather than an epidemic of disease. Recognizing this indolent behavior, most guidelines recommend the active surveillance as an alternative in properly selected patients. The experience with this approach in our country is limited.

Objectives: To describe the clinical characteristics and the outcome of PTC tumor growth during active surveillance.

Methods: The diagnosis of PTC was based on ultrasonography (US)-guided fine-needle aspiration biopsy. When the PTC measurement was 15 mm or less, we offered two management options: observation alone or surgical treatment. We included 22 patients with PTC: without: (i) US regional lymph-node metastasis or clinical distant metastasis, (ii) US extrathyroidal extension or (iii) tumors located adjacent to the recurrent laryngeal nerve or trachea. They were followed-up with thyroglobulin and thyroglobulin antibodies measurements and ultrasound examination twice per year. PTC progression was defined when: 1) tumor’s size increased ≥3 mm, ii) novel appearance of lymph-node metastasis, and iii) duplication of thyroglobulin levels. For patients with these features, surgery was recommended.

Results: The frequency of patients who showed tumor enlargement was 13% after a median of 3-years (range 1–16 y) of follow-up, without any evidence of nodal or distant metastases. Additionally, 10% of patients presented tumor diameter decrease. Five out of 22 patients underwent surgical treatment due to: i) patient’s decision or, ii) tumor located adjacent to the trachea with duplication of serum thyroglobulin levels. These 5 patients were rendered with no evidence of disease after a median of 36 months (range 24–72 m) of follow-up.

Conclusions: This is the first experience performed in Argentina considering the active surveillance in patients with PTC. Although surgical treatment continues to be the usual choice for most patients, this new alternative seems to be easily applicable in centers with experience in the management of patients with thyroid cancer.
OBJECTIVES: Our objective was to assess to comparison of ultrasonography features of follicular thyroid adenoma (FTA) and nodular hyperplasia (NH) by using the most recently published guidelines for the US-based management of thyroid nodules, the Korean thyroid imaging reporting and data system (K-TIRADS).

METHODS: From January 2010 to December 2011, 106 patients who underwent preoperative thyroid ultrasonography and thyroid surgery were included. The US features of each thyroid nodule were retrospectively reviewed according to the K-TIRADS.

RESULTS: Of the 106 nodules (mean size, 3.8 ± 1.6 cm), 22 were FTAs (mean size, 4.1 ± 1.2 cm) and 84 were NHs (mean size: 3.3 ± 1.6 cm). A statistically significant difference was found between FTA and NH regarding the halo (p = 0.005), while no significant differences were observed in the solidity, echogenicity, shape, orientation, calcification, or vascularity of the lesion (p > 0.05). The FTAs belonged to K-TIRADS categories 3 (n = 15) and 4 (n = 7), while the NHs belonged to K-TIRADS categories 2 (n = 1), 3 (n = 71), 4 (n = 16), and 5 (n = 1). There was no statistically significant difference in the distribution of K-TIRADS categories between FTAs and NHs (p = 0.19).

CONCLUSION: Ultrasonographic features were not helpful for distinguishing FTA from NH, although FTAs showed a high prevalence of having halo on ultrasonography.

Table 1. (for Abstract P2-04-112)

<table>
<thead>
<tr>
<th>Time after RFA session</th>
<th>6 month</th>
<th>1 year</th>
<th>2 year</th>
<th>3 year</th>
<th>4 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule reduction after RFA (median)</td>
<td>56%</td>
<td>63%</td>
<td>66%</td>
<td>66%</td>
<td>66%</td>
<td>67%</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>15.97%</td>
<td>18.98%</td>
<td>18.88%</td>
<td>24.86%</td>
<td>20.72%</td>
<td>18.84%</td>
</tr>
<tr>
<td>Present at follow-up</td>
<td>207</td>
<td>191</td>
<td>144</td>
<td>99</td>
<td>85</td>
<td>74</td>
</tr>
</tbody>
</table>

Poster Presentations

Eur Thyroid J 2018;7(suppl 1):1–118
DOI: 10.1159/000491542
Introduction: Ultrasoundography is the key element in evaluation of thyroid nodules and ultrasonographic (US) features, such as microcalcifications (mC), taller-than-wide (TtW) and irregular margins (iM), are associated with a higher risk of malignancy (EU-TIRADS 5).

Objective: Evaluate the prevalence and likelihood ratio (LHR) of three suspected US characteristics (mC, TtW and iM), comparing patients with histological results of thyroid carcinoma and patients with histological findings of nodular hyperplasia at our institution from June 2015 to December 2017.

Materials and Methods: Cross-sectional study. A total of 133 patients were evaluated, of these 73 had histology of nodular hyperplasia (benign) and 60 had histology of thyroid carcinoma (malign) after partial or total thyroidectomy. We recorded the cytological diagnosis, the size of the nodule (the largest diameter), the US suspicion findings (mC, TtW and iM) and the histology of thyroid. The data were analysed descriptively and inductively using SPSS v20.0.

Results: Of the 133 patients, 80.5% (n = 107) were female, with a mean age of 58.0 ± 15.74 years, the mean nodule size in the group with benign histology was 37.03 ± 14.67 mm and in the group with malign histology 26.35 ± 14.99 mm.

From the histology of malignant nodules: 91.7% (n = 55) were papillary carcinomas, 5.0% (n = 3) follicular carcinomas, 1.7% (n = 1) medullary carcinoma and 1.7% (n = 1) anaplastic carcinoma.

In patients with malignant histology, 63.3% (n = 38) had at least one suspected US characteristic and 72.6% (n = 53) had none of these characteristics in patients with benign histology.

In papillary carcinoma the US characteristics were distributed as follows: mC 30/55, iM 14/55, TtW 4/55; in follicular carcinoma: mC 3/3, iM 1/3, TtW 1/3; in medullary carcinoma: TtW 1/1; in anaplastic carcinoma: iM 1/1.

The three US features had a statistically significant association with malignancy (mC p = 0.002; TtW p = 0.027; iM p = 0.000).

The TtW characteristic had the highest specificity of 98.6% and positive LHR of 7.14; the iM had a specificity of 97.3% and the highest value of LHR of 9.89 and the mC had a specificity of 73.8% and LHR of 1.99. These three characteristics had low sensitivity (10.0%, 26.7% and 51.7%, respectively).

Conclusion: In our study, the papillary carcinoma was the most prevalent and microcalcifications were the most prevalent US characteristic, but with less specificity.

All three characteristics were associated with the occurrence of malignancy, but the irregular margins were the best predictor with a LHR-positive near 10.

ARE THE ULTRASONOGRAPHIC CHARACTERISTICS A GOOD PREDICTOR OF THYROID CARCINOMA? - A CROSS-SECTIONAL STUDY OF A CENTRAL HOSPITAL
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P2-05-115
DEVELOPMENT AND VALIDATION OF THE VOICE HANDICAP INDEX-10 FOR THYROID CANCER (VHI-10T)
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Objectives: Many patients complain of voice problems after thyroid cancer surgery. Currently, the most important method to evaluate voice problems of thyroid cancer patients is the Voice Handicap Index-30 (VHI-30), which consists of 30 items. However, since it takes a long time to complete the questionnaire, an easier and short-form of questionnaire reflecting the voice changes after thyroidectomy was needed. Therefore, in this study, we tried to develop the miniature VHI that can be easily performed in clinical practice to track the changes in voice of thyroid cancer patients.

Methods: We analyzed the Voice Handicap Index-30 (VHI-30) in patients who underwent thyroidectomy from January 2010 to December. VHI 30 was taken at the time before surgery and at 1 month, 6 months, and 12 months after thyroidectomy. The items were chosen in the best way to show the difference between before and after surgery. First, based on the clinical consensus, candidates were selected. And statistical analysis that compares the validity of the short-form questionnaire with the VHI-30 was performed in those patients group representing voice problems of thyroid cancer.

Results: When mean scores and mean differences were obtained by collecting all 236 viewpoints, 12 items with little difference between before and after surgery were excluded. We selected four candidates and confirmed that they can represent the VHI-30. Candidates presented good changes in speech over time. Therefore, the candidate group considering the domain was finally selected. It showed over 94% of VHI-30 explanatory power (R square = 0.94) and the ratio of VHI-30 was more than 0.33. In addition, it showed the same pattern with VHI-30 in changes of voice problems before and after surgery.

Conclusion: Through the results, we can conclude that VHI-10T can be performed more easily and reflects vocal characteristics in patients with thyroid cancer more accurately.

P2-05-116
FACTORS PREDICTING THE RECOVERY OF UNILATERAL VOCAL FOLD PARALYSIS AFTER THYROIDECTOMY
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Background: We used voice analysis and clinicopathological factors to explore the prognosis of unilateral vocal fold paralysis after thyroid surgery.

Methods: The medical records of 63 females who developed unilateral vocal fold paralysis after thyroidectomy were reviewed. All patients were divided into two groups: those who recovered from vocal fold paralysis and those who did not. We analyzed clinical parameters and voice analysis results in a search for correlations with recovery from paralysis.

Results: Of the 63 patients, 37 (58%) recovered from paralysis. A small tumor size, incomplete paralysis, the absence of arytenoid tilting, no compensatory movement of the normal side, lower postoperative shimer, a higher postoperative maximum phonation time (MPT), and lower postoperative subglottic pressure correlated significantly with recovery from vocal fold paralysis. Multivariate analysis confirmed that the absence of compensatory movement of the normal side on videostroboscopy was independently prognostic. A postoperative MPT of 6.86 appeared to be optimal for prediction of recovery. Most patients recovered within 6 months, but those with incomplete paralysis recovered about 3 months earlier. At the 12-month follow-up, the thyroidectomy-related voice questionnaire scores had returned to preoperative values in only 12 patients (19.9%); 51 patients (81.0%) did not fully recover.

Conclusion: Compensatory movement of the normal side evident on videostroboscopy was a poor prognostic factor. Voice analysis can be help-
f ul in counseling vocal fold paralysis patients after thyroidectomy, and early intervention may be considered in patients who are expected to have a poor prognosis.

**P2-05-117**

**UTILITY OF A CALCULATED RADIOIODINE DOSE METHOD IN PATIENTS WITH HYPERTHYROIDISM**

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**Objectives:** There is still controversy regarding the best method to determine the radioiodine-131(I-131) activity necessary for an optimal treatment of hyperthyroidism. The aim of our study was to compare the clinical outcomes of patients with hyperthyroidism using an individualized dosimetry method versus fixed activity doses of I-131. The second objective was to analyze possible independent predictor factors related to cure.

**Material and Methods:** 143 hyperthyroid patients treated with an individualized I-131 dose (ID) and 102 treated with a fixed dose (FD) at Punta Europa Hospital in Algeciras were followed prospectively during a year. In the ID group, biokinetic and morphological parameters were estimated from planar scintigraphic images obtained at 4, 24 and 96 hours after injection of I-123 and I-131 activities were calculated to deliver 120 Gy to the thyroid using Matheod specific dosimetry method. Both groups were compared through bivariate and multivariate statistical analysis to identify potential independent factors associated with the cure of hyperthyroidism.

**Results:** 106 patients treated with ID (74%) were euthyroid at the end of the year compared to only 37 of the FD group (26%), p < 0.0005. Regarding hypothyroidism, 33 patients of the group with ID (23%) were hypothyroid versus 45 in the FD (44%), p < 0.0001. Median I-131 doses used in Graves’ disease were 5.3 ± 3.6 and 10 ± 2 mCi in patients with ID and FD, respectively (p < 0.0005). There was no significant differences between I-131 doses in multinodular goiter/toxic adenoma with ID or FD. Using an individualized dose protocol was independently and positively associated with euthyroidism (odds ratio [OR] 5.18, 95% confidence interval [CI] 2.84–9.44, p < 0.0005). Euthyroidism was also more common in multinodular goiter/toxic adenoma than Graves’ disease in the multivariate analysis (OR 4.94; 95% CI 1.12–5.09, p < 0.026).

**Conclusions:** Treatment of hyperthyroidism with an individualized I-131 algorithm instead of the commonly used fixed dose protocol clearly improves clinical outcomes after a year in patients with hyperthyroidism. In Graves’ disease, improvement can be achieved using much lower I-131 doses and there-
magnified 3D surgical views with intuitive motion of instruments, which may result in better peri-neural and lymph node dissections. Davinci Xi improves its design with less instrument collision compared to Davinci Si, giving better instrument movements in the limited space of transoral surgery. This study summarizes the initial surgical outcome of transoral robotic thyroidectomy by single surgeon.

**Methods:** From September 2017 to February 2018, six patients underwent transoral robotic thyroidectomy for benign and malignant thyroid diseases. Four robotic arm technique with three vestibular ports and one right axillary port using Davinci Xi system was used. The surgical indications include Graves’ disease, symptomatic benign thyroid nodules <4 cm, and malignant thyroid nodules <2 cm. The surgical outcomes are retrospectively reviewed.

**Results:** A total of six patients (five female, one male; mean age 42.3 ± 1.5 years, range 22–63 years) underwent transoral robotic thyroidectomy surgery. Five patients received unilateral lobectomy with or without unilateral central neck lymph node dissection. One patient received bilateral total thyroidectomy. A total of 421 patients underwent thyroidectomy in Yonsei University Hospital. Of those, we identified 7,264 patients underwent lobectomy and selected 4,944 patients who could be candidates for active surveillance (Group A). Likewise, we identified 808 patients underwent total thyroidectomy (TT) with CCND plus mRND and selected 421 patients who could be candidates for active surveillance (Group B). Of the 4,944 patients in group A, 29 patients underwent second-stage completion total thyroidectomy (TT) with mRND because of lateral LN recurrences (Group C). Clinicopathologic features and surgical outcomes were analyzed by retrospective medical chart review. Mean follow-up duration was 78.2 ± 52.3 months.

**Result** In this study, group B showed significantly more aggressive pathologic findings than group A in terms of multicentricity (46.7% vs. 10.1%; p = 0.000), bilaterality (30.8% vs. 0.2%; p = 0.0000), ETE (57.7% vs. 26.8%; p = 0.0000), central LN metastasis (CLNM) (73.1% vs. 20.7%; p = 0.0000), central LN ratio (0.53 ± 0.22 vs. 0.11 ± 0.03; p = 0.013), lateral LN metastasis (LLNM) (100% vs. 0%; p = 0.0000), Total LN ratio (0.30 ± 0.12 vs. 0.11 ± 0.03; p = 0.031). DFS was lower in the group B than in the group A (p = 0.045). There were no significant differences between group B and C in clinicopathologic findings, but DFS was lower in the group B than in the group C (p = 0.033).

**Conclusion:** In conclusion, we demonstrated that once the rescue surgery was performed during active surveillance, the surgical outcomes could be worse than those after immediate surgery in low-risk PTMC patients. Furthermore, even if mRND was done after lobectomy due to recurrence, recurrence rate and DFS were lower than those of the rescue surgery during active surveillance.

**Context:** Thyroid diseases are common among elder patients. The improvement on health resources access and extended life expectancy raised the feasibility to perform thyroidectomy for the geriatric population.
Case Report: Male patient, 91 years-old, previously autonomous, was sent to the Accident & Emergency Department due to progressive dyspnea with type 2 respiratory insufficiency in context of a bulky cervical mass.

He had been evaluated in 2015 at an Oncology outpatient clinic in another institution due to an incidentally discovered thyroid nodule of 6.6x5.2 cm with mediastinal extension. Fine needle-aspiration (FNA) results revealed TTF1 positivity, diffuse thyroglobulin (Tg) positivity and follicular cell pattern with cytological atypia—Bethesda IV (suspicous for follicular neoplasm).

Due to the asymptomatic clinical picture, previous history of chronic B lymphocytic leukemia (0 IA), along with elder age, the patient delayed the decision for thyroidectomy.

One year-later, the mass presented significant growth on CT scan – 8x7.2x14.5 cm; extension to hyoid bone and supra aortic vessels, left deviation of medium line structures and right deviation of carotid space vascular structures. Instead of an extensive and compressive behavior, the mass had regular contour and no evidence of invasiveness. A 2nd FNA confirmed the previous known diagnose of thyroid origin tumor. Bronchofibroscopy showed significant extrinsic compression of the trachea, with a minimum caliber of 4 mm, and no vegetant endotracheal component.

Thyroid functional tests were normal, with markedly elevated thyroglobulin (TSH 1.5 uUI/mL; T4 1.0 ng/dL; Tg 224520 ng/mL; calcitonin 7.8 pg/mL; negative Tg and TPO antibodies).

The patient was submitted to an urgent near-total thyroidectomy with no relevant complications during the peri-operative period and markedly improvement of the respiratory distress.

Histologically, the diagnosis was Hürthle Cell Carcinoma, extensively invasive of extra-tumor thyroid parenchyma as well as of venous vessels, with multiple necrosis foci – T3aNxMx.

Conclusion: Although we must consider the risk of surgery in geriatric patients, the use of updated surgical and anaesthesiologic techniques can reduce operative time and incidence of complications. Due to longer life expectancy, an individualized evaluation beyond chronological age must be performed to minimize potential risks associated with increased clinical aggressiveness related to delaying surgical intervention.

P2-05-125
SURVEY ON PERCEPTION AND ACCEPTANCE OF TRANS-ORAL THYROIDECTOMY
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Introduction: Trans-oral thyroidectomy (TOT) has showed promising results with excellent cosmetic outcome. However, safety and completeness of operation have been the major concerns for clinicians. It is unclear how general population understand and perceive the benefit of TOT and in what extent of morbidity they accepted. In this study, we evaluated the perception and acceptance of trans-orl thyroidectomy in general population, patients and health care provider.

Method: 765 self-administrated questionnaires were distributed in waiting hall, clinic, ward and operation theatre in two hospitals. Questions focused on factors influencing the choice of surgical approach, understandings, perceptions & desire on TOT and maximal accepted risk of complications, cost, recovery and oncological outcome.

Result: 713 (93.2%) completed questionnaires were collected. Majority of participants were female (67.0%) with median age of 44. 22.2% of participants were medical-related staffs. In general, participants perceived TOT was neutral to slightly better than conventional thyroidectomy (CT) in terms of complication, cosmos, pain, cost and recovery duration. Five hundred and six participants (71.0%) prefer TOT to CT for benign thyroid disease. However, only about 15.6% accepted additional 5% or more risk of complications and 26% agreed to pay extra $10,000 for TOT.

Comparing to others, medical-related staff preferred TOT had a better cosmos (5.98 vs. 5.57, p < 0.001) but lesser extent of benefits on complications, pain, cost and recovery over CT (p < 0.001). They were also less keen on TOT for benign condition (61.5% vs. 73.7%, p = 0.003). Similarly, TOT for benign condition is less preferred in participants with prior thyroidectomy than those did not (55.1% vs 72.9%, p = 0.001).

If TOT did not cure thyroid cancer well, 26.1% still preferred TOT over CT. They were at lower education level (p = 0.001) and accepted a higher 10-year recurrence risk (≥ 5%) compared to those prefer CT. (18.9% vs. 9.3%, p = 0.006).

Conclusion: TOT were perceived to have a superior outcome over CT in general population. There were discrepancy in preference on TOT between participants with and without understanding of thyroidectomy. Before making decision on surgical approach, patients should be better explained on the potential over-perceived benefits of TOT.

P2-05-124
SUBSTERNAL GOITER: IT IS POSSIBLE TO PREDICT THE NEED FOR AN EXTRA-CERVICAL APPROACH?
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Introduction: Sternotomy for substernal goiter is associated with greater morbidity than a cervical approach to thyroidectomy.

Aims: To investigate the correlation between the dimension of the mediastinal portion of the thyroid gland and the need for an extra-cervical approach for substernal goiter.

Methods: A retrospective review of a database with patients that underwent thyroidectomy between January 2012 and October 2017 was performed. We identified 123 patients treated for substernal goiter. Of these 123 patients, 7 required an extra-cervical approach and 116 patients required a cervical incision. Medical records and preoperative CT scans were reviewed. It was performed the measurement of cranio-caudal length and the diameter of the mediastinal component of the thyroid gland and the diameter of the thoracic inlet in all patients with substernal goiter. ROC analysis was performed to determine the cut-off value for the craniocaudal length and the diameter of the craniocaudal thyroid mass, which significantly predict the need of an extra-cervical approach for substernal goiter.

Results: The ROC analysis of craniocaudal length and the diameter of the mediastinal component identified ≥34.5 mm and 53.3 mm as the cut-off values with maximum accuracy, respectively. The craniocaudal length of the thyroid mass below the thoracic inlet ≥34.5 mm and the diameter of the mediastinal component ≥53.3 mm were significantly associated with the need of an extra-cervical approach (p = 0.005 and = 0.015, respectively). We also analyzed the ratio between the diameter of the mediastinal component and the diameter of the thoracic inlet, and the ROC analysis of this ratio identified ≥1.24 as the cut-off value with maximum accuracy. A ratio ≥1.24 was significantly associated with the need of an extra-cervical approach (p = 0.03).

For predicting an extra-cervical approach, the sensitivity, specificity, positive predictive value and negative predictive value of the cut-off value for this ratio was 89%, 100%, 100%, 33%, respectively.

Conclusion: Preoperative CT provides essential information on substernal goiter with respect to the extent of mediastinal involvement and is helpful to predict the necessity of an extra-cervical approach. The ratio between the diameter of the mediastinal component and the thoracic inlet ≥1.24 was a significant determining factor for an extra-cervical approach. This information can be obtained by a trained head and neck surgeon.
Transport and Targets

P2-06-126
THE PLEIOTROPIC FUNCTIONALITY OF ENDONGENOUS 3-IODOTHYRONAMINE (T1AM) AND SYNTHETIC THYRONAMINE-LIKE ANALOGS: A POWERFUL TOOL TO TARGET INTERLINKED DISEASES SUCH AS OBESITY AND NEURODEGENERATION

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Accumulating evidence has suggested the presence of a strong correlation between obesity and neurodegeneration. Neurodegenerative diseases (NDDs) are characterized by a progressive loss of memory and cognition, which ultimately leads to death. This deterioration is mostly due to inflammation triggered by aberrant protein deposition, oxidative stress and modification in lipid pathways. Because of these multifactorial aspects, the design of multi-target directed ligand (MTDL) could represent a potential strategy for the treatment of NDDs. In this context, the polypharmacology described in detail for naturally occurring 3-iodothyronamine (T1AM), and rapidly emerging also for thyronamine-like analogs SG-1 and SG-2, may provide a novel pleiotropic therapeutic approach for the treatment of NDDs.

With the aim to provide a detailed characterization of the pharmacological profile of these new drug candidates, in the present work we evaluated their ability to promote lipolysis in HepG2 cells, as well as, to activate clearing pathways, such as autophagy (ATG) and ubiquitin proteasome (UP) in human glioblastoma cells (U87-MG).

Methods: Cultured HepG2 cells were incubated for 24 h with 10 μM T1AM or SG-2 and Oil-red O staining was used to monitor intracellular lipid accumulation. Cell culture supernatants were also collected and analyzed for free glycerol release.

In another set of experiments, cultured U87-MG cells were treated with 1 μM T1AM, SG-1, SG-2 or vehicle for 30 min, 4, 8 and 24 h and the induction of ATG was monitored morphologically by using transmission electron microscopy (TEM) and immunofluorescence (IF) microscopy. Ultrastructural morphometry, based on the stoichiometric binding of immunogold particles, allowed the quantitative evaluation of ATG and UP component (i.e. LC3 and P20s, respectively) within autophagosomes and autophagoproteasomes. RT-qPCR and Western blot assays were applied to detect the expression of ATG and UP indicators.

Results: A significant decrease in lipid accumulation was observed in HepG2 cells treated with T1AM or SG-2, possibly due to increased lipolytic activity, further confirmed by accumulation of glycerol (an end product of triglyceride lipolysis) in the culture media.

Treatment with T1AM, SG-1 or SG-2 induced autophagy in U87-MG cells, by promoting autophagosome formation and up-regulating LC3-II expression and p62 degradation.

Notably, increased 20S proteasome recruitment to autophagosome was observed, suggesting that these compounds might modulate both ATG and UP protein clearing pathways within the autophagoproteasomes.

Conclusions: Our studies highlight the potential of T1AM and its synthetic analogs, SG-1 and SG-2, as novel drugs for the treatment of obesity and NDDs.

P2-06-127
IDENTIFICATION OF ZINC TRANSPORTER ZNT8 IN THYROID TISSUES FROM CHILDREN AND ADOLESCENTS WITH THYROID DISEASES

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Introduction: Recent studies have revealed the presence of zinc and the expression of zinc transporter (ZnT) family members in most endocrine cell types. It has been demonstrated that the ZnT family plays an important role in the synthesis and secretion of different hormones. Furthermore, ZnT8 (zinc transporter-8 autoantibodies) together with GADA (glutamic acid decarboxylase antibodies), IAA (insulin autoantibodies) and IA-2Ab (islet antigen-2 antibodies) are markers of autoimmunity in patients with type 1 diabetes mellitus (T1DM). We studied the expression of ZnT8 transporter in thyroid tissues from patients with thyroid nodular goiter (TNG).

Material and Methods: The study was performed in the group consisting of 17 patients with thyroid nodular hyperplasia (mean age, 17.8 years ± 4 years) and patients with pancreatic tumor as a positive controls. Patients were recruited from Polish endocrine centers. The ZnT8 expression protein was evaluated using immunohistochemistry. The specimens were paraffin embedded tissues, derived from the pediatric patients, who had thyroid nodular hyperplasia. The antibody against ZnT8 was goat polyclonal antibody (Santa Cruz Biotechnology USA; sc-98243). The antigen was retrieval was done using high pH (PTLink DAKO) and antibody was incubated in 4°C overnight in 1:50 dilution.

Results: In all of the examined cases we observed the ZnT8 expression in the thyroid follicular cells. He staining was strong and diffuse and observed in almost all thyroid follicular cells. The staining was observed in the cytoplasm. However in 2 out of 17 cases we observed C cells hyperplasia and ZnT8 expression was identified in those cells, also in the cytoplasm and the perinuclear area of the hyperplastic C cells.

Conclusion: According to our knowledge this is the first investigation which identified ZnT8 transporter in pediatric thyroid tissues. Further studies in thyrocytes covered by an autoimmune process are scheduled to confirm ZnT8 as a new thyroid autoantigen.

P2-06-128
REGIONAL HYPERPERMHERA ENHANCES SELECTIVE MESENCHYMAL STEM CELL MIGRATION TOWARDS THE TUMOR STROMA

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Regional hyperthermia is a local treatment that overcomes the barrier of the normal tissue temperature. This treatment is intended to improve the delivery of drugs and radiotherapy to the tumor. The heat induced by the hyperthermia can lead to an increase in the sensitivity of the tumor cells to these treatments. However, the efficacy of regional hyperthermia is limited by the ability of the cells to migrate towards the treatment site. To overcome this limitation, mesenchymal stem cells (MSCs) can be used as vehicles to deliver therapeutic agents to the tumor site.

The strong tropism of mesenchymal stem cells (MSCs) for tumors provides the basis for a “Trojan Horse”-like therapy approach, in which genetically modified MSCs deliver a therapeutic gene into the critical microenvironment of growing tumors. Due to its dual role as reporter and therapy gene, the sodium iodide symporter (NIS) allows detailed noninvasive imaging of transgene expression and, subsequently a highly effective application of therapeutic radionuclides. To enhance the selective migratory properties of MSCs to the tumor stroma and thereby trigger targeted delivery of the NIS gene to the tumor, we are examining the pre-treatment of tumors with regional hyperthermia, as heat induces the secretion of immunomodulatory chemo kines, cytokines and growth factors, well-known attractants of MSCs. Human hepatocellular carcinoma cells (HuH7) were heat-treated in a water bath at 41°C for 1 h, followed by incubation at 37°C for 0–48 h. Chemokine mRNA analysis by quantitative real-time PCR indicated a substantial increase in expression levels of chemokines and growth factors after heat exposure,
P2-06-129
TRANSMEMBRANE PROTEINS AS TARGETS OF 3-IODOTHYRONAMINE
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Over the last years many effects of the thyroid hormone derivative 3-iodothyronamine (3-T1AM) were observed after application in rodents. This lead to the conclusion that 3-T1AM is a multi-target ligand. The first identified target of 3-T1AM is the trace amine-associated receptor 1 (TAAR1) belong to the class A G-protein-coupled receptors (GPCR). TAAR1 signaling is known to activate Gs/adenyl cyclase pathway. Application of pharmacological doses of 3-T1AM induced metabolic and anapyrexic effects in rodents, which might be centrally mediated in the hypothalamus. Besides TAAR1 3-T1AM is capable to modify the function of other GPCRs belonging to the aminergic receptors such as the alpha 2 A adrenergic receptor (ADRA2A) or the serotonin 1B receptor (HT1b). In addition, transient receptor potential channels (TRPs) identified as a novel target of 3-T1AM. This superfamily of ion channels are expressed in tissues that influence energy balance and metabolism such as hypothalamus. Previous studies suggested that 3-T1AM acts as a cooling agent to directly affect TRPM8 activation in different cell types. It is well-stablished that TRPM8 is expressed in rodent hypothalamus and plays a pivotal role in thermoregulation. In this study we aim to analyze the functional network of 3-T1AM in three different murine hypothalamic cell lines, GT1-7, N329 and N41. These cell lines express a variety of aminergic GPCRs in addition to different TRPs. Functional characterization was performed in terms of activation of the Gs and Gi/o in addition to Ca2+ imaging and patch clamp recording to obtain a complete picture of activated pathways. The effect of activated GPCRs is rather small, however, application of 3-T1AM in N41 cells recording to obtain a complete picture of activated pathways. The effect of chemosensitizing qualities. Hyperthermia itself may also have additive or synergistic therapeutic effects based on its own anitcancer properties and its well characterized radio- and chemosensitizing qualities.

P2-06-130
SINGLE-NUCLEOTIDE MISSENSE VARIANTS OF TRACE AMINE-ASSOCIATED RECEPTOR 1 IN MENTAL DISORDERS
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Background and Objectives: The G protein-coupled receptor trace amine associated receptor 1 (TAAR1) is stimulated with nanomolar affinity by 3-iodothyronamine (T1AM), an endogenous messenger with close structural similarity to thyroid hormone. The region of the chromosome 6 where the human genes for TAAR are located was associated with neuropsychiatric disorders in linkage studies. We performed screening for TAAR1 single nucleotide polymorphisms (SNVs) in a heterogeneous group of patients suffering from unselected neuropsychiatric disorders.

Materials and Methods: We recruited 80 patients receiving treatment at the Psychiatry Clinic, University of Pisa, for some form of psychopathology, defined as an acute disturbance of mental functions, leading to a significant decline in (inter)personal functioning with respect to a previously attained level of functioning. These were compared to 75 healthy controls. Genomic DNA was isolated from saliva samples by standard methods and quantified. We screened by Sanger sequencing three partially overlapping amplicons spanning the coding region and the 5’- and 3’-UTR. Three in silico tools available in dbSNP29.2 were used to assess the functional effect of the detected variants. SNP&GO (http://snps-and-go.biocomp.unibo.it/snp-and-go/index.html), SNAP (https://rostlab.org/services/snap), PhD-SNP (http://snps.biofold.org/phdsnp/phd-snp.html). The residual variation intolerance score (RVIS) (http://chgv.org/GenicIntolerance) was applied, and the evolutionary conservation of the detected variants was assessed (Blossum62 matrix).

Results: We detected 12 non-synonymous SNPs. Three of the variants, namely p.Arg123Cys (rs8192618), p.Tyr131Cys (rs41286174), and p.Cys263Arg (rs142169206), were predicted to be damaging by all the in silico tools used. These variants were observed in 3 patients, corresponding to a minor allele frequency (MAF) of 0.006, significantly higher than the MAF reported for the general population in public database (National Center for Biotechnology Information, dbSNP, http://www.ncbi.nlm.nih.gov/SNP/). None of these SNPs were observed in controls. The p.Arg123Cys variant, located at the transition between transmembrane helix 1 and the N-terminal tail at the extracellular side of the receptor, and p.Cys263Arg variant, located in the sixth transmembrane domain, result in sub- or non-functional receptors from functional in vitro characterization. The p.Tyr131Cys variant, located in the second cytoplasmic loop, was associated with the apparently neutral p.Tyr123Cys variant (rs37140762), in the only patient affected by frontotemporal dementia. All the 3 variants are conserved among TAAR1 orthologous. Finally, from RVIS analysis, TAAR1 resulted among 34.6% of the most intolerant of human genes.

Conclusions: In this screening of TAAR1 SNPs, we identified 3 heterozygous missense variants, which could produce a detrimental functional change in the receptor and have an etiological role in mental disorders.
peripheral blood DCs both ex vivo and in vitro. However, little is known about effects exerted by the hypothalamus-pituitary-thyroid-axis on APCs. Thyrotropin (TSH) receptor expression was described earlier on murine DCs and TSH stimulation was shown to augment the phagocytic properties and secretion of proinflammatory cytokines of DCs.

The aim of the present study was to analyze the effect of systemically administered TSH on human blood mononuclear cells ex vivo.

**Methods and Results:** The study was performed in patients thyroidectomized because of differentiated thyroid carcinoma and qualified for recombinant human TSH (rhTSH) administration from standard indications. Blood samples for the cytometric analysis of peripheral blood mononuclear cells (PBMC) were collected from patients at 2 time points: (i) directly before the commencement of TSH administration and (ii) 5 days after first TSH injection. The whole blood quantitative and phenotypic analysis of APCs and other immunology cells was performed by flow cytometry.

Administration of rhTSH increased the percentage of CD16+ cells in lymphocyte fraction of PBMC but not CD16- monocyte subpopulations. Analysis revealed also an increased percentage of one of the conventional (c) DC subset – CD141hi/BDCA3 cDCs while the percentage of CD1c+/BDCA1 cDC subset was not affected by thyrotropin. TSH administration had no effect on the percentage of plasmacytoid (p) DCs in peripheral blood of study participants. TSH administration had no effect on the surface expression of CD86 – one of the major costimulatory molecules – neither in the whole PBMC fraction nor in particular DCs subtypes.

**Conclusions:** Obtained results revealed an effect of rhTSH administration on particular cellular elements of immunoregulatory system. An increased percentage of CD16+ cells in lymphocyte but not monocyte fraction of PBMCs indicates an effect of rhTSH on CD16+ NK cells subpopulation with no effect on any of CD16- monocyte subpopulations. A significant quantitative changes in the CD141hi cDCs subpopulation but not CD1c+ cDCs nor pDC show a selective influence of rhTSH on naturally occurring human peripheral blood DCs.

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**P2-06-132**

**METABOLISM AND AVAILABILITY OF 3-IODOTHYRONAMINE IN MOUSE BRAIN SLICES**

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**Background and Objectives:** Administration of exogenous 3-iodothyronamine (T1AM) in isolated mouse brain slices has been reported to rescue long term potentiation from beta amyloid toxicity. This protective effect was elicited after short-term (10 min) exposure to micromolar T1AM, but owing to the complexities of T1AM transport, distribution and metabolism, its active concentration at receptor level is unclear. In the present work, we used this preparation to determine the availability of T1AM in the perfusion buffer after exogenous administration. 3-iodothyroacetic acid (T1A), the major T1AM metabolite, was also assayed.

**Materials and Methods:** Horizontal brain slices containing the hippocampus/entorhinal cortex were obtained from wild type mice and continuously perfused with carbon-bubbled aCSF solution (mM: NaCl, 119; KCl, 2.5; CaCl2, 2; MgSO4, 1.2; NaH2PO4, 1; NaHCO3, 6.2; glucose, 10; HEPES, 10) using a peristaltic pump at a rate of 2 ml/min. The effluent was collected over time intervals of 5–10 min. After equilibration, T1AM was delivered to slices through general perfusion for 10 min at the nominal concentration of 5 μM/l. The effluent continued to be collected for a washout period of 45 min afterwards. T1AM and its metabolite 3-iodothyroacetic acid (T1A) were assayed in the perfusion buffer by mass spectrometry coupled to liquid chromatography.

**Results:** During T1AM perfusion, T1AM concentration in the effluent increased from 107 ± 2 to 343 ± 2 nmol/l in the 0–5 and 5–10 min interval, respectively. In the same samples, T1A was detected at concentration averaging 166 ± 56 and 195 ± 32 nmol/l, respectively. In the washout phase, overall T1AM release and T1A release averaged 4.9 ± 0.4 nmol and 6.5 ± 0.7 nmol, respectively, while an additional 2.5 ± 0.6 nmol of T1A were released during T1AM infusion.

**Conclusions:** Brain slices take up exogenous T1AM, which is progressively released over 45 min either unchanged or after oxidation to T1A. T1AM concentration in the effluent buffer, which can be considered as an estimate of extracellular T1AM concentration, undergoes phasic changes, and it is 20-fold to 100-fold lower than the administered concentration; T1A concentration in the effluent buffer is on the same order as T1AM concentration.

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**P2-06-133**

**CDSL, A NEW PUTATIVE THYROID HORMONE DEPENDENT BIOMARKER**


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Measurement of TSH levels in relation to the concentrations of free thyroid hormones, fT4 and fT3, are the basis for the biochemical diagnosis of thyroid dysfunction. As this relation is no longer valid in certain clinical conditions such as resistance to TH receptor (TR) β, TSH secreting pituitary adenomas or central hypothyroidism, new and independent biomarkers of thyroid function are urgently required. In an attempt to identify new TH dependent biomarkers, we here analysed the plasma proteome of otherwise healthy human volunteers (n = 16) under the daily application of 250 μg T4 for 8 weeks and compared this to an experimental T4 thyrotoxicosis (1 mg/L) of 2 weeks in mice (n = 4). In both models, the recovery after stopping exogenous T4 was followed (8 weeks in humans or 2 weeks in mice). We identified 16 concordantly expressed genes in both mice and men. 3 of these putative targets were also altered in liver transcriptome of the T4-treated mice. Literature research pointed on liver, bone and the lymphoid system as tissues with highest target gene expression. To confirm the new target gene expression in these tissues, we performed an independent mouse study (n = 6–8) with 3 differently treated groups. One group was rendered hypothyroid by administration of methimazol (0.1% w/v) and perchlorate (0.2% w/v) in the drinking water. Another group received T4 (1 mg/L) comparable to the previous study and a third group T3 (0.5 mg/L) in the drinking water. Subsequent gene expression analysis by qPCR revealed changes in 8 genes in the liver, 4 genes in the bone and 1 gene in the spleen. Across the different tissues the target gene CDSL showed robust changes which could be reproduced in residential M1 macrophages. They further could be confirmed following short term administration of T4 (4 days) or T3 (1 day). These data suggest that CDSL may serve as a biomarker for TH action which is able to rapidly respond to changes in TH. This work was supported by grants from the Deutsche Forschungsgemeinschaft (MI242/5-1 and BR915/12-1).

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**P2-06-134**

**LAT3: A DIRECT EFFLUX OF THYROID HORMONES ACROSS THE MEMBRANE CAN NOT BE OBSERVED**

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Thyroid hormones (TH) need to be distributed throughout the body and transported from the blood stream to the cells and between cells. This transport is facilitated by TH transporters among which the L-type amino acid transporters (LATs) have recently gained attention. The members of the LAT family are proteins with a topology of 12 transmembrane helices incorporated into the plasma membrane, allowing the transport of neutral amino acids and TH hormones, fT4 and fT3, are the basis for the biochemical diagnosis of thyroid dysfunction. As this relation is no longer valid in certain clinical conditions such as resistance to TH receptor (TR) β, TSH secreting pituitary adenomas or central hypothyroidism, new and independent biomarkers of thyroid function are urgently required. In an attempt to identify new TH dependent biomarkers, we here analysed the plasma proteome of otherwise healthy human volunteers (n = 16) under the daily application of 250 μg T4 for 8 weeks and compared this to an experimental T4 thyrotoxicosis (1 mg/L) of 2 weeks in mice (n = 8). In both models, the recovery after stopping exogenous T4 was followed (8 weeks in humans or 2 weeks in mice). We identified 16 concordantly expressed genes in both mice and men. 3 of these putative targets were also altered in liver transcriptome of the T4-treated mice. Literature research pointed on liver, bone and the lymphoid system as tissues with highest target gene expression. To confirm the new target gene expression in these tissues, we performed an independent mouse study (n = 6–8) with 3 differently treated groups. One group was rendered hypothyroid by administration of methimazol (0.1% w/v) and perchlorate (0.2% w/v) in the drinking water. Another group received T4 (1 mg/L) comparable to the previous study and a third group T3 (0.5 mg/L) in the drinking water. Subsequent gene expression analysis by qPCR revealed changes in 8 genes in the liver, 4 genes in the bone and 1 gene in the spleen. Across the different tissues the target gene CDSL showed robust changes which could be reproduced in residential M1 macrophages. They further could be confirmed following short term administration of T4 (4 days) or T3 (1 day). These data suggest that CDSL may serve as a biomarker for TH action which is able to rapidly respond to changes in TH. This work was supported by grants from the Deutsche Forschungsgemeinschaft (MI242/5-1 and BR915/12-1).
The objective was to examine experimentally whether LAT3 can by itself facilitate the export of TH across the membrane of HEK293 cells. In order to preload the cell with TH, stably transfected HEK293 cells were established, which expressed the imported TH transporter LAT2 together with its essential import partner, the sodium-dependent anion transporter 2 (SLC5A2). To observe a direct effect of LAT3 on TH efflux, transient LAT3 transfection of the stably transfected LAT2/4F2hc-HEK293 cells and the same cell line with an additional transient LAT3 transfection were measured and compared.

The efflux assays revealed equally low quantities of 3,3'-T2 released by all investigated cell lines, failing to show direct efflux mediated by LAT3. Additionally, the 3,3'-T2 efflux’s pH dependency was measured, resulting in reduced levels of 3,3'-T2 efflux in a low pH of 5.5. An interaction between LAT2 and LAT3 in the HEK293 cells was suggested and gene expression analyses were conducted, using flow cytometry and western blot. The expression analyses revealed no significant reduction of LAT2 expression in the stably transfected LAT2/4F2hc HEK293 cells upon transient transfection with LAT3. In contrast to previous LAT2 mutagenesis, model guided LAT3 mutants could unfortunately not significantly enhance neither import nor export of TH.

Altogether, our findings suggest that LAT3 plays a role in the transport of TH across the cell membrane, but not through direct TH efflux, but rather indirectly by down regulation of the LAT2 induced TH uptake.

**Treatment**

**P2-07-135 SECOND INTERIM ANALYSIS OF RIFTOS MKI, A GLOBAL, NON-INTERVENTIONAL STUDY ASSESSING THE USE OF MULTIKINASE INHIBITORS (MKIS) IN THE TREATMENT OF PATIENTS WITH ASYMPTOMATIC RADIOACTIVEIODINE-REFRACTORY DIFFERENTIATED THYROID CANCER (RAI-R DTC): A SUBGROUP ANALYSIS OF EUROPEAN PATIENTS**

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**Background:** Sorafenib and lenvatinib are oral MKIs approved for the treatment of RAI-R DTC; however, there is no consensus on when patients with asymptomatic RAI-R DTC should start MKI treatment. We have previously reported global data from an interim analysis of RIFTOS MKI (Brose MS et al, JCO, 2017, abstract 6084).

**Methods:** RIFTOS MKI is an ongoing, global, non-interventional study enrolling patients with asymptomatic RAI-R progressive DTC from Europe, Japan, USA, and the rest of the world. The study is designed to assess the time to symptomatic progression from study entry in the real-life setting; two cohorts were defined by the treating physician’s decision to initiate a MKI at study entry (yes or no). Here we report results for the combined subgroup of 5 European countries (France, Germany, Greece, the Netherlands, and Spain) from the planned second interim analysis. No comparisons between cohorts were made.

**Results:** A total of 146 patients (49% male) were enrolled in Europe and valid for analysis. The median duration of observation from study initiation was 9.8 months. At study entry, the median age was 68 years and most patients had an ECOG performance status of 0 or 1 (95%) and distant metastases (90%). The most common history was papillary (64%) and the median time from initial diagnosis of DTC to study entry was 6 years. The median administered cumulative activity of prior RAI treatment was 11.10 GBq. RAI refractoriness was mainly due to a lack of RAI uptake (72%). In total, 36 (25%) patients were treated with sorafenib and 17 (12%) treated with lenvatinib at any time during the study. Of the 36 sorafenib-treated patients, the median duration of sorafenib treatment was 8.6 months (IQR: 3.2–17.0), and 78% received an initial dose of 800 mg/day. Of these 36 patients, 31 were included in the sorafenib safety analysis, 30.31 (97%) had ≥1 adverse event (AE), and 7/31 (23%) had ≥1 serious AE; hand-foot skin reaction (HFSR) was reported in 15/31 patients (48%), and grade 3 HFSR was reported in 3/31 patients (10%).

**Conclusions:** The RIFTOS MKI study is the largest non-interventional study in RAI-R DTC. European data on patient characteristics from the second interim analysis are consistent with those reported for the global population. Safety data from sorafenib-treated patients in Europe is consistent with the known safety profile of sorafenib.

Clinical trial registration: NCT02303444.


Chisato Tomoda, Kiminori Sugino, Takayuki Ishigaki, Tomoaki Tanaka, Yuna Ogiimi, Chie Masaki, Junko Akaishi, Kyomi Hames Yamada, Tomonori Yabuta, Akifumi Suzuki, Kenichi Matsuji, Takashi Uruno, Keiko Ohiwada, Wataru Kitagawa, Mitsuji Nagahama, Koichi Ito

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**Objectives:** Cause-specific mortality from well differentiated thyroid cancer is rare. The cause of death in the majority of patients with thyroid carcinoma is distant metastases, often lung metastases causing respiratory insufficiency. Local disease may also cause massive hemorrhage from the major vessels of the neck or direct compression of the trachea. Recently, there has been a trend away from local recurrence as the primary cause of death. The aim of this study was to compare in detail patients dying of well differentiated thyroid carcinoma at initial treatment between 1971–1997 (THEN: N = 99) and 2006–2017 (NOW: N = 111) at a single institution.

**Material and Methods:** This was a retrospective chart review with follow-up. Patients’ data were collected on age, sex, stage, tumor pathological findings, size of tumor, treatment, recurrence, cause of death, and length of survival.

**Results:** The median ages at initial treatment in THEN and NOW were 58.7 years and 60.8 years, respectively (p = 0.228). The survival times from initial treatment to death were 106.4 months in THEN and 122.4 months in NOW (P = 0.264). At the time of death, 82% and 33% in both groups had pulmonary metastases and bone metastases, respectively. Survival from pulmonary metastasis to death was 30.3 months in THEN and 52.6 months in NOW (P = 0.001). The most common specific cause of death was respiratory insufficiency in both groups, followed by recurrence of local disease (airway obstruction (THEN: 11.6% vs NOW: 10.5%) and hemorrhage from tumor (15.9% vs 9.3%)). Anaplastic change from well differentiated carcinoma was seen in 38.4% of THEN and 29.7% of NOW.

**Conclusion:** Most patients died due to distant metastases, but death resulting from local disease still occurred. Survival from distant metastasis to death in NOW was long compared to THEN.
SURGICAL MANAGEMENT OF AIRWAY IN LOCALLYADVANCED THYROID CANCER

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Background: Surgery remains the main treatment for locally advanced thyroid cancer invading the upper airway. We attempted to preserve the laryngeal skeleton by performing vertical hemilyrargopharyngectomy (VHLP) in patients requiring total laryngectomy and sternomcleidomastoid (SCM) muscle flap for reconstruction defect in thyroid cancer involving the trachea cases.

Methods: From January 2005 to December 2016, thyroid cancer patients hospitalized in Seoul St. Mary Hospital involved in this study. We have applied VHLP in locally advanced thyroid cancer with laryngeal invasion in three cases which are needs to take a total laryngectomy, and describe eight cases of thyroid cancer involving the trachea reconstructed with SCM muscle flap. We evaluate oncological and functional results from medical record retrospectively.

Results: Three patients had advanced thyroid cancer with laryngeal skeleton invasion and eight patients had trachea invasion. The first case was laryngeal invasion by spindle cell carcinoma of thyroid with paraglottic space invasion, the second case was papillary carcinoma with paraglottic space invasion, and the third case was anaplastic carcinoma with pyriform sinus invasion. In the case of anaplastic carcinoma, the cancer was recuror locally and the patient died 6 months after surgery and other two cases were NED (no evidence of disease) state with 5–10 years follow-up.

Conclusion: VHLP is one of the good surgical procedure to preserve the laryngeal function in the surgical treatment of locally advanced head and neck cancer especially deeply invading into the larynx. The SCM muscle flap method is a good substitute to solve this problem especially mid size tracheal invasion cases.

TKI THERAPY IN LOCALLYADVANCED THYROID CANCER: A CASE REPORT

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Introduction: Tyrosine kinase inhibitor (TKI) therapy has been approved for use in patients with progressive-advanced radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC). We report a case of TKI use in a patient with unresectable local disease in a DTC at presentation who went on to have sufficient disease response to permit surgery and pathological assessment. Few cases of TKI use in this scenario have been reported, and therefore the clinical and pathological response in this setting is poorly understood.

Case Report: A 73-year-old female presenting with haemoptysis and dysphonia was found to have a locally advanced left thyroid mass and vocal cord palsy. Tracheoscopy demonstrated upper tracheal invasion and allowed biopsy and airway debulking. Imaging confirmed the extent of local disease and an ipsilateral central neck node with no distant metastases. Histopathological analysis reported a follicular variant of papillary thyroid cancer (PTC). Following discussion, the tumour was deemed unresectable due to local extent and patient comorbidities. 14 months of TKI therapy was commenced. Sorafenib was poorly tolerated with cardiac toxicity. Lenvatinib was then commenced. Following discussion, the tumour was deemed unresectable due to local extent and was noted. This subsequently allowed successful surgical resection with a total thyroidectomy and central neck dissection with no evidence of residual macroscopic disease. Histopathology confirmed a well-differentiated PTC, with no significant change in tumour morphology compared with the diagnostic biopsy. There were pathological features of tumour regression including wide-spread scarring, prominent inflammatory changes and fibrosis which were thought to represent tumour response to TKIs.

Conclusion: Locally advanced thyroid cancer management is variable and depends on the extent of invasion of critical structures within the neck, as well as overall disease burden, tumour biology and patient-related factors. To achieve surgical clearance of disease vital structures may need to be sacrificed leading to functional impairment and cosmetic deformity. Historically for patients deemed unsuitable for surgery, limited options were available. In this case, TKI therapy in a locally advanced unresectable tumour reduced tumour size and infiltration to a degree that surgical resection of macroscopic disease was possible, without requiring airway resection. Microscopically there was evidence of dramatic regression. This case raises the possibility that TKIs may have a neoadjuvant role in selected cases of locally advanced DTC to reduce tumour volume and therefore morbidity of subsequent surgical resection.

SINGLE INSTITUTION EXPERIENCE OF LENVATINIB FOR PATIENTS WITH RADIOIODINE-REFRACTORY DIFFERENTIATED THYROID CARCINOMA

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Introduction: Lenvatinib is approved for treating radioiodine-refractory advanced thyroid carcinoma (RRDTC). However, only a few patients are eligible for lenvatinib treatment in real-world clinical practice because RRDTc does not always progress rapidly or cause symptoms. Little has been reported regarding experience with lenvatinib therapy in clinical practice. The present study aimed to determine the effects of lenvatinib in real-world patients at a single institution.

Material and Methods: We retrospectively reviewed data from 42 patients (female, 31; median age, 66 [range, 33–83] years; median follow-up, 15.2 [range, 1–34.2] months; median treatment duration, 13.4 months; prior tyrosine kinase therapy, n = 4) between May 2015 and January 2018 at our hospital. Effects were evaluated according to the RECIST criteria. Overall survival (OS), time to treatment failure (TTF), and progression-free survival (PFS) were calculated using the Kaplan-Meier method.

Results: Indications for lenvatinib therapy for 23 (55%) of our patients were the same as those in a phase 3 clinical trial. Median OS, median TTF, and median PFS were not reached (NR) [15.5–NR], 28.9 [13.7–NR], and 13.8 [5.0–NR] months, respectively. The outcomes were partial response, stable disease, and progressive disease in 29 (69%), 8 (19%), and 8 patients (19%), respectively. Factors related to OS were poor general status, size of target lesion, and tumour doubling time. Lenvatinib was continued for 13 (31%) of 41 patients with progressive disease and overall permissible status.

Conclusion: Although the characteristics and indications of the patients differed from those in the clinical trial, lenvatinib proved effective for actual patients with RRDTc.

THYROID CANCER SURVIVAL IN A SINGLE INSTITUTION IN NORTHERN ENGLAND

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Background: Thyroid cancer survival was highlighted in EUROCARE-4 as being worse in England than many other European countries. Data on thyroid cancer survival by cancer stage are not available in England. The aim of the study was to ascertain 1-, 5- and 10-year survival in patients attending the Northern Centre for Cancer Care, a tertiary centre in Northern England.
Results: Mean age of patients at diagnosis was 46.4 years (SD = 15.7) and 79% were female. Overall survival at 1, 5 and 10 years was 99% (n = 313), 97% (n = 308) and 88% (n = 170) respectively. Overall survival was greater in women than men (1-, 5- and 10-year 99.6%, 98.4%, 90.4% vs 97%, 94% and 78% respectively). Proportions for each tumour stage were: stage I, 62.7% (n = 198); stage II, 24.3% (n = 77); stage III, 5.4% (n = 17); and stage IV, 7.6% (n = 24). Five-year overall survival for stages I, II, III and IV was 98.5%, 98.7%, 82.4% and 95.8% respectively. Ten-year overall survival for stages I, II, III and IV was 93%, 88.7%, 58.3% and 71.2% respectively.

Conclusion: EUROCARE-5 reported overall 1- and 5-year survival in Europe for people with thyroid cancer diagnosed between 2000–2007 of 90% and 98.7%, 82.4% and 95.8% respectively. Ten-year overall survival for stages I, II, III and IV was 93%, 88.7%, 58.3% and 71.2% respectively.

Method: Data were reviewed for 420 patients identified by searching the histopathology database of our centre for new diagnoses of differentiated thyroid cancer between 1996 and 2010. Review of electronic hospital records yielded data on tumour stage (TNM 5th edition) and 1-, 5- and 10-year survival for 316 patients. Survival status and year of death were provided by Public Health England.

Poster Presentations

Table 1. (for Abstract P2-07-141)

<table>
<thead>
<tr>
<th></th>
<th>Post-operative evaluation (median time from surgery 6 months)</th>
<th>Reclassification based on the result of the ptWBS</th>
<th>First post-RRA evaluation(*) (median time from RRA 7.3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ExR</td>
<td>BiR</td>
<td>StR</td>
</tr>
<tr>
<td>Low Risk</td>
<td>382/807 (47.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>41/807 (50.9%)</td>
<td>27</td>
<td>4.9</td>
</tr>
<tr>
<td>High Risk</td>
<td>13/807 (1.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(*) 785/807 patients (97.3%).

Results: see Table 1.

Conclusions: 3. Dynamic risk restratification could begin immediately after surgery, taking into account the value of Tg, TgAb and the result of neck US. 4. The results of the ptWBS, did not change the further diagnostic and therapeutic strategy in most of the LR and IR patients. 5. The main impact of RRA in LR and IR is the effect on serum Tg levels, which is one of the cornerstone of dynamic risk restratification, even more relevant after 131-I therapy.

P2-07-142

AN ACCURATE CHARACTERIZATION OF THYROID MICROCARCINOMAS DETERMINES A MORE APPROPRIATE CLINICAL MANAGEMENT

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In the last few years the incidence of thyroid carcinoma has increased considerably. However, the increase in incidence doesn’t seem to have a significant impact on survival, which remains unchanged. This discrepancy reflects the indolent course of the pathology as well as the use of diagnostic techniques with higher sensitivity in detecting very small tumors. In these cases, the risks of treatment (surgery, 131I, L-thyroxine) could outweigh the benefits. However, in early stages, even aggressive tumors can appear as microcarcinomas and, if not treated appropriately, they can progress, with a higher risk of recurrence (and perhaps of mortality).

The aim of the study was to identify reliable prognostic factors in patients with mPTC, in order to stratify the risk in as much detail as possible to choose the best therapeutic strategy. 404 cases of papillary mPTC were treated at our institution between 1996 and 2016, with a follow-up of at least two years. We considered as potential prognostic factors sex, age, histologic variant, TNM, possible multifocality and associated thyroid diseases. Furthermore, the therapy performed and the course of the disease over time were recorded. A comparison between the group of patients treated with 131I and those not treated with 131I was also made. Moreover, we reclassified microcarcinomas with minimal extrathyroidal extension (ETE) previously classified as pT3 (TNM 2009) according to TNM 2017 which consider such tumors as pT1 (TNM 2017).

Results: a statistically significant association was found between the disease recurrence and the histological variant (mostly sclerosing variant), lymph node metastasis, non- incidental finding. The association is not statistically significant for multifocality (also associated with lymph node metastasis at diagnosis), age ≥50 years, associated thyroiditis. Of the 95 cases classified as pT3 (for TNM 2009), 49.5 would today be considered pT1, for which a less aggressive treatment is recommended. The group of patients not treated with 131I presents more favorable characteristics at diagnosis: smaller diameter, less aggressive histologic variant, unifocality, absence of lymph node metastasis and ETE. In this group the percentage of recurrence is extremely low (0.5%), mortality is zero and the response is “incomplete” in only 2.5%.

Conclusions: despite the thyroid microcarcinoma has an excellent prognosis, we showed that some tumors have more aggressive features, more often associated with disease recurrence. For such cases a more aggressive treat-
ment is advisable. In low-risk patients, we cannot confirm any indication to radio-
metabolic therapy, the probability of relapse being negligible.

**P2-07-143**  
**IMPACT OF THE STIMULATION METHOD USED FOR 131I-THYROID CANCER**  
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**Objectives:** Recombinant human TSH (rhTSH) has been approved for 131I thyroid remnant ablation (RRA) in patients with differentiated thyroid cancer (DTC). Nowadays, 131I-therapy for metastasis is performed after L-thyroxine withdrawal with subsequent hypothyroidism and rhTSH stimulation is reserved to compassionate cases. About 20% of patients treated for RRA need to be re-treated for biochemical evidence of disease (BED) or structural evidence of disease (SED). The aim of this study was to compare the impact of the method used to administer the first 131I-therapy (rhTSH vs Hypothyroidism) in patients with persistent disease, BED or SED, after 131I thyroid RRA.

**Methods:** 198 DTC consecutive patients with persistence of disease after total thyroidectomy and 131I RRA were analysed: 102 patients were treated in euthyroidism (EU-group) and 96 in hypothyroidism (HYPO-group).

**Results:** epidemiological and pathological data were similar in the two groups (age, p = 0.45, sex, p = 0.78, 7th ACC/TNM staging, p = 0.41, ATA risk class, p = 0.62; histology, p = 0.77). The main reason of 131I-therapy was similar in the two groups: for BED in 56/102 (55%) and 50/96 (52%) in EU and HYPO-group, respectively; for SED in 46/102 (45%) and 46/96 (48%) in EU and HYPO-group, respectively, p = 0.47. A similar 131I-activity was administered in the two groups (4259.4 ± 677 mCi in EU-group; 4371.9 ± 627 mCi in HYPO-group, p = 0.16). The whole-body scan (WBS) post-131I-therapy was positive in 76/102 (75%) patients of EU-group and 84/96 (88%) patients of HYPO-group: the positivity was for residual thyroid tissue in 58/76 (76%) and 65/84 (77%), lymph node metastasis in 9/76 (12%) and 13/84 (16%), distant metastasis in 9/76 (12%) and 6/84 (7%) patients in EU and HYPO-group, respectively (p = 0.15). Six months after first 131I-therapy, 11/75 (15%) and 18/84 (21%) patients of EU and HYPO-group were respectively in clinical remission (p = 0.27); 64/75 (85%) and 66/84 (79%) patients of EU and HYPO-group respectively had a persistent disease: 25/64 (39%) and 32/66 (48%) patients of EU and HYPO-group, respectively, had a BED; 39/64 (61%) and 33/66 (52%) of EU and HYPO-group respectively presented a SED (p = 0.28). After 6 years of follow-up there was no significant difference in outcome between the two groups regardless of the therapeutic strategies: 53/98 (54%) and 50/96 (52%) patients of EU and HYPO-group respectively were in clinical remission, p = 0.78.

**Conclusions:** WBS post-131I-therapy, first control and final outcome were similar in the two groups. These data confirmed that there were no differences regarding the method used to administer 131I-therapy (rhTSH vs Hypo).

**P2-07-144**  
**DELAYED RADIOIODINE REMNANT ABLATION (RRA) DOES NOT IMPACT ON THE OUTCOME OF INTERMEDIATE RISK FOR RECURRENT DIFFERENTIATED THYROID CANCER PATIENTS (IR-DTC)**  
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**Background:** Selective use of 131I was advocated by ATA guidelines for IR-DTC. The post-operative evaluation, 3–4 mths after total thyroidectomy, should be considered in the decision making to perform or not RRA. However, the available data on the impact of delayed RRA on the outcome of IR pts, are conflicting.

**Patients and Methods:** We retrospectively evaluated the data of 311 consecutive IR-DTC pts followed at our institution for a median of 5.9 yrs. All patients performed RRA with 30 mCi 131I after recombinant TSH (rhTSH). We divided pts in Group-A (RRA <6 mths from surgery – 101 pts) and Group-B (RRA >6 mths from surgery – 210 pts).

**Results:** The median time elapsed between surgery and RRA was 3.4 mths in Group-A and 7.3 mths in Group-B. The two groups were similar for gender distribution (female 75.6 vs 67.6% – p = 0.17) and age (median 44.7 vs 47.1 yrs – p = 0.18). Classic variant PTC (43.6 vs 42.4%), follicular variant (10.9 vs 14.8%), FTC (5 vs 4.3%) and aggressive variants PTC (40.6 vs 38.6%) were similarly distributed in Group-A and B (p = 0.821), as well as tumor dimension (median 4.2 vs 2 cm – p = 0.13), multifocality (55.4 vs 53.3% – p = 0.73), lymph node metastases at histology (26.7 vs 27.6% – p = 0.87). At the first post-operative evaluation (median 6 mths), no differences in lymphnode metastases at neck (6.9 vs 5.7% – p = 0.67), were noted. At the first control after RRA (median 7 mths), no difference in Excellent (58.2 vs 62.3%), Biochemical (7.1 vs 5.8%), Structural (6.1 vs 5.8%) and Indeterminate Response (28.6 vs 26.1%), were noted (p = 0.91). At the end of follow-up (median 5.9 yrs), there were no difference in Excellent (74.5 vs 76.9%), Biochemical (2 vs 2%), Structural (10.2 vs 7.7%) and Indeterminate Response (13.3 vs 13%) (p = 0.9), as far as in the number of 131I courses performed during the follow-up, only RRA (80.6 vs 82.2%), RRA + one 131I (12.2 vs 8.2%) or RRA + two or more 131I (7.2 vs 9.6%) (p = 0.67).

**Conclusions:** 1) In IR-DTC pts, RRA performed <6 mths or ≥6 mths showed the same efficacy, both at the first control after ablation (median 7 mths) and at the end of follow-up (median 5.9 yrs); 2) No difference in the total number of 131I courses were noted between the two groups; 3) IR-DTC could critically and safely reassessed in the year following the surgery before deciding to perform RRA.

**Autoimmunity**

**P3-01-145**  
**THE EFFECT OF RADIOIODINE TREATMENT ON TRAB, ANTI-TPO, AND ANTI-TG IN GRAVES’ DISEASE**  
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**Background:** In Graves’ disease (GD) immunocompetent cells infiltrate thyroid tissue with release of TSH-receptor stimulating antibodies (TRAb) resulting in hyperthyroidism. The uptake of iodine in thyroid follicular cells is a prerequisite for the production of thyroid hormones, therefore radioidine is used as a treatment modality resulting in a local destruction of thyroid tissue. It may seem paradoxical that this treatment elicits an increase of TRAb with a peak typically 3–6 mths from surgery, followed by a slow decline, in some patients for several years. The aim was to study whether all patients respond to radioiodine. Monday, September 17th, 2018 Poster Session 3
in the same manner and if anti-thyroperoxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies also increase.

Method: This is a prospective observational study where all GD patients admitted to the Department of Oncology for treatment with radioiodine during August 2016 until May 2017 were included. 131 patients were registered and admitted to the Department of Oncology for treatment with radioiodine during the same period. Ultrasonic (anti-TG) antibodies also increase.

Results: After three months a fold change above 1.1 was found in 66% of GD patients while the remaining 34% did not change or decreased in TRAB. This was also demonstrated for anti-TPO and anti-TG where the former showed an increase in 73% and the latter an increase in 52% while 27% and 48% decreased/unchanged. A significant positive correlation was found for TRAB and anti-TPO but not for anti-TG. In the group where TRAB increased, patients born outside Sweden were overrepresented (30%) compared to the group that decreased (18%) but this was not significant, neither were differences in age or smoking. In the group with an increase in TRAB the median fold change was 5.1. The median age was 48 years in the group with fold change >5.1 and 59 years in the group with fold change <5.1. The proportion of women below the median age (51.5 years) was significantly higher in the group that increased in TRAB compared to those that decreased/unchanged, 66% vs 34%.

Conclusion: Treatment with radioiodine elicits an increase in all three thyroid antibodies but not in all GD patients. The proportion of responders varied between antibodies and was affected by age resulting in a stronger immune response with increase of TRAB in the pre-menopausal age. There were no effects of smoking on the immune response neither in responders nor in non-responders.

P3-01-147
AUTOIMMUNE THYROID DISEASE PREVALENCE IN AN ITALIAN-COHORT OF PATIENTS WITH PROLACTINOMA

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Introduction: Prolactin may exert immunological effects and favor the onset of autoimmune diseases. Recently a higher prevalence of autoimmune thyroiditis has been reported in patients with prolactinoma in areas with sufficient iodine intake.

Purpose: The aim of our study was to evaluate the prevalence of autoimmune thyroiditis in a retrospective cohort of patients with prolactinoma (PRL) compared to an age-and sex-matched control group represented by subjects with non-secreting pituitary adenomas (NFPA).

Materials and Methods: We enrolled 130 patients (93F / 37M, age 36.5 ± 13.1 years, m ± SD) with PRL (93 micro / 37 macro) and 88 subjects (66F / 22M; age 39.7 ± 13.9 years, m ± SD) with NFPA (54 micro / 30 macro), with normal prolactin values not upon specific therapy. The diagnosis of autoimmune thyroid diseases [Graves Disease (GD) and chronic autoimmune thyroiditis, (AITD)] was based on the presence of at least two of the following criteria: 1) impaired thyroid function (primary hypothyroidism or hyperthyroidism); 2) positive anti-thyroid antibodies (anti-thyroglobulin antibodies (TgAb) and/or anti-thyroperoxidase (TPOAb) ≥100 U/ml, anti-TSH receptor antibodies (TRAb) > 2 U/L; 3) typical thyroid ultrasound pattern (diffuse or focal hypoechogenicity). TPOAb and TgAb were measured by chemiluminescence and TRAb by an immunoenzymatic assay. Thyroid ultrasound was performed using a color doppler apparatus and a 7.5 MHz linear probe. Thyroid volume was calculated using the ellipsoid formula (width × depth × length × 0.524).

Results: Median prolactin was significantly higher in PRL (98.3 ng/ml) than in NFPA (10.8 ng / ml, p = <0.0001), as expected. The prevalence of autoimmune thyroid diseases was 18.5% (24/130) in patients with PRL (2/24 with GD and 22/24 with AITD) compared to 9.1% (8/88) in subjects with NFPA. Although the prevalence is almost double in the PRL group, it does not reach statistical significance (p = 0.078), likely due to the sample size. Estimated thyroid volume (10.8 mL vs 11 mL, p = ns) and the presence of uni- or multinodular goiter (28.7% versus 36.1%, p = ns) did not differ between the two groups.

Conclusions: Our preliminary data suggest a higher prevalence of autoimmune thyroid diseases in patients with prolactinoma, as previously reported in literature, also in an area with mild iodine deficiency.

P3-01-146
TSH RHYTHM IN RESISTANCE TO THYROID HORMONE BETAl WITH AUTOIMMUNE THYROID DISEASE AND TYPE 2 DIABETES MELLITUS

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In resistance to thyroid hormone β (RTH-β), mutations in the thyroid hormone receptor isoform β results in symptoms of both increased and decreased TH action depending on the tissues’ predominant receptor isoform expression. TSH circadian rhythm under the effect of different types of autoimmune thyroid disease (AITD) in RTH-β and type 2 diabetes mellitus (T2DM) has not been observed. Here we present an RTH-β family with different accompanying AITD in which both genetically-diagnosed members also had concomitant T2DM. We observed the index patient (Case 1) through gestation and 2 years postpartum, and assessed the circadian rhythm of circulating TSH, FT4 and FT3 in both subjects. We found that the natural progression of AITD is independent of inherent RTH-β. In Case 1, the presence of RTH-β did not increase disease duration or progression toward permanent hypothyroidism after the development of postpartum thyroids (PPT). An analysis of the circadian rhythm of TSH in RTH-β at baseline thyroid hormone levels showed that despite stably elevated FT4 and FT3, nocturnal TSH increase was evident, starting at approximately 7 PM, whereas in RTH-β with Grave’s disease (GD) (Case 2), TSH was suppressed to the low detection limit with no observable TSH surge though pulsatility remains. Glucose metabolism was independent of TFT results, but TSH rhythm may be absent in uncontrolled diabetes. The presence of different AITD in this family and the occurrence of PPT in one subject allowed the observation of glucose changes under variations of thyroid hormone levels. In Case 1, the most dramatic change in TH results was during the hypothyroid phase of PPT, at which basal glucose and insulin was still comparable to baseline levels. On the other hand, no nocturnal TSH increase was observed for unmanaged diabetes in Case 2. In conclusion, TSH circadian rhythm may be preserved in RTH with HT in controlled glycaemia, while the TSH nocturnal surge was absent in RTH with GD in uncontrolled diabetes. Although it is unknown whether thyroid hormone or glucose level has a greater impact on TSH variation in RTH-β patients, the treatment of hormonal disturbance and hyperglycemia may be synergetic toward normalizing nocturnal TSH surge.

P3-01-148
THYROGLOBULIN ANTIBODIES ARE ASSOCIATED WITH SYMPTOM BURDEN IN PATIENTS WITH HASHIMOTO'S THYROIDITIS

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Objectives: Hashimoto thyroiditis (HT) is the most common form of autoimmune thyroid disorders, caused by autoantibodies to thyroglobulin (TgAb) and thyroid peroxidase (TPOAb), and today there is rising interest in influence of thyroid antibodies on human health. In our study we have included large cohort of patients with HT, previously characterised according to antropometric and clinical parameters, to investigate differences among them in regard to levothyroline (LT4) therapy intake and possible influence of thyroid autoimmunity on symptom burden.

Methods: In the period from 2013 to 2017 we collected data from 491 HT patient that have been admitted on Department for Nuclear Medicine at the University Hospital Split, including 455 females (93%) and 36 males (7%). Patients were diagnosed with HT based on clinical examination, thyroid ultra-
sound presentation, thyroid hormones values and positivity to TPOAb and TgAb, according to ETA recommendations and guidelines for Management of Subclinical Hypothyroidism.

Also, we collected detailed information on patient’s medical status including personal anamnesis, anthropometric and cardiovascular measurements, symptoms load, clinical classification of goitre.

For statistical analysis we used Mann-Whitney test, Kolmogorov-Smirnov test, Spearman rank correlation test, χ²-test.

Results: We have found significant association of TgAb levels with the number of symptoms in the group of patients without therapy, and to lesser extent similar association in a case of TPOAb. Among 16 evaluated hypothyroidism symptoms, face edema, edema of the eyes, fragile hair and constipation were significantly increased in patients with elevated TgAb levels. The two subgroups of HT patients, depending on the LT4 therapy, differ significantly for several clinical parameters, moreover we observe significantly higher number of symptoms in the group of HT patients on therapy, mostly dry and rough skin, sensitivity to coldness and cold skin. It may be explained by lower biological effectiveness of synthetic LT4 and difference in tissue deiodinase activity. Also, we have found positive correlation between T4 and age in HT patients on therapy suggesting that the introduction of LT4 therapy modifies the influence of aging on thyroid hormone levels.

Conclusions: TgAb have important effect on general health and clinical manifestations of HT, and elevated TgAb level may cause the observed symptom burden in HT patients, leading to conclusion that not all HT patients may be clustered in one group. The symptoms in patients with HT should be further differentiated to those that are truly caused by hypothyroidism and those that develop due to autoimmunity per se.

P3-01-149
INCREASED EXPRESSION AND ACTIVITY OF NLRP3 AND NLR4C INFLAMMASOMES IN PERIPHERAL BLOOD MONONUCLEAR CELLS ARE ASSOCIATED WITH AUTOIMMUNE THYROIDITIS
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Objectives: Inflammasomes are important members of the innate immune system and have been linked to a variety of autoimmune disorders. The present study aimed to investigate whether aberrant expression and activity of inflammasomes are involved in the pathogenesis of autoimmune thyroiditis (AIT).

Methods: We recruited a cross-sectional population including 50 AIT patients and 50 matched controls. Peripheral blood mononuclear cells (PBMCs) and serum samples were collected. Expression of pro- and active IL-1β and IL-18 and inflammasome components (NLRP1, NLRP3, NLR4C, AIM2, ASC, CASP1) in PBMCs were determined at the mRNA level by real-time PCR and at the protein level by Western-blot. Concentration of IL-18 and β2-microglobulin in serum was assayed with enzyme-linked immunosorbent assay (ELISA).

Results: Expression of NLRP3, NLR4C, pro IL-1β and pro IL-18 mRNA and protein were significantly elevated in PBMCs from patients with AIT compared with those from healthy controls, while no difference was observed in NLRP1, AIM2, ASC and pro caspase-1 expression. PBMCs from AIT patients expressed higher levels of active caspase-1 and active IL-18 than controls, but equal level of active IL-1β. Serum IL-18 level was significantly higher in AIT group than control group, while serum IL-1β level was not different between the two groups.

Conclusions: We have showed for the first time that increased expression of NLRP3, NLR4C, active caspase-1, active IL-18 in PBMCs and elevated IL-18 in serum from patients with autoimmune thyroiditis, which indicating the participation of NLR4C and NLR3 inflammasomes in the pathogenesis of AIT. Our work has suggested that NLRP3 and NLR4C may be potential therapeutic targets and biomarkers for AIT.

P3-01-150
RELATIONSHIP BETWEEN QUALITY OF LIFE AND THYROID STATUS IN GRAVES’ DISEASE
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Aims: The aim of this study was evaluated the quality of life and cognitive function in GD patients in different conditions, with and without ocular disease.

Methods: One hundred and fifth four patients with GD were analyzed, 54 of them had ophthalmopathy. All of them were evaluated with Clinical Activity Score (CAS), Health-related quality of life (HR-QoL) and Mini-Mental State Examination (MMSE). Patients with ophthalmopathy were also evaluated with Graves’ Obitopathy Quality of Life Questionnaire (GO-QoL).

Results: Patients with hyperthyroidism presented a greater impairment in quality of life when compared to euthyroidism group, especially in physical role functioning (59.62 x 82.81, p = 0.0061) and emotional role functioning (61.54 x 82.81, p = 0.0093). A lower score in physical role functioning was found at both subgroups with active disease, in hyperthyroidism and euthyroidism using thionamides (p 0.0281). A lower score was also seen in visual function between patients with hyperthyroidism and euthyroidism (88.93 x 95.17, p = 0.0268), but no difference was found in appearance. No significant difference was found in cognitive function, by MMSE punctuation, between patients in euthyroidism and hyperthyroidism, as well as in subgroups. Younger ages at diagnosis, euthyroidism and absence of ophthalmopathy were factors associated with better quality of life, as well as a shorter disease duration was a factor associated with better recall (p < 0.0001), attention and calculation (p 0.0193).

Conclusions: A great impairment in quality of life among patients with active GD was evidenced, even in those receiving thionamides and with normal thyroid function. Ophthalmopathy was a factor associated with a poor quality of life and no clear evidence of cognitive impairment was demonstrated.

P3-01-151
THYROID DYSFUNCTION INDUCED BY IMMUNE-CHECK POINT INHIBITORS
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Introduction: Immune checkpoint inhibitors have an important role in the treatment of malignant tumors. Nivolumab and Pembrolizumab are anti-programmed death-1 monoclonal antibodies used in the treatment of lung cancer and may induce immune-related adverse effects, including in endocrine glands. The aim of this study was to evaluate the prevalence of thyroid disorders induced by these drugs.

Methods: Retrospective and descriptive study of patients with non-small cells lung cancer (NSCLC) treated with Nivolumab and Pembrolizumab since 2015.

Results: Twenty-nine patients (86.2% male, mean age 61.1 ± 8.1 years) with NSCLC were included; 24 (82.8%) were treated with nivolumab (3 mg/kg every 2 weeks) and 5 (17.2%) were treated with pembrolizumab (2 mg/kg every 3 weeks). Thyroid function was assessed before treatment in the majority of patients (96.6%) and all had normal thyroid function. One patient (3.4%) had previous hypothyroidism, compensated with levothyroxine treatment. Thyroid function was monitored during the course of treatment in the majority of patients (93.1%) and in about half of the patients (51.7%, n = 15), the first thyroid evaluation occurred following the first cycle of treatment. During treatment, 27.6% (n = 8) developed thyroid dysfunction (5 patients had thyrotoxicosis/ isolated elevated free T4, 1 associated with subsequent hypothyroidism; 2 de novo hypothyroidism and 1 worsening of previous hypothyroidism).
All patients who had thyroid dysfunction were treated with nivolumab. One patient, later on, had ACTH deficiency. Most patients were asymptomatic and thyroid evaluation was assessed routinely. Thyroid disorders occurred a median of 56.5 days (IQR 14.3–104.5) after the initiation of nivolumab. Thyroid autoimmunity was evaluated in 3 patients with thyroid dysfunction and was negative in all. In two patients, thyroid function follow-up was not possible due to patients’ death.

Conclusion: Immune checkpoint inhibitors may cause asymptomatic autoimmune thyroid disorders. The prevalence of thyroid dysfunction is variable, ranging from 6% to 20% in previous studies. In our study, the prevalence of thyroid dysfunction was higher probably due to screening for this adverse side effect very early in the course of treatment in order to prevent the negative impact of thyroid dysfunction on the quality of life and on the clinical outcome.

**PI-01-152**

**INCREASED 24-H PULSE WAVE VELOCITY IN NEWLY DIAGNOSED PATIENTS WITH Graves’ DISEASE COMPARED TO EUTHYROID CONTROLS**

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Introduction: Hyperthyroidism including Graves’ Disease (GD) is associated with increased cardiovascular risk (CVD). There are several possible mechanisms but these are not fully understood. Arterial stiffness is a well-established risk marker of CVD. The association between arterial stiffness and GD remains elusive.

Objective: We aimed to investigate whether arterial stiffness differs in patients newly diagnosed with Graves’ Disease compared to euthyroid controls.

Methods: 32 newly diagnosed patients with GD (<14 days of antithyroid drugs) and 30 euthyroid controls were included. Ambulatory (24-h) blood pressure, pulse wave velocity (PWV), and central augmentation index (AIX) were measured on the non-dominant arm using the Arteriograph24. Office PWV and AIX were measured in the supine position after 10 minutes rest and 8 hours fasting using the Sphygmocor XCEL device. Differences between groups were accessed using the independent student t-test or Wilcoxon rank-sum test when appropriate.

Results: Patients with GD and controls were comparable regarding age (GD vs controls: 38.4 ± 37.8 years, p = 0.85), sex (GD vs controls: 73.5% vs 73.3% female, p = 0.88), and mean arterial pressure (GD vs controls: 85.9 vs 86.8 mm Hg, p = 0.71). Patients were hyperthyroid with mean free triiodothyronine level of 12.7 pmol/L (IQR: 8.9–16.9). Among GD patients 24-h PWV was increased (9.1 m/s (95% CI: 8.6–9.6) vs 7.6 m/s (95% CI: 7.2–8.0), p < 0.001). The difference between groups remained significant in a multiple regression analysis adjusted for age, sex, low-density lipoprotein, 24-h heart rate, and 24-h mean arterial pressure (24-h PWV difference GD vs controls: 1.1 m/s (95% CI: 0.6–1.6), p < 0.001). 24-h pulse pressure was increased in GD (57 mm Hg (95% CI: 54–60) vs 51 mm Hg (95% CI: 48–53), p < 0.001) and remained in a regression model adjusted for age, sex, low-density lipoprotein, and 24-h heart rate (24-h PP difference GD vs controls: 6.1 mm Hg (95% CI: 1.2–10.9), p = 0.006). Looking isolated at day and night period both PWV and PP were significantly increased in GD. Office PWV (GD vs controls: 6.6 vs 6.5 m/s, p = 0.31) and AIX were comparable.

Conclusion: Arterial stiffness is increased in patients newly diagnosed with Graves’ Disease compared to euthyroid controls. Diurnal measures of arterial stiffness in terms of 24-h pulse wave velocity and 24-h pulse pressure were increased whereas office measures in the resting condition were comparable. Our data need replication but may add a piece to the puzzle of understanding excess cardiovascular morbidity in hyperthyroidism, including Graves’ Disease.

**PI-01-153**

**GRAVES’ DISEASE: RELAPSE AFTER A SINGLE COURSE OF ATD PLUS PARENTERAL CORTICOSTEROIDS PULSE THERAPY**

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Introduction: Treatment options of Graves’ disease (GD) include antithyroid drugs (ATD), radioiodine therapy, and surgery. The overall remission rate after a course of ATD varies between 30–50%. The contribution of age, sex, smoking, and immunosuppressive drugs plus ATD on GD recurrence differ between studies.

Aim: We investigated whether the addition of parenteral steroids, administered for thyroid related orbitopathy (TAO), to a standard ATD treatment reduces the risk of GD recurrence.

Methods: We retrospectively studied 162 patients who received ATD continuously for almost 18 months from GD diagnosis. Parenteral methylprednisolone (MPDS) was administered because of active TAO, with a cumulative dose of 4,500 mg in 12 weeks. Patients’ clinical and biochemical characteristics were evaluated every 3 months. The cut-off value of ≤40 years as putative predictor variable for recurrent GD was obtained by Receiver Operator Curve (ROC) analyses. We investigated the relationship between GD recurrence and several variables by Cox proportional-hazards analysis (HR). Independent predictors were identified by the Wald test (W) with a p-value < 0.05.

Results: Patients included 118 females and 44 males with mean age 41.3 ± 1.2 years, and mean body mass index (BMI) 24.5 ± 4.6. Of them, 39.5% (64/162) were smokers, and 47.5% (77/162) presented TAO. ATD therapy duration was 26.4 ± 9.3 months, and was mostly (75.3% of cases) according to the BR scheme. Forty-three patients (26.5%) received MPDS because active TAO. After a mean follow-up of 24 months (1–103) after ATD withdrawn, 59.9% experienced GD recurrence while 40.1% remained euthyroid. BMI, smoking, presence and grade of TAO, type of ATD therapy, thyroid function and TRAb levels were not different in patients with or without GD recurrence. The rate of GD recurrence in patients ≤40 years was significantly higher than in older patients (71.6% vs. 51.6%, respectively p = 0.01). MPDS, age ≥40 and female sex were significantly associated with a lower GD recurrence rate (HR = 0.55 (0.33–0.92), 0.61 (0.43–0.94), and 0.65 (0.43–0.98), respectively). However, in the subgroup of patients <40 years female sex, HR = 0.51 (0.31–0.91), and MPDS were also associated with a lower GD relapse rate (HR = 0.35 (0.14–0.89).

Conclusions: Age ≥40, female sex, and pulse MPDS are independent protective factors for GD recurrence; the effect of MPDS seems stronger in younger patients.

**PI-01-154**

**DOSE-DEPENDENCY OF METHIMAZOLE-INDUCED AGRANULOCYTOIS:**

**A RETROSPECTIVE COHORT STUDY INVOLVING 15,054 PATIENTS WITH Graves’ DISEASE AT A SINGLE MEDICAL INSTITUTION IN JAPAN**

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Context: Some reports have suggested that higher doses of methimazole may be more likely to cause agranulocytosis.

Objectives: The purpose of this study was to analyze the dose dependency of methimazole-induced agranulocytosis.

Methods: A total of 15,054 patients with new-onset Graves’ disease initially treated with methimazole at Ito Hospital between 2005 and 2016 were retrospectively reviewed.

Main Outcome Measure: Incidence of methimazole-induced agranulocytosis.

Results: The median age of patients was 40 years (range, 4–92 years). The male-to-female ratio was 1.36. Initial doses included 5 mg/d (n = 374), 10
P3-02-155

POLYMORPHISMS OF TGFβ1 GENE AND ITS RECEPTORS (TGFBR1 AND TGFBR2) MAY IMPACT THYROID TUMOR AGRESSIVENESS

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Thyroid cancer incidence has presented a massive increase in the last 20 years. According to our National Institute of Cancer/Brazil (INCA) the estimative for 2016 was 5870 new cases diagnosed in Brazilian women. TGFβ-1 is a multifunctional cytokine that plays a significant role in a number of biological processes and regulation of immune system. Derogulation of TGF-β1 signaling, especially by genetic polymorphisms in the regulatory region, has been associated with the development of several human diseases, such as cancer, fibrosis, and autoimmune diseases. The aim of this study was to evaluate the impact of the inheritance of the different genotypes of polymorphisms in TGFβ1 (rs1800469, rs1800472, rs1800473, rs1800481), genes in the susceptibility to thyroid nodules, and agressiveness of thyroid nodules. Three hundred and thirty nine patients (287 females, 52 males, mean age 46.1 ± 14.4 years) with malignant and benign thyroid nodules were analyzed. None of the analyzed polymorphisms were in the Hardy–Weinberg equilibrium. None of the analyzed polymorphisms were able to differentiate malignant from benign nodules, or any of histological types and histopathological features that influence PTC prognosis. However, two TGFβ1 gene polymorphisms were associated with aggressiveness: patients carrying polymorphic or heterozygous genotypes (AA or AG) of rs1800469 polymorphism had greater chances of having not encapsulated thyroid tumors (OR = 3.323, 95% CI: 1.366–7.647, p = 0.0097); the same happened to patients with the heterozygous genotype (AG) of rs1800472 polymorphism which have 3 times more chance to present lymph node metastasis at diagnosis when compared to wild type patients (OR = 3.461, 95% CI: 1.078–11.114, p = 0.0469). On the contrary, the inheritance of the altered genotypes of the TGFβ1 gene receptor (TGFBR1) rs10512263 polymorphism provided lower risk of invasion (OR = 0.37, 95% CI: 0.160–0.8127, p = 0.0173). In conclusion, these data suggest that polymorphisms in TGFβ1 and TGFBR1 genes do not modulate susceptibility to thyroid cancer, but may be related to tumor characteristics of aggressiveness.

P3-02-156

INHIBITORY EFFECT OF URSOLIC ACID AND ITS ISOMERS OLEANOLIC ACID ON HUMAN PAPILLARY THYROID CANCER CELL TPC-1

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Objectives: To compare the inhibitory effect of oleanolic acid and ursolic acid isomers on human papillary thyroid cancer cell TPC-1.

Methods: TPC-1 cells were cultured with complete medium containing various concentrations of oleanolic acid or ursolic acid (0, 3, 6, and 12 μM) for 48 h. MTT was performed to examine the growth of TPC-1 cells in a dose-dependent manner, while oleanolic acid had no effect on the growth of TPC-1 cells in this concentration range (P > 0.05). The results of treatment with oleanolic acid (3, 6 and 12 μM) significantly increased apoptosis of TPC-1 cells at 48 h in a dose-dependent manner, compared with treatment with 0 μM of oleanolic acid whereas ursolic acid increased apoptosis of TPC-1 cells only in high concentration (12 μM). The results showed that ursolic acid significantly increased the number of TPC-1 cells in the S phase in a dose-dependent manner. The results showed that in the G0/G1 phase in high concentration (12 μM). Compared with the negative control group and oleanolic acid group, the expressions of Bcl-2 in the negative control group was decreased, while the expressions of Bax, Caspase-9 were observably increased. Compared with the negative control group and oleanolic acid group, the expressions of Bcl-2 in oleanolic acid group was increased. RNA-Seq results showed that 29 identical differential genes for the two compounds, 1006 different differential genes. KEGG enrichment analysis, it was mainly enriched in PI3K/AKT, Focal adhesion, and Bcl-2/Bax signal pathways with treatment ursolic acid. Oleanolic acid was mainly enriched in Oxidative phosphorylation and VEGF signaling pathways.

Conclusion: Ursolic acid and oleanolic acid, both belonging to pentacyclic triterpene carboxylic acid, are extensively researched, and are isomers yet. The inhibitory effect of ursolic acid on TPC-1 cell was stronger than that of oleanolic acid, but its mechanism of apoptosis is different.
Methods: We collected and analyzed DNA from peripheral blood of 185 PTC patients and 154 healthy controls. More than 90 polymorphic sites distributed in the three different HLA-G gene region were characterized by Sanger sequencing. Haplotypes of each HLA-G gene region were first identified to further construct the HLA-G extended haplotypes. HLA-G extended haplotypes were compared between PTC patients and controls, as well as in PTC patients between the different histopathological features, using Fisher exact test, in which odds ratio (OR), confidence interval (CI) and P-values were calculated. P-values below 0.05 were considered to be significant.

Results: We identified 33 different HLA-G extended haplotypes in PTC patients and 41 in controls. Compared to controls, the 0104a(promoter):01:04:01(coding):UTR-3(3'UTR) extended haplotype was underrepresented in PTC patients, however, the difference did not reach significance (OR = 0.3541, CI 95%=0.1360–0.9219). The occurrence of HLA-G extended haplotypes was less frequent (OR = 0.2842, CI 95%=0.0821–0.9836), while the 0104a(promoter):01:04:01(coding):UTR-3(3'UTR) extended haplotype was more frequent (OR = 11.2857, CI 95%: 1.3438–94.7784). The 0103a(promoter):01:03:01:02:UTR-3(3'UTR) extended haplotype was also associated with the presence of Hashimoto’s thyroiditis (OR = 0.0094). The 0104a(promoter):01:04:01(coding):UTR-3(3'UTR) extended haplotype was more frequent (OR = 11.2857, CI 95%: 1.3438–94.7784) in PTC patients presenting tumor multicentricity (OR = 0.2842, CI 95%=0.0821–0.9836, P = 0.0362), while the 010102a(promoter):01:01:12(+324G):coding:UTR-02(5'UTR) extended haplotype was less frequent in PTC patients presenting thyroidal extension.

Conclusions: Regarding histopathological features of PTC, the 0104a(promoter):01:04:01(coding):UTR-3(3'UTR) extended haplotype was less frequent in PTC patients and controls, as well as in PTC patients between the different histopathological features, using Fisher exact test, in which odds ratio (OR), confidence interval (CI) and P-values were calculated. P-values below 0.05 were considered to be significant.

P3-02-158
DETECTION OF SOMATIC CHANGES IN THYROID NODULES IN CZECH CHILDREN AND ADOLESCENT PATIENTS
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Objectives: Although thyroid nodules occur less frequently in children and adolescent patients than in adults, thyroid carcinomas are the eighth most frequent cancer in children and adolescents. Among them, papillary thyroid carcinomas (PTC) are the most common form. Somatic mutations in thyroid carcinomas (PTC) are the most frequent cancer in children and adolescents. Among them, papillary thyroid carcinomas (PTC) are the most common form. Somatic mutations in RET/PTC1 and RET/PTC2 rearrangements belong to the main studied genetic changes in thyroid nodules. Mutations in RET and TERT are associated with a worse prognosis and response to the therapy. RAS mutations are detected mainly in follicular variant of PTC. The aim of this study was the genetic analysis of thyroid nodules in Czech children and adolescent patients. DNA and RNA were isolated from 85 fresh-frozen thyroid nodules. Mutations in RET/PTC1 and RET/PTC2 rearrangements were analyzed by NGS using Nextera XT kit (Miseq, Illumina). Haplotypes of each genes were detected mainly in follicular variant of PTC. RET/PTC1 and RET/PTC2 rearrangements belong to the main genetic analysis of thyroid nodules in Czech children and adolescent patients. Among them, papillary thyroid carcinomas are the eighth most common form. Somatic mutations in thyroid carcinomas (PTC) are the most frequent cancer in children and adolescents. Among them, papillary thyroid carcinomas (PTC) are the most common form. Somatic mutations in RET/PTC1 and RET/PTC2 rearrangements belong to the main studied genetic changes in thyroid nodules. Mutations in RET and TERT are associated with a worse prognosis and response to the therapy. RAS mutations are detected mainly in follicular variant of PTC.

Methods: We analyzed, in vitro, the effect of irradiation in NTHY cells caused by up-regulation of NADPH oxidase DUOX1 in DNA damage and in RET/PTC rearrangement in thyroid cells at post-irradiation. Methods: We analyzed, in vitro, the effect of irradiation in NTHY cells caused by up-regulation of NADPH oxidase DUOX1 in DNA damage and in RET/PTC rearrangement in thyroid cells at post-irradiation.

Results: Preliminary data from human thyroid cells show that chromatin loading and activation from day 3 post-irradiation of the kinase ATR, which is crucial for genome integrity, is impaired respectively, by catalase, a scavenger of H2O2, and diphenileniodonium (DPI), an inhibitor of NADPH oxidases. Analysis of replication speed by DNA combing shows a decrease of the speed from day 3 post-IR, which is also reversed by DPI. Chromatin Immunoprecipitation-quantitative PCR (ChIP-QPCR) analysis shows that, while GAPDH, CCND2 genes, in addition to RET and CDD6 genes, break 30 min after irradiation due to stochastic damage, there is only an enrichment of hH2AX (a marker of double-strand breaks) in genomic regions mapping between RET and CCDC6 gene at day 4 post-irradiation. Immunohistochemistry performed on thyroid tissues showed that hH2AX is greater in PTC tissues than in normal thyroid tissues.

Conclusions: These data suggest that a radio-induced oxidative stress may promote a replicative stress involved in DNA breakage in a region between RET and CCDC6. The impact of DUOX1 as a major source of radio-induced H2O2 on the endogenous replicative stress underlying the formation of RET/PTC1 translocation is under investigation. Moreover, the expression of DUOX1 is greater in PTC tissues than in normal thyroid tissues.
**Objective:** In Korea, the national health insurance system covers the entire population. Patients with a lower socioeconomic status are supported by the medical aid system. In this study, we examined the association of the medical insurance status of thyroid cancer patients with prognostic factors and their disease-free survival outcomes after thyroidectomy.

**Methods:** We retrospectively reviewed 127 patients who underwent surgical treatment for thyroid papillary cancer at the Seoul Medical Center between 2008 and 2017. Patients were stratified into two groups based on their insurance status: the national health insurance registered group (n = 93). And the medical aid covered group (n = 34). The survival rate was calculated using the Kaplan-Meier method.

**Results:** Tumor size of the national health insurance registered group was larger than the medical aid covered group (0.83 cm vs 1.30 cm, \( p = 0.037 \)). The frequency of multifocality was 24% in the medical aid covered group and 11% in the national health insurance registered group (\( p = 0.047 \)). Metastasis at level III and IV was more frequent in the medical aid covered group (11% vs 3%, \( p = 0.029 \)). The frequency of extrathyroidal extension was 17% in the medical aid covered group and 6% in the national health insurance registered group (\( p = 0.048 \)). Multivariate analysis determined that age (\( p = 0.037 \)) and the TNM stage (\( p = 0.029 \)) were independent prognostic factors of disease-free survival. The medical insurance status was a statistically significant prognostic factor for thyroid cancer patients (\( p = 0.047 \)).

**Conclusion:** The medical insurance status reflects the socioeconomic status of a patient, and thus, it can influence prognostic factors of thyroid cancer patients.

**Introduction:** According to the subanalysis of the SELECT study, the change in tumor size conferred by lenvatinib was associated with a decline in Thyroglobulin (Tg) levels, which is often used as a measure of successful tumor treatment. Here we present one clinical case with lenvatinib, which confirms the results of clinical trial in real clinical practice.

**Case Report:** Patient N., 1957, female with papillary thyroid carcinoma TxNxM1, IV. Surgery and radioactive-iodine therapy were contraindicated because of massive tumor bulk and coexistent diseases (mellitus diabetes type 2, obesity III). Computed tomography (CT) of Dec, 16: tumor sizes: 4.63x5.7x7.8 cm left lobe, 3.3x2.6x7.8 cm right lobe, tumor activity in lungs (maximal in S9–2.1x1.8 cm), in mediastinal node (2.2 cm), the right lobe is closely attached to the trachea, deforming its lumen at the I-II cartilages level. Tg level was 359.6 ng/ml. Lenvatinib 24 mg was admitted in Apr,17. CT of June, 17 (in 8 weeks after lenvatinib administration): decrease tumor sizes (3.0x1.9x4.8 cm left lobe, 2.5x2.4x4.8 cm right lobe), tumor activity in lungs (S9–1.7x1.2 cm), in mediastinal node (1.7 cm). Partial response (>50%). Tg level was 131.7 ng/ml. CT of Feb, 18 (after 9 courses of lenvatinib): continuous decrease tumor sizes (3.0x1.4x3.4 cm left lobe, 3.6x2.5x4.1 cm right lobe), tumor activity in lungs (S9–1.5x1.3 cm). Stabilization. Tg level was 98.8 ng/ml. The adverse effects (AE) related to the treatment were stomatitis and arterial hypertension. They were reversible symptomatically and controlled by antihypertension therapy. Patient continues treatment.

**Conclusion:** Our results confirmed that lenvatinib induced expressed early-on-treatment response at 8 week after administration followed by a slower but continuous decrease in tumor size. And tumor reduction was also associated with a decline in Tg level, which was decreased to 72% of the baseline. AE were managed without dose modification of lenvatinib. Thus lenvatinib is a promising therapy that can significantly improve outcome of patients with DTC.
POORLY DIFFERENTIATED THYROID CANCER – A RARE BUT CHALLENGING DISEASE

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Introduction: Poorly differentiated thyroid cancer (PDTC) is a follicular cell neoplasm that shows limited evidence of follicular cell differentiation. PDTC is a rare malignancy, accounting for 0.3–6.7% of all thyroid cancers. It is generally considered in the middle of the spectrum between differentiated thyroid cancer (DTC) and anaplastic thyroid cancer. PDTC has more aggressive clinical behavior than DTC, often presents at an advanced stage and has a propensity for local recurrence and distant metastases. The ability of PDTC and its metastases to concentrate radioactive iodine (RAI) is crucial for the treatment. Multimodality therapy is usually applied.

Sorafenib is an emerging therapeutic option in the treatment of RAI-refractory advanced or metastatic thyroid cancer, especially with multiple pulmonary metastases.

Case Report: We present a case of a 47-year-old male who underwent thyroidectomy and modified lymph node dissection for insular variant of PDTC in the left lobe. Chest computed tomography (CT) showed pulmonary metastases before the thyroid surgery. The tumor was staged as pT4aN1aM1 according to the 7th edition of American Joint Committee on Cancer classification. High-dose RAI ablation was performed and the posttreatment whole body scan showed uptake in the right thyroid bed and right upper mediastinum. The pulmonary metastases were not RAI-avid. Three months later the control CT scan demonstrated disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST). An adjuvant external beam radiation therapy was performed to the neck and the chest. Therapy with Sorafenib was initiated and 4 months later the disease was classified as stable according to RECIST. After 1 year of targeted therapy, the patient noticed several bilateral neck masses. Fine-needle aspiration cytology proved metastatic lymph nodes of PDTC and the CT scan showed disease progression. Thyroglobulin (Tg) in the needle washout was strongly positive, as well as the serum Tg under thyroid hormone suppression.

Taking the high Tg production into consideration, a lymph node dissection followed by a second high-dose RAI therapy was recommended to achieve locoregional control of PDTC.

Conclusion: Aggressive clinical behavior of PDTC and the difference in RAI avidity of metastases require multimodality therapy and ongoing risk classification.

UNUSUAL COEXISTENCE OF FOLLICULAR THYROID CARCINOMA AND PRIMARY HYPERPARATHYROIDISM

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Introduction: Follicular thyroid carcinoma (FTC) is a well-differentiated thyroid tumor and affects predominantly females. Its incidence has decreased during the decades predominantly due to the implementation of strict medical criteria for vascular and capsular invasion and the definition of the follicular variant of papillary thyroid carcinoma (PTC) as a separate group. FTC is classified into 2 categories based on the degree of invasion: widely and minimally invasive. The main difference of FTC from PTC is the typical unifocal location and the absence of lymph node metastases. FTC is prone to early hematogenous metastases, usually to the lungs and bone.

Primary hyperparathyroidism (PHPT) is a condition of parathyroid hormone (PTH) overproduction resulting from hyperplasia or adenoma of one or more parathyroid glands. It affects predominantly women in postmenopausal age. In the recent decades PHPT has become more often an incidental finding during neck ultrasound for thyroid disorders.

Both FTC and PHPT affect women in the 6th decade of life, but their coexistence is rare.

UNUSUAL DIAGNOSIS PRESENTATION OF DIFFERENTIATED THYROID CARCINOMA: UNEXPECTED FINDS

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Background: Differentiated thyroid carcinoma (DTC) typically presents as an indolent nodal lesion with a good prognosis, most of which are accidentally discovered (by cervical ultrasound, altered palpation/inspection of the patient’s neck). In these present cases reports, both patients were diagnosed with DTC by finding metastases, one of them at a distance, through lung nodules and another in lymph node of a parathyroidectomy product. 

Cases Report: First case, a 48-year-old woman with chronic renal disease in dialysis and tertiary hyperparathyroidism, underwent parathyroidectomy for posterior implant in the upper limb. During the histopathological evaluation of the parathyroidectomy product, metastatic papillary carcinoma was observed in the cervical lymph node, suggestive of a primary thyroid site. Subsequently, the patient underwent total thyroidectomy, with left cervical emptying surgery. Anatomopathologic of thyroidectomy product confirms papillary carcinoma, with a classic, follicular and oncocytic variant of 1.1 cm.

Second case, a 76-year-old male patient, a former smoker, started with dyspnea on minimal efforts. Report of total thyroidectomy 40 years ago, for goiter. He underwent chest tomography with evidence of multiple bilateral pulmonary nodules, and it was indicated biopsies of lesions. Histopathological findings revealed moderately differentiated adenocarcinoma with a follicular architectural pattern and immunohistochemistry suggestive of a primary thyroid site. Patient was then submitted to radioiodine therapy (cumulative dose of 320 mCi), presenting an unsatisfactory biochemical response.

Conclusions: Papillary thyroid carcinoma commonly presents regional lymph node metastases, as in the first case. On the other hand, follicular thyroid carcinoma usually presents distant metastasis, with bone or pulmonary involvement, as in the second case. However, due to the indolent nature, the metastatic disease will rarely be the initial presentation of DTC. The usual manifestation occurs by nodular goiter or compressive symptoms (dysphagia, dyspnea, hoarseness, local pain), which results in detailed investigation. In addition, many cases are accidentally diagnosed by performing examinations for other causes. Although DTC is commonly investigated through fine needle aspiration (FNA) of suspected thyroid nodules, the clinical cases presented show that unusual forms of diagnosis are possible, but unfortunately occur in more advanced stages of the disease, presenting a more reserved prognosis.
Background: Papillary and follicular carcinomas are considered differentiated thyroid carcinomas and are responsible for at least 94% of thyroid carcinomas. In these cases, distant metastases are rare, representing the most frequent lung and bone sites. In this case report, we described a patient with follicular variant of papillary carcinoma whose onset of illness was lumbar compressive symptoms due bone metastasis.

Case-Report: Patient, 57 years old, female, with diagnosis of metastatic follicular variant of papillary carcinoma (pT1NOM1). Referral lumbar pain for 3 years and muscle weakness in right leg, with CT scan of lumbosacral spine, with evidence of expansive massive, vascularized solid formation in right L5 and sacral wing showing signs of invasion of the vertebral canal, adjacent muscle planes and right iliac bone, measuring 9.6 × 8× 7.8 cm. Subjected to paravertebral lesion biopsy, with diagnosis of metastatic follicular variant of papillary carcinoma. She performed US of thyroid, with multiple bilateral solid nodules of variable dimensions, the largest calcified in the left lobe, 15 mm. The patient underwent total thyroidectomy with anatomopathological evidence of papillary carcinoma, multifocal, follicular variant, measuring 1 cm, 0.4 cm and 0.3 cm, without vascular, capsular or perineural invasion. Subsequently, submitted to local external radiotherapy for severe pain, 5 sessions of 4 Gy (accumulated dose 20Gy), with partial improvement. During follow-up, chemoembolization of the right internal iliac artery branch and right L4-Ilmum artery was performed with hystoacril and lipiodol, with significant reduction of pain and muscle weakness. After 4 months, MRI was performed with evidence of tumor reduction of approximately 24%, with a lesion of 7.3×7.3×5.8 cm. Distant metastases of differentiated thyroid carcinoma are rare, but represent an important clinical morbidity factor, especially when it results in compressive symptoms, as strong pain and progressive muscle weakness. Radiotherapy and chemoembolization represent possible therapeutic options in cases of unfeasibility to use tyrosine kinase inhibitors or surgical impossibility, such as unresectable lesions or high cardiovascular risk.
PAPILLARY THYROID MICROCARCINOMA
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Introduction: According to the World Health Organization, papillary thyroid microcarcinoma (PTmC) is a papillary thyroid cancer (PTC) measuring 10 mm or less in size. There has been a recent worldwide increase in the incidence of thyroid cancer, largely attributed to an increase in the incidence of PTC and more precisely to an increase in the incidence of PTmC. The management of PTmC continues to be an area of controversy and has resulted in wide differences in recommended management, ranging from observation to an aggressive approach with total thyroidectomy, central lymph node dissection and radioiodine ablation therapy.

Case Report: We present the case of A.M 29 years of age who underwent dexter lobectomy for a papillary thyroid microcarcinoma. Before the dexter lobectomy we have these results Tsh = 1.1 ft4 = 3.5 ft4 = 13.5 tiroglobulina 63.9, Calcitonin 1.5, Ca 2.36, phosphorous 1.29, magnesium 0.71 Thyroid ultrasonography: Lob dexter with a size of 25×16 mm, a solid nodule with 44×14×31. Near is another nodule 7 mm. Lob sinister with size of 22×16 mm, a solid nodule with 44×10 mm. Trachea is deviated from the left. No Lymphadenopathy. Fine needle aspiration of dexter lobule. Typical tiroeclita, mature lymphocyte and coloidal substance. Negative Tir 2. It is referred to intervention of dexter lobectomy. The material is exame by anatomopathologist. Macroscopically is a dark neoforation about 3 cm. In the distance of 0.7 cm from the first nodule is a second nodule about 0.6 cm. Diagnosis: papillary thyroid microcarcinoma. pT1a (m).

Diagnosis and Treatment

PAPILLARY AND FOLLICULAR THYROID CANCER IN AMERICAN THYROID ASSOCIATION HIGH RISK PATIENTS
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Background: The 2015 American Thyroid Association (ATA) risk stratification system for differentiated thyroid cancer (DTC) is designed to predict disease recurrence, but earlier studies showed that it is also a predictor of disease-specific survival. However, these studies only comprised patients with papillary thyroid cancer (PTC) or made no distinction between PTC and follicular thyroid cancer (FTC). Therefore, we aimed to compare survival and disease-specific recurrence, but earlier studies showed that it is also a predictor of disease-specific survival. However, these studies only comprised patients with papillary thyroid cancer (PTC) or made no distinction between PTC and follicular thyroid cancer (FTC). Therefore, we aimed to compare survival and disease-specific recurrence, but earlier studies showed that it is also a predictor of disease-specific survival.

Table 1. Comparison of diagnostic performances between CS and combined CS and CB (for Abstract P3-04-170)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Criteria 1</th>
<th>Criteria 2</th>
<th>Criteria 3</th>
<th>Criteria 4</th>
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<tbody>
<tr>
<td></td>
<td>CS</td>
<td>CS+CB</td>
<td>P</td>
<td>CS</td>
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<tr>
<td>Sensitivity</td>
<td>97.26%</td>
<td>99.23%</td>
<td>0.001</td>
<td>94.66%</td>
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<tr>
<td>Specificity</td>
<td>44.12%</td>
<td>73.91%</td>
<td>&lt;0.001</td>
<td>52.80%</td>
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<td>Accuracy</td>
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<td>&lt;0.001</td>
<td>85.34%</td>
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<tr>
<td>PPV</td>
<td>87.50%</td>
<td>97.92%</td>
<td>&lt;0.001</td>
<td>87.50%</td>
</tr>
<tr>
<td>NPV</td>
<td>80.00%</td>
<td>88.54%</td>
<td>0.123</td>
<td>73.91%</td>
</tr>
</tbody>
</table>

Poster Presentations
response to therapy between PTC and FTC in a European population of ATA High Risk (ATA-HR) patients.

**Methods:** Adult patients diagnosed and/or treated for DTC at the Erasmus MC between January 2002 and December 2015, and fulfilling the ATA-HR 2015 criteria, were included. Demographical, disease, treatment, ATA response to therapy at final follow-up, and mortality characteristics were retrospectively obtained from patient records. Overall survival (OS) and disease specific survival (DSS) were analyzed using the Kaplan-Meier (KM) method. The Cox proportional hazards model was used to compare the effect of PTC and FTC on survival.

**Results:** We included 237 patients (62% women) with ATA-HR; 143 patients (60%) had FTC, the others FTC. Mean age was 59 years and median follow-up 71 months. During follow-up, 83 patients died of which 62 (26%) due to thyroid cancer. No significant differences between PTC and FTC regarding disease specific mortality were seen.

At final follow-up, 61 patients (26%) had excellent response, while 130 (55%) had persistent structural disease. There was no significant difference between PTC and FTC for these outcomes.

For DTC, 10-year OS and DSS were 59% and 68% respectively. Adjusted for age and sex, no significant differences for both OS and DSS were seen between PTC and FTC (p = 0.95 and p = 0.65 respectively).

Further, for FTC, old patients (age ≥ 55) had a significant worse DSS than young patients (age < 55); 10-year DSS 54% vs. 87%, Hazard Ratio 5.4, p < 0.001. This pattern was also seen for PTC and FTC separately (p < 0.001 and p = 0.039 respectively).

**Conclusion:** In a European population of ATA High Risk patients, no significant differences between PTC and FTC regarding both OS and DSS were seen. Additionally, over 50% of both FTC and PTC patients had persistent structural disease at final follow-up. Furthermore, age is a major determinant of DSS in these High Risk patients both for PTC and FTC.

**P3-04-174**

**DIGOXIN TREATMENT FOR HEART DISEASE IS ASSOCIATED WITH A HIGHER TUMOR DIFFERENTIATION STATUS AND FAVORABLE CLINICAL OUTCOME IN NON-MEDULLARY THYROID CANCER PATIENTS**

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**Objectives:** Non-medullary thyroid cancer (NMTC) is the most frequent endocrine tumor with in most cases a good prognosis. Unfortunately, 30–40% of patients with metastatic NMTC are unresponsive to 131I radioactive iodide (RAI) treatment as a result of tumor dedifferentiation. Autophagy has emerged as an important mechanism involved in NMTC dedifferentiation. Furthermore, activation of autophagy by cardiac glycosides such as digoxin has been demonstrated to induce effective in vitro redifferentiation of poorly differentiated and anaplastic thyroid cancer cell lines, thereby restoring sensitivity to RAI treatment. However, the in vivo effects of digoxin treatment on tumor differentiation in NMTC patients remains unclear.

**Methods:** In the present retrospective clinical study, archived tumor material obtained from NMTC patients that received digoxin as treatment of heart disease before and after NMTC diagnosis was investigated. By a national PALGA-PHARMO database search, 11 digoxin-treated NMTC patients were included encompassing all major histological NMTC subtypes. In addition, 11 control NMTC patients never treated with digoxin were included that were matched for age, gender, histological tumor type, TNM staging, genetic profile and co-medication. Molecular tumor characteristics were analyzed and clinical follow-up data were gathered.

**Results:** Assessment of autophagy activity by immunofluorescent LC3 staining indicated that tumor material from digoxin-treated NMTC patients exhibited significantly higher autophagy activity as compared to tumor material of matched control NMTC patients. Whole transcriptomics analysis was performed by RNA sequencing demonstrating profoundly higher expression of thyroid-specific genes in all 11 tumor tissues obtained from digoxin-treated NMTC patients as compared to the matched control NMTC patients. Digoxin-treated NMTC patients also showed favorable clinical outcomes compared to matched control NMTC patients not treated with digoxin.

**Conclusions:** Treatment of NMTC patients with digoxin before and after NMTC diagnosis is associated with a higher tumor differentiation status as compared to tumor tissue from closely matched NMTC patients not treated with digoxin. These in vivo data confirm our previous in vitro findings and provide accumulating evidence that digoxin could represent a beneficial adjunctive treatment modality to improve RAI sensitivity in patients with RAI-refractory thyroid carcinoma.

**P3-04-173**

**CURATIVE THERMAL-ABLATION OF BONE METASTASES TO PREVENT VERTEBRAL RELATED EVENTS IN PATIENTS WITH NON-MEDULLARY THYROID CARCINOMA**

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**Purpose:** Bone metastases are frequent in patients with metastatic non-medullary thyroid carcinoma and results in high rate of complications, especially in the spine. A preventive curative treatment of vertebral metastases (VMs) could be of interest to decrease the occurrence of Vertebral Related Events (VREs).

**Methods:** This single center study retrospectively evaluates a preventive strategy that used thermal-ablation techniques (cryotherapy or radiofrequency-ablation) to treat VMs in patients with metastatic non-medullary thyroid carcinoma. The inclusion criteria were: asymptomatic VMs and thermal-ablation in a curative intent of all existing VMs. During the follow-up, new VMs were not considered as additional thermal-ablations because local destruction strategy was challenged by bone disease progression and systemic approaches were preferred. These untreated metastases were used as a control group in our study. Patients’, tumors’ and treatments’ characteristics were reported. The entire imaging file during the follow-up were reviewed to report the rate of complete local treatment (no residual tumor at MRI and/or PET-CT scan) at 3, 12 and 24 months, the occurrence of new VMs and the rate of VREs (vertebral fracture, epiduritis or spinal cord compression). We compared the rate of VREs between the complete and incomplete local treatments and between the treated and the untreated VMs.

**Results:** Between January 2008 and February 2017, 28 patients had thermal-ablation to cure all their VMs (n = 41 treated VMs). The mean follow-up for treated VMs was 2.7 ± 1.6 [1.0–6.6] years. The rate of complete local treatment at 3, 12 and 24 months were 87.8%, 82.9% and 75.6% respectively. The rate of VREs was significantly lower for metastases that demonstrated a complete local treatment at 3 months: 0% vs. 60% (epiduritis, n = 3), p = 0.001, odds ratio = 0.4 [95% CI = 0.137–1.17]. New VMs occurred in 11 patients (=19 untreated VMs). The mean follow-up for untreated VMs was 2.4 ± 1.2 [1.1–5.9] years. Despite the lack of difference in terms of metastases’ characteristics, the rate of VREs was significantly lower for treated VMs compared to untreated VMs: 7.3% (epiduritis, n = 3) versus 36.8% (epiduritis, n = 6 and vertebral fracture, n = 1), p = 0.008, odds ratio = 0.135 [95% CI: 0.030–0.607]. VRE free survival at 2 years was higher in treated VMs compared to the untreated VMs: 92.9 ± 2.9% versus 63.8 ± 5.9% p = 0.003.

**Conclusion:** A curative thermal-ablation of VMs decreases the rate of VREs in non-medullary thyroid carcinoma patients.
P3-04-175
METASTATIC PAPILLARY THYROID CARCINOMA TREATED WITH LENVATINIB
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Introduction: Papillary thyroid carcinoma (PTC) accounts for approximately 85% of thyroid cancers. Most cases are clinically indolent and the 10-year-disease-specific-mortality for differentiated thyroid carcinoma (DTC) is less than 5%. Primary treatment is surgery, sometimes followed by radiiodine ablation (RAIT), with systemic therapies reserved for patients with metastatic disease refractory to surgery and RAIT. Lenvatinib is an oral tyrosine kinase inhibitor (TKI) and its use in PTC results from the SELECT trial in which it was demonstrated that increases survival in patients with recurrent/refractory PTC. The negative side effects of this therapy must be addressed specially in the management of toxicity with these drugs.

We report a case of a patient with PTC treated with lenvatinib.

Case Report: A 34-year-old female presented with a cervical mass. Neck ultrasound (US) showed a solid, hypoechoic nodule with 45 mm and irregular margins in the right lobe of the thyroid with suspicious ipsilateral lymph nodes. On histology, it was compatible with PTC and in January 2013 she was submitted to a total thyroidectomy with right modified radical neck dissection. Histology showed PTC with capsular, lymphatic and vascular invasion (pT4N1b M0 R1) and extra-thyroidal extension. Following surgery, she underwent RAIT with 150 mCi of 131I.

In March 2014, because of high thyroglobulin (Tg) levels with a negative US, a PET-scan was performed and showed pulmonary metastases. The patient underwent a second RAIT with 200 mCi of 131I. Nine months after the patient was admitted due to abscesses in lung metastases. The full 24 mg daily dose was not tolerated due to side effects (gastro-intestinal, hypertension and proteinuria) and was reduced to 14 mg daily.

She was proposed for treatment with lenvatinib 24 mg/day. There was a decrease in the Tg levels and a reduction in the metastatic lesions. The full 24 mg daily dose of lenvatinib was well tolerated and proteinuria returned to 1+ for >3+ proteinuria, lenvatinib treatment should be interrupted until proteinuria returns to 1+. For patients with chronic, resistant proteinuria, lenvatinib treatment should be stopped. Skin toxicities should be managed with moisturisers or emollients and soap substitutes.

Conclusion: These guidelines represent the first UK published guidance on lenvatinib in this setting. Careful management of emergent AEs for patients initiated on lenvatinib is essential to enable patients to remain on the optimal dose regime. Prophylaxis, regular monitoring and symptomatic management with appropriate short treatment breaks and, for persistent AEs, dose reductions, are recommended.

P3-04-176
MANAGEMENT OF ADVERSE EVENTS DURING TREATMENT WITH LENVATINIB FOR THYROID CANCER
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Background: Lenvatinib (Lenvima®) is an oral multi-kinase inhibitor approved for the treatment of adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma refractory to radioactive iodine (RR-DTC) which has recently been made available in the UK. A review of the current evidence-based literature was undertaken to inform the development of expert consensus-based guidance for the routine management of adverse events (AEs) associated with lenvatinib for RR-DTC.

Methods: PubMed was searched on October 24th 2017 using the search terms ‘lenvatinib’ and ‘thyroid cancer’. Expert opinion-based recommendations for the clinical management of AEs were developed by UK experts in thyroid cancer and drug development based on the available evidence and their clinical experience at a roundtable meeting.

Results: Blood pressure (BP) should be monitored 1 week after initiation of lenvatinib and every 2 weeks for the first 2 months. For patients with systolic BP ≥140 mm Hg to <160 mm Hg or diastolic BP ≥90 mm Hg to <100 mm Hg, lenvatinib therapy should be continued but antihypertensive therapy initiated or intensified. For patients who remain hypertensive, a treatment break can be considered with lenvatinib reinitiated at a reduced dose once the patient’s blood pressure has stabilised for at least 48 hours. For diarrhoea, interventions should be focused on symptomatic management when Grade 1 or 2 diarrhoea first emerges. Initial treatment should be with loperamide. A 1-week treatment interruption should be considered if diarrhoea persists.

Conclusions: These guidelines are based on the available data and expert opinion and are intended to help inform the management of AEs with lenvatinib. They are reviewed on a regular basis and updated as more evidence is available.

P3-04-177
THE USING OF THYRO-ID GENETIC PANEL IN THE DETECTION OF SOMATIC MUTATIONS IN THYROID NODES
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Objectives: The thyroid nodules are preoperatively sonographically examined and a sample (fine needle aspiration biopsy; FNAB) is taken from the suspicious nodules. FNAB is important for a cytological assessment and FNAB is important for the diagnosis of papillary thyroid cancer (PTC). The genetic analysis could precise diagnosis and solve undistinguished cases. One approach in the genetic analysis is search of mutations in genes using the next generation sequencing (NGS).

Methods: DNA was isolated from 46 FNAB with Bethesda system 3–6. Samples were analyzed by NGS using Thyro-ID kit (4 bases) focused on analysis of 14 genes. Genes were KRA S (exon 2, 3 and 4), NRAS (exon 2 and 3), HRAS (exon 2 and 3), BRAF (exon 15), EGFR (exon 18–21), TP53 (exon 4–9), PTEN (exon 5–8), PIK3CA (exons 10 and 21), CDKN2A (exon 1 and 2), NOTCH (exon 26 and 27), CTNNB1 (exon 1), AKT1 (exon 1), TERT (promoter) and TSHR (exon 6, 8 and 9) were included in this kit. Targeted exons of genes were amplified by a mixture of specific primers and libraries were sequenced on Miseq (Illumina).

Results: The mutation Q66K with synonymous variant G60G in KRA S gene (exon 3) in 1 of 46 (2%) patients was found. The mutations Q61R (exon 3) in 6 of 46 (13%) patients and Q66K in 1 of 46 (2%) patients in NRAS gene were found. The mutation Q61R in HRAS gene (exon 3) in 2 of 46 (4%) patients was found. The pathogenic mutation V600E in BRAF gene (exon 15) in 7 of 46 (15%) patients was found, of which the variant C228T in TERT gene promoter in 2 patients was found. In other genes known polymorphisms or unknown variants were found that will be confirmed. In total, mutations were found in 4 of 24 (17%) patients with Bethesda category 3, in 5 of 10 (50%) patients with category 4, in 6 of 10 (60%) patients with category 5 and in 2 of 2 (100%) patients with category 6.

Conclusion: This NGS panel is very sensitive and is able to find many mutations from the large spectrum of genes from a small amount of material in patient samples. In summary, the detection rate of mutations was 17 of 46 (37%). The highest mutation detection rate was in Bethesda category 6.

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P3-04-178

CLINICAL VALUE OF A PREABLATION SCAN IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

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The standard treatment in patients with differentiated thyroid carcinoma (DTC) consists of thyroidectomy and subsequent I-131 ablation. A preablation scan is a diagnostic I-131 scan before starting ablation, potentially altering later clinical management. However, in the current guidelines, there is no consensus regarding the use of a preablation scan nor regarding treatment adjustments based on an increased preablation I-131 uptake. Therefore, the objective of this study was to evaluate the value of a preablation scan in the treatment of differentiated thyroid carcinoma.

Methods: We included 262 consecutive DTC patients diagnosed from January 2005 until July 2015 at the University Medical Center Groningen. We collected data on patient characteristics, preablation scan outcomes, and treatment. The primary endpoint was the percentage of patients with an uptake >5%. In addition, we performed binary logistic regression to study risk factors for an uptake >5%. We studied altered clinical management and clinical complaints. Finally, we studied the association between uptake and ablation success.

Results: The uptake at the preablation scan was >5% in 52 of 262 patients (19.8%). Risk factors for an uptake >5% were a two-step surgical procedure (OR 2.7, 95% CI 1.5–5.0), and surgery in non-tertiary hospital (OR 4.1, 95% CI 1.9–8.9). In 32 of 52 patients (61.5%) with an uptake >5% the clinical management was changed by decreasing I-131 dosage (n = 7), performing additional surgery (n = 5) and prescribing anti-inflammatory drugs (to avoid radiation thyroiditis and neck edema) (n = 24). In patients with an uptake >5%, 15 out of 52 patients (28.8%) reported clinical complaints after I-131 ablation. An increased uptake at the preablation scan was not associated with a worse ablation success (OR 1.0, 95% CI 0.9–1.1).

Conclusion: Based on the current findings we conclude that the preablation scan proves to be of value for clinical management and treatment changes in the setting of a tertiary academic endocrine clinic. One out of five DTC patients had an uptake >5%. The preablation scan results led to alterations of treatment including increased I-131 dosages, additional performed surgeries and additional prescription of anti-inflammatory drugs.

P3-04-179

PROGNOSTIC VALUE OF TNM CLASSIFICATION SYSTEM FOR DIFFERENTIATED THYROID CANCER (8TH EDITION VERSUS 7TH EDITION)

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Introduction: The TNM classification system of the AJCC/UICC is the most used staging system for differentiated thyroid carcinoma (DTC). The 8th edition introduced major changes, including age cut-off, relevance of extrathyroidal extension and classification of nodal disease.

Our goal was to assess the prognostic value of the 8th edition compared to the 7th edition, in patients with DTC.

Methods: Retrospective study of 913 consecutive patients, who underwent surgery for DTC between 2000 and 2012. Response to therapy was assessed using the 2015 ATA classification system. The association between variables was assessed using chi-square test.

Results: Based on the 8th edition, 71% of previously T3 patients (due to extrathyroid extension) were downgraded to T1/T2; 35% were downstaged due to the classification of nodal disease and 23% were downstaged due to the change of the age cut-off from 45 to 55 years old.

Persistent disease was more common in T3 patients who were downgraded to T1 (11% versus 3% p = 0.001) or T2 (37% versus 7% p = 0.005) compared to T1 or T2 patients, respectively, according to the 7th edition. These patients were more likely to have biochemical incomplete response (T1 patients: 7% versus 2% p = 0.007; T2 patients: 19% versus 3%, p = 0.001) but there were no differences regarding structural incomplete response or disease specific mortality. T3 patients downgraded to T1 were also more likely to be treated with radioiodine (13% versus 95%; p = 0.001).

N1 patients who were downgraded to stage II were more prone to have persistent disease compared to stage II patients according to the 7th edition (N1a: 27.3% versus 4.8%; p = 0.003; N1b 37.2% versus 12.5%; p = 0.001).

N1a patients were also more likely to have biochemical incomplete response (12.5% versus 1.5%; p = 0.025) and N1b, structural incomplete response (25% versus 7%; p = 0.012). There were no differences regarding recurrence of disease or disease-specific mortality.

There was no significant difference regarding outcome between patients who were downstaged due to the age cut-off and stage I/II patients with <45 years old, namely recurrence rate, persistence of disease or disease-specific mortality.

Discussion: Staging of DTC according to the 8th edition AJCC/UICC staging system results in marked downstaging. Biochemical incomplete response is more common in T3 patients who were downgraded to T1/T2 and N1 patients downstaged to stage II. Structural incomplete response is more common in N1b patients downstaged to stage II. Although this may be relevant for disease management, it does not seem to affect disease-specific mortality.

P3-04-180

EVALUATION OF THE EFFECT ON RADIOIODINE AVIDITY BY PATIENT AGE AND THE INTERVAL FOR RADIOIODINE THERAPY: A RETROSPECTIVE STUDY

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Aims: It is well known that younger patients will have more benefits from radioiodine therapy. On the other hand, from clinical experience, we know that elder patients are likely to have less benefits. Meanwhile, Higashi and colleagues has reported that the interval between thyroidectomy and radioiodine therapy will also impact the outcome, and radioiodine therapy was recommended within 6 month from the initial surgery.

The aim of this study is to retrospectively evaluate the effect of the age and the interval for radioiodine therapy by using radioiodine avidity of the metastatic lesions of papillary thyroid cancer (PTC).

Methods: From January 2007 to December 2016, 136 adult cases of initial radioiodine therapy for distant metastasis of PTC were performed. The total group had 27 male, 109 female, average age of initial surgery was 52.9. The total group was compared by dividing the total group into three groups by age of initial surgery: 21–40, 41–60 and over 61. The total group was also divided by the interval of 24 month for initial radioiodine therapy. Finally, the three groups divided by age was once more divided by 24 month interval for initial radioiodine therapy. Avidity rates of each group was compared.

Results: The total group had only 23.5% in avidity rate. In each age group, the avidity rate was 21–40:46.3%, 41–60:15.8% and over 61:12.3%. The group which had radioiodine therapy within 24 month had avidity rate of 39.6% and was significant compared to those after 24 month (avidity rate 13.3%, p < 0.01). With each age group divided by interval of 24 month, avidity rate were higher when treated earlier (21–40:62.5% vs 36.0%, 41–60:55.6% vs 3.4%, over 61:21.4% vs 3.4%). Significance in avidity rate was only seen in the eldest group compared to the youngest group when radioiodine therapy were given within 24 month (p < 0.01). Only the middle age group had significance by the interval for initial radioiodine therapy, (p = 0.00001)

Even with the comparison of avidity rate only, patients under 40 at the time of initial surgery had the best avidity rate. Patients 41–60 at the time of initial surgery had an acceptable avidity rate if treated within 24 month.

Conclusions: Radioiodine therapy can have benefits for patients with distant metastasis of PTC, especially if treated within 24 month after initial surgery and younger than 60 when initial surgery was performed.
P3-05-181

CHALLENGING CASES DURING THYROID ULTRASOUND

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Objective: To visualize troublesome lesions and structures during thyroid ultrasound examination and to improve your ability to reach an accurate diagnosis in a brief examination time.

Method: During recent 10 years of experience in thyroid ultrasound examination, we have often encountered diverse troublesome lesions and normal variations. We tried to demonstrate and contrast these confusing cases with typical findings.

Results: Pseudo-lesions mimicking thyroid malignancy
Extrathyroidal abnormality;
1. Pharyngoesophageal diverticulum
2. Parathyroid adenoma
3. Extrathyroidal fat tissue
4. Bony structures; the transverse vertebral process of cervical spine or a cervical rib
5. Artifacts caused by SCM muscle interface
6. Incomplete ossification of thyroid cartilage
7. Filler injection

Intrathyroidal abnormality
1. Focal parenchymal disease; subacute thyroiditis
2. Vascular structures; confluence of intrathyroidal vessels
3. Thyroid malignancy, easy to be missed
4. Diffuse sclerosing variant
5. Artifacts caused by SCM muscle interface
6. Incomplete ossification of thyroid cartilage
7. Filler injection

Other various cases of malignancies

Conclusion: Through this scientific exhibition, you would be acquainted with relatively common problems that cannot be missed while doing a thyroid ultrasound and also you could be supported to improve your ability to reach an accurate diagnosis in a brief examination time.

P3-05-182

IN-HOSPITAL AND COMMUNITY FOLLOW-UP FOR LARGE THYROID NODULES: RISK STRATIFICATION, PATIENTS’ SELECTION AND OUTCOME

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Objective: The aim of the study was to assess the outcome of clinical follow-up and risk stratification in large thyroid nodules managed in hospital and within the community.

Methods: All patients with thyroid nodules ≥3 cm who underwent ultrasound-guided FNA biopsies between 1/2009–1/2013 were followed until August 1st 2017. Follow-up data was collected using an integrated hospital-community system. Collected data included demographics, sonographic descriptions, cytology and histology.

Results: 141 nodules from 131 patients were included. Of these, 37/141 (26%) nodules were referred for surgery on initial investigation and 12/37 (32%) were found to be malignant. The remaining 104/141 (74%) were referred for follow-up. In the follow-up group, 41 (39%) underwent repeated FNA, 37 (36%) were followed clinically, and 26 (25%) did not comply with follow-up recommendations. Median follow-up was 53.5 months. None of the patients in the cohort developed a regional or distal disease. During the follow-up period, additional 24 nodules from 23 patients underwent thyroid operations and malignancy was found in a single nodule (4%). When comparing indications for surgery, 22 nodules (59%) operated initially were due to non-benign cytology, compared with a single nodule (4%) in nodules operated during follow-up. Non-benign cytology was significantly associated with malignancy when compared to other indications such as growth and patients’ wishes (p = 0.01). The false negative (FN) rate of benign aspiration was 6.7% (2/30).

In a univariate analysis, hypoechochogenicity, irregular margins and overall TIRADS score were significantly associated with malignancy (p = 0.012; p < 0.001 and p = 0.003, respectively). Microcalcifications demonstrated a borderline significant association with malignancy (p = 0.081).

The mean change in a nodule size during the follow-up was a 7% reduction, with no significant trend of change over time.

Conclusion: Large thyroid nodules should be managed similarly to other thyroid nodules, with selection for surgery based on clinical and sonographic suspicion rather than on size alone.

P3-05-183

ULTRASONOGRAPHIC CHARACTERISTICS OF THE HYPERFUNCTIONING THYROID NODULE AND ASSOCIATED FACTORS FOR SUPPRESSED TSH

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Objective: Thyroid scan is a good tool for diagnosis of hyperfunctioning thyroid nodule (HTN), however it has been limited in use in a primary clinical practice, because of its inconvenience and limited accessibility. This study aimed to analyze ultrasonographic (US) characteristics of thyroid nodule to predict hyperfunctioning.

Methods: We included 114 patients who presented with hot spots on thyroid scan from 2008 to 2017 in a tertiary hospital. Among them, we analyzed US characteristics of 73 HTN patients except toxic multi-nodular goiter, unclear US images, history of surgery or medication for thyroid disease. The control group consisted of 188 patients with cold lesion on thyroid scan during the same period. Nodule size was analyzed using maximal diameter and 3D-estimated volume. Malignancy risk of each HTN was classified by EU-TIRADS. Suppressed TSH was defined as serum level lower 0.4 uIU/mL. We compared US characteristics of HTNs between two groups with or without TSH suppression.

Results: The mean age of patients with HTN was 46.9 ± 16.3 years, and women was 58 (79.5%). Nodule size was 2.20 ± 1.2 cm and volume was 5.2 ±
ROLE OF HISTOGRAM ANALYSIS OF GRAYSCALE SONOGRAMS TO DIFFERENTIATE THYROID NODULES IDENTIFIED BY 18F-FDG PET-CT: PRELIMINARY REPORT

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Objective: We assessed whether histogram analysis using gray scale sonogram can differentiate benign nodules, primary thyroid malignancies and non-thyroidal metastatic nodules in thyroid nodules detected by 18F-FDG PET-CT.

Methods: From January 2010 to June 2013, 71 thyroid nodules 1 cm or larger from 71 patients identified by 18F-FDG PET-CT that underwent subsequent gray-scale ultrasound with ultrasound-guided fineneedle aspiration or core needle biopsy were included in this study. Each gray-scale ultrasound feature was retrospectively reviewed and categorized according to Korean thyroid imaging reporting and data system (K-TIRADS). Histogram parameters (skewness, kurtosis, intensity, uniformity, entropy) were extracted from gray-scale ultrasound. Statistical analysis was performed using chi-square test or Mann-Whitney test.

Results: The 71 nodules comprised 30 (42.3%) benign thyroid lesions, 30 (42.3%) primary thyroid malignancies and 11 (15.4%) metastatic lesions to thyroid. Tumor size, K-TIRADS, histogram parameters were significantly different between benign and malignant thyroid nodules (p < 0.011, p < 0.000, and p < 0.02), and metastatic thyroid nodules had a higher rate of malignancy (46% vs 24%, p < 0.0001). The overall malignancy rate did not significantly differ in the two periods. Sensitivity and specificity of the high and low risk sub-classification were similar in the two previous study (2000–2008) carried out using the Bethesda reporting system. The purpose was to determine the malignancy risk associated with each class, the sensitivity, the specificity, the PPV, the NPV of both reporting systems, to ascertain any differences between the two classifications.

From 2009 to 2016, 461 nodules showing risk of malignancy according to SIAPEC (TIR 3A, TIR 3B, TIR 4, TIR 5) were selected; 555 nodules encompassing similar risk categories were collected between 2000 and 2008. All nodules underwent surgery and histological examination. In the 2009–2017 series, the malignancy rate was 10% in TIR 3A class, 46% in TIR 3B, 97% in TIR 4 and 100% in TIR 5. The rate of malignancy was significantly different between TIR 3A and TIR 3B (κ2 = 32, p = 0.000). In the 2000–2008 series the malignancy rate was 5% in the class named by us as THY2a (corresponding to AUS/FLUS of the Bethesda classification), 25% in THY3b class (corresponding to Follicular neoplasia), 78% in THY4 and 98% in THY5. In 2009–2017 TIR 3 class as a whole significantly increased from 53% to 65% vs 2000–2008 (p = 0.00), while the TIR 4 class significantly decreased from 10% to 9% (p = 0.000); TIR 3B increased from 35% to 49% (p = 0.000), with a higher rate of malignancy (46% vs 24%, p < 0.0001). The overall malignancy rate did not significantly differ in the two periods. Sensitivity and specificity of the high and low risk sub-classification were similar in the two periods. Statistical analysis confirmed a good sensitivity (93% with 95% CI 90.3–96.2%) and a high NPV (90.4% with 95% IC 86.4–93.4%).

Both Bethesda and SIAPEC classification systems showed similar power in predicting malignancy in the whole series of thyroid nodules. The higher rate of malignancy in TIR 3b category in 2009–2017 could be due to the recent trend to classify as TIR 3B those specimens with nuclear features of papillary carcinoma too mild or focal to be included in the suspicious category (TIR 4), as proposed by SIAPEC.
Although the FNR did not increase as the nodules enlarged among the overall nodules \( (p = 0.766) \), the FNR was higher in nodules with a high suspicion US pattern (K-TIRADS 5) \( (p < 0.001) \) and there was a trend towards an increasing FNR as the score of K-TIRADS increased \( (p < 0.001) \). In low or high suspicion nodules (K-TIRADS 3 and 5), there was no significant difference in FNR according to the nodule size; however, among the intermediate suspicion nodules (K-TIRADS 4), the FNR was significantly higher in large nodules \( \geq 3 \ cm, \ p = 0.039 \) with a trend towards an increasing FNR as the nodules enlarged \( (p = 0.028) \).

**Conclusion:** The impact of nodule size on the FNR differed according to the US pattern. A large nodule size \( (\geq 3 \ cm) \) showed a higher FNR than smaller nodules among the intermediate suspicion nodules.

**P3-05-187**

**THE LEVEL OF TSH AS A RISK FACTOR OF MALIGNANCY OF THYROID NODULES**

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TSH is a factor of development, which stimulates proliferation of thyroid nodules. However, its role as malignancy predictor of thyroid nodules is still under discussion.

**Methods:** The records of all patients with nodules from January 2016 till February 2018 in our clinic were evaluated. Patients with known thyroid cancer and autoimmune thyroid diseases were excluded. Patients underwent fine-needle aspiration biopsy (FNAB) under ultrasonographic guidance. The level of TSH was investigated in all cases. Patients with nodules Bethesda category IV-V and category II \( \geq 40 \) mm underwent histologic study to define the final diagnosis.

**Results:** The FNAB analysis of 138 thyroid nodules was carried out. All the patients were divided according to Bethesda categories. The mean age was 55.3. The mean figures of TSH level were 1.68 mkU/ml. In the category Bethesda I an average level of TSH was 1.6 mkU/ml. The number of patients with TSH more than 2.5 mkU/ml was 14.2%. In the category Bethesda II an average TSH level was 1.23 mkU/ml, the number of patients with TSH more than 2.5 mkU/ml was 13%. In the category Bethesda III an average TSH level was 1.74 mkU/ml, the number of patients with TSH more than 2.5 mkU/ml – 14.8%. In the category Bethesda IV an average TSH level was 1.9 mkU/ml, the number of patients with TSH more than 2.5 mkU/ml – 13%. In the category Bethesda V an average level of TSH was 1.6 mkU/ml. The number of patients with TSH more than 2.5 mkU/ml – 38%.

Thus, the TSH level was correlated with Bethesda category \( (r = 0.313, \ p = 0.01) \) and with histopathological diagnosis \( (r = 0.277, \ p = 0.016) \). The TSH level was higher in the category Bethesda V \( (p = 0.004) \). The number of patients with TSH \( > 22.5 \) mkU/ml was higher in the category of Bethesda V in comparison with category Bethesda II \( (p = 0.02) \). The analysis of preoperative level of patients’ TSH, who experienced FNAB, showed that TSH level was significantly higher in malignancy than in benign nodules: 2.23 mkU/ml vs 1.23 mkU/ml accordingly \( (p = 0.006) \).

**Conclusions:** TSH level could serve as a predictive risk factor of thyroid cancer.

**P3-05-188**

**SONOGRAPHICALLY ESTIMATED RISKS OF MALIGNANCY FOR THYROID NODULES COMPUTED WITH FIVE STANDARD CLASSIFICATION SYSTEMS: CHANGES OVER TIME AND THEIR RELATION TO MALIGNANCY**

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**Objective:** Over 50% of newly diagnosed thyroid nodules are either cytologically benign or presumed to be benign on the basis of low-suspicion sonographic findings. The strategies used for their long-term surveillance are based mainly on the estimated residual risk of malignancy calculated with various ultrasonographic classification systems (e.g., Thyroid Image Reporting and Data Systems [TIRADS]). We conducted a longitudinal study to evaluate the temporal stability of the initial risk estimates computed with five widely used systems and to determine whether risk-class increases during follow-up are indeed predictive of malignancy.

**Methods:** We re-analyzed data prospectively collected at a single academic referral center on 232 patients (age: 54.1 \( \pm 13.7 \) years) with 432 asymptomatic, sonographically or cytologically benign thyroid nodules at baseline (T0) and 122 new nodules that were present five years later (T5). At both time points, the sonographically-estimated risk of malignancy was calculated according to the American Association of Clinical Endocrinologists, American College of Endocrinology/Associazione Medici Endocrinologi, the American College of Radiologists’ TIRADS, the American Thyroid Association’s 2015 practice guidelines, the European Thyroid Association’s TIRADS (EU-TIRADS), and the TIRADS of the Korean Society of Thyroid Radiology (K-TIRADS).

**Results:** For T0 to T1 (13.2–29.4%) of the original nodules, depending on the system used, the estimated malignancy risk increased over the 5-year interval. Of the nodules whose baseline risk had not warranted cytological assessment, very few (6.3–8.3%) met the criteria for cytology at the 5-year evaluation. Biopsy was indicated for only 4 to 8 (3.3–6.6%) of the new nodules based on T5 risk estimates. Despite these changes, none of the 232 patients was ever diagnosed with a cancer.

**Conclusions:** Ultrasound-based risk classes of presumably benign thyroid nodules remain fairly stable over time, and changes warranting biopsy are rare indeed. The appearance of new nodules is a frequent event, but very few (<5%) are classified as high-risk, and only the 3–7% meet the criteria for cytological assessment or re-assessment. Collectively, these findings support the view that patients with presumably benign thyroid nodules can be safely followed with less intensive protocols.

**P3-05-189**

**THYROID INCIDENTALOMAS DETECTED BY 18F FLUORODEOXYGLUCOSE PET/CT**

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**Objectives:** Each year about 1500 full body 18F Fluorodeoxyglucose (FDG) positron-emission tomography/computer tomography (PET/CT) scans are performed at the University hospital in Umeå. Patients from the whole northern region are referred. Scans are mainly performed during an oncological investigation. In the literature 0.1–4.8% of these scans show an increased focal FDG uptake in the thyroid, i.e. a thyroid incidentaloma (TI). The metabolism can be semi-quantitatively assessed by a Standardized Uptake Value (SUV). A high SUV has been found to correlate with increased risk for malignancy. However, an FDG PET/CT cannot determine if a TI is benign or malignant with certainty.

There are currently no known reports regarding the frequency of malignant TIs in Swedish material. In this retrospective study the incidence of TI in Northern Sweden during 2012–2017 was assessed. Also, for patients resident in Västerbotten county, frequency of malignant TIs and correlation between the SUV and malignancy was investigated.
Pregnancy, Iodine and Rare Diseases

P3-06-191
MATERNAL THYROID PARAMETERS IN PREGNANT WOMEN WITH DIFFERENT ETHNIC BACKGROUNDS: DO ETHNICITY-SPECIFIC REFERENCE RANGES IMPROVE THE DIAGNOSIS OF SUBCLINICAL HYPOTHYROIDISM?
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Objective: Guidelines on the management of thyroid dysfunction during pregnancy have recently been updated and, for the diagnosis of subclinical hypothyroidism (SCH), a thyroid-stimulating hormone (TSH) upper reference limit (cut-off) of 4.0 mIU/L has been proposed when no institutional values are available. It is also suggested that serum TSH and thyroid autoimmunity (TAI) may be different according to the ethnic background of the women. We therefore determined the prevalence of TAI and SCH in pregnant women with different ethnic backgrounds and, to define SCH, we used different first trimester TSH upper reference cut-offs (institutional, ethnicity-specific, 2.5 mIU/L [Endocrine Society] and 4.0 mIU/L [American Thyroid Association]).

Design: Cross-sectional data analysis of 1683 pregnant women nested within an ongoing prospective database of pregnant women.

Method: The study was performed in a single centre in Brussels, Belgium. During the first antenatal visit, thyroid peroxidase antibodies (TPO-abs), TSH and free T4 (FT4) were measured and baseline characteristics recorded. Data from 481 women with sub-Saharan (SaBg; 28.6%), 754 North African (NaBg; 44.8%) and 448 Caucasian (CaBg; 26.6%) backgrounds were analysed. For the calculation of TSH reference ranges, women with TAI, outliers, twin and assisted pregnancies were excluded.

Results: The prevalence of TAI was significantly lower in the SaBg group than in NaBgs and CaBg groups (3.3% vs 8.6% and 11.1%; P < 0.001, respectively). Median TSH was significantly lower in SaBg and NaBg groups as compared with the CaBg group (1.3 and 1.4 vs 1.5 mIU/L; P = 0.006 and 0.014, respectively). The prevalence of women with SCH was comparable between all groups when 2.5 mIU/L was used as cut-off, but when 4.0 mIU/L or the institutional cut-off (3.74 mIU/L) was used, it was significantly higher in the CaBg group vs the NaBg group (5.4% vs 2.1% and 7.1% vs 3.3%, P = 0.008 and 0.013, respectively). The use of ethnicity-specific cut-offs did not change the prevalence of SCH as compared to the use of institutional cut-offs. However, when these cut-offs were used, the prevalence of SCH reduced by >70% (4.5% instead of 16.7%; P < 0.001) relative to the 2.5 mIU/L cut-off.

Conclusions: Pregnant women with a sub-Saharan African background had a lower prevalence of TAI and TSH levels as compared with women from other backgrounds.

P3-05-190
CLINICAL UTILITY OF THE NEW ATA 2015 ESTIMATED RISK OF MALIGNANCY FOR SONOGRAPHIC CATEGORIES FOR THYROID NODULES: A SINGLE CENTER RETROSPECTIVE STUDY OF 641 NODULES FROM 515 PATIENTS
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Thyroid nodules are a common and benign clinical problem in most of the cases. Although differentiated thyroid cancer is becoming increasingly prevalent, in many cases these tumors have an indolent behaviour. In 2015, ATA guidelines classified thyroid nodules into 5 categories based on their sonographic appearance. For each category, guided FNA was recommended depending on the estimated risk of malignancy based on sonographic patterns and nodule size.

Objective: To evaluate the clinical utility of sonographic patterns described in the ATA 2015 guidelines.

Methods: We performed a retrospective observational study including 641 nodules from 515 patients, in whom we performed a thyroid ultrasound. Nodules were classified prospectively into one of the 5 ATA categories. Some nodules, which could not be assigned to any ATA category, were defined as “Non-ATA”, corresponding to solid, isoechoic/hyperechoic nodules with suspicious sonographic features (irregular margins, microcalcifications, taller than wide shape or extrathyroidal extension) as well as those heteroechoic.

Results: 82.3% of the patients were females. Mean age was 52 ± 13 years. According to ATA sonographic categories: 8.6% of the nodules were benign, 19% were very low suspicion, 46.4% low suspicion, 15.2% intermediate suspicion, 5.5% high suspicion, and 5.3% were “Non-ATA”.

FNA was indicated in 278 nodules, 101 surgeries were performed, (41 hemithyroidectomy, 60 total thyroidectomy), and malignancy was found in 19 patients. We defined benign nodules as those with either a benign cytology or histology. Malignancy rates were 0% in benign and very low suspicion nodules, 3.2% in low suspicion nodules, 0% in intermediate suspicion nodules, 46.2% in high suspicion nodules and 13.6% in “Non ATA” nodules. When considering indeterminate cytologies (Bethesda III and IV), having an ATA high risk pattern was associated with malignancy in 80% of the cases, whereas “Non ATA”, low suspicion and intermediate suspicion nodules were associated with 16.7%, 21.4% and 0% risk of malignancy.

Conclusions: In our study, intermediate suspicion category had a lower risk of malignancy than expected. There are some non-classifiable nodules (“Non-ATA”) in which the risk of malignancy is similar to the expected for an intermediate sonographic suspicion nodule. The combination of an indeterminate cytology (Bethesda III and IV) with a high suspicion ATA sonographic pattern was associated to a higher rate of malignancy, favouring surgery in these cases.
in the leucine-rich region of the extracellular N-terminal domain of the TSH receptor have been reported.

Patients: A 38-year-old woman was seen during the first trimester of her second pregnancy for weight loss (5 kg), nausea and vomiting. Thyroid function test revealed thyrotoxicosis with increased FT3 = 8.3 ng/dl (normal range 2.4–4.1 ng/dl) and freeT4 = 2.3 ng/dl (0.8–1.3 ng/dl) concentrations and low TSH < 0.03 mU/l levels without anti-TSH receptor antibody. Thyroid ultrasound showed a normal-sized and homogeneous thyroid gland with diffuse hyper-vascularization. Thyrotoxicosis persisted at 2nd trimester (FT3 = 7.0 ng/dl, FT4 = 1.3 ng/dl) and improved spontaneously during the 3rd trimester (T3 = 3.5 ng/dl, T4 = 1.3 ng/dl). She gave birth to an euthyroid girl (3300 gr, 48 cm). Interestingly she presented similar symptoms with a loss of 6 kg during the first trimester of her first pregnancy. Her mother reported similar symptoms during her first pregnancy. At the age of 66 years, she had normal thyroid function (TSH = 0.92 mU/L) and high gonadotropin (LH = 26.8 IU/L, FSH = 85.7 IU/L) levels.

Results: DNA sequencing of this woman and her mother, led to identify a heterozygous variant (c.1789 G>A) changing Valine to Isoleucine residue at codon 597 in the exon 10 of the TSH receptor. Functional studies of this mutant receptor showed low cell surface expression (28% of the wild type receptor), high constitutive activity in regard to the basal level of cAMP and IP3 production (2 to 2.5-fold higher), reduced response to TSH compared to that of wild type receptor (average 50%). This Val597Ile mutant presented a dose-dependent increase in cAMP in response to chorionic gonadotrophin and luteinizing hormone whereas the wild type receptor was insensitive to those hormones except at high concentration of chorionic gonadotrophin.

Conclusion: We describe familial gestational hyperthyroidism due to a new variant in TSH receptor gene with hCG hypersensitivity. This amino-acid, located in the 5th transmembrane helix of the receptor, is highly conserved among the receptors for TSH and LH in different species. We analyzed clinical and hormonal data related to the increased constitutive activity of the Val507Ile receptor and thyroid hypersensitivity to hCG and LH in women of this family.

FAMILIAL SELENOCYSTEINE TRANSFERT RNA MUTATION: CLINICAL, BIOCHEMICAL AND HORMONAL EVALUATION OF TWO MUTATED PATIENTS
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Introduction: Iodothyronine deiodinases are selenoproteins whose selenocysteines (Sec) are introduced on tRNA[Sec]Sec by a complex machinery involving tRNA[Sec]. Recently we reported a mutation in the TRU-TCA1-1 gene encoding for tRNA[Sec]Sec that resulted in reduced expression of stress-related selenoproteins. The predominant and pronounced multisystem abnormalities, abnormal thyroid function test (euthyroid hyperthyroxinemia) and selenium deficiency. Here we describe clinical, biochemical and thyroid evaluation of two new patients of two families harbouring the same tRNA[Sec]Sec mutation.

Patients and Results: A 13-year-old patient was seen for Hashimoto’s disease with raised FT3 (4.6 pg/ml, normal range 2–4.2 pg/ml), normal FT4 and TSH concentrations. He had not clinical complaint. During a 6-year disease with raised FT3 (4.6 pg/ml, normal range 2–4.2 pg/ml), normal FT4 and TSH concentrations. He had not clinical complaint.

Conclusion: We report two members of a family with C65G mutation in the TRU-TCA1-1 gene encoding for tRNA[Sec]Sec. The two patients were clinically asymptomatic. In the index patient with homozygote mutation, follow-up of the thyroid function revealed euthyroid hyperthyroxinemia suggesting impaired deiodinase activity, and in the two members of the family stress-related selenoproteins (GPX1, SOD) concentrations were decreased implying that this tRNA[Sec]Sec mutation could differentially impact selenoproteins synthesis and/or activity.

EFFECT OF VARIOUS DOSES OF IODINE ON THYROID GLAND IN PREGNANT AND LACTATING WOMEN, ON THE EXAMPLE OF REGIONAL STUDIES IN RUSSIAN FEDERATION (RF)
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Relevance: Question of standards of iodine intake in pregnant and lactating women remains relevant. One of important reasons preventing adequate sufficiency of iodine is iron deficiency in pregnant women.

Aim of Study: to determine status and function of thyroid gland, in pregnant and lactating women with and without antibodies to thyroid gland, on the background of taking different doses of iodine in 3 different regions of RF with different iodine sufficiency.

Materials and Methods: Our study included 414 women in the 1 trimester of pregnancy (18–42 y.o.) and 256 newborns. They were divided into 2 groups: 1st group – women, receiving potassium iodide at a dose of 200 mcg/day, newborns breastfed for women, receiving potassium iodide 200 mcg/day; 2nd group – women and newborns, receiving 300 mcg/day, respectively.

The study assessed level of TSH, FT4, Anti-TPO, urinary excretion of iodine, hemoglobin, erythrocyte, hematocrit, serum iron, ferritin, thyroid ultrasound at baseline and after 3 months.

Results: Initially, in all three regions, median iodinuria was below the threshold level (150 µg/l). After 3 months, a significant increase in the level of iodinuria in group 2 (96 µg/l at baseline and 259 µg/L at 3 months) was noted. When comparing level of iodinuria at baseline in pregnant women with anemia and without it (threshold level Hb 110 g/l), statistically significant differences were found, (median iodinuria was 105 and 145 µg/l, respectively). Against the background of taking different doses, there was no increase of Anti-TPO. When comparing the iodine content of infants who are breastfed, there were no significant differences between the groups. Normal concentration of iodine in the urine was 58.6% in the newborns in the first group and 71% in the second group. The levels of TSH were not statistically different; there were no increase above 5 mU/l.

Conclusions: We can say that in order to achieve optimal iodinuria, level of iodine intake should correspond to at least 250 µg/day. For now, initial urinary excretion of iodine does not correspond to normal iodine supply, which indicates the need for preconception treatment in regions with proven iodine deficiency. Decrease of serum ferritin below 15 ng/ml (corresponding to latent iron deficiency) detected in each four pregnant women increases risk of non-effective iodine prevention by 1.5 times, so the optimal iodine maintenance in this group should be at least 300 µg/day.

Study was carried out by RSF grant N17-75-30035 (2017).
CLINICAL MANIFESTATIONS OF RTH Beta IN THE PEDIATRIC AGE

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Objectives: The objective of the present study was to revise clinical data of patients affected with resistance to thyroid hormone beta syndrome (RTHβ) diagnosed in the pediatric age.

Methods: 36 patients (16 males and 20 females) with RTHβ were studied; in particular we retrieved genetic, biochemical, thyroid US and anthropometric data, from the medical records at diagnosis (n=36) and follow-up (n=11) of these patients.

Results: all patients harbored known mutations of the THRβ gene. 17 patients inherited the disease from the mother, 11 from the father and the remaining had de novo mutations. 18 familial cases were diagnosed at birth by genetic analysis, in the remaining 10 cases the pediatric patient was the index case. In sporadic and index cases, inappropriate TSH secretion was found during investigations performed because of failure to thrive (7 cases), tachycardia (1 case), behavioral abnormalities or attention deficit hyperactivity disorder (ADHD) (3 cases) or by routine screening of thyroid function (4 cases). In one patient, RTHβ was diagnosed at 14 years before total thyroidectomy for a papillary thyroid cancer (PTC). Follow up data suggest that failure to thrive is rescued before the age of 4 years, although several patients maintain a low-normal BMI also in adulthood. The majority of the patients were asymptomatic, while 3 patients were treated with TRIAC for thyrotropic features or ADHD, all with a clinical improvement. Two patients with sinus tachycardia were treated with atenolol one by the age of 16 months and one by the age of 16 years. A slight increased thyroid gland was found in 12 patients. None of the patients had thyroid nodules with the exception of the one with PTC.

Conclusions: as previously reported most of the patients with RTHβ are asymptomatic and do not require specific treatments. Since failure to thrive and behavioral or cardiac problems are the most common clinical signs at diagnosis, TSH-reflex based strategy of thyroid function should be carefully interpreted in the pediatric age. In fact, in symptomatic RTHβ children a precocious diagnosis is warranted as they may benefit from the treatment with TRIAC or beta-blockers.

TREATMENT OF HYPOTHYROIDISM DURING PREGNANCY AND THE POSTPARTUM PERIOD – A RETROSPECTIVE STUDY

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Background: Hypothyroidism is the most common thyroid disorder in pregnancy (3–5%) and is associated with adverse long-term outcomes of the newborn (mainly regarding neuropsychological and intellectual development). There is inconsistency in the literature regarding the management in the postpartum period of women diagnosed with hypothyroidism during pregnancy.

Objective: To determine whether continuation or discontinuation of levothyroxine (LT4) treatment is essential in the postpartum period.

Methods: We conducted a retrospective case file study of women with new-onset subclinical or overt hypothyroidism during pregnancy. We assessed medical records between 2013 and 2017. Follow-up (FU) was up to 1 year postpartum. We excluded women with thyroid disorders in the past and those that were lost to FU after delivery. The study included 147 women (mean age±SD: 31.3 ± 5.6 years, mean body weight gain of 12.9 ± 5.2 kg during pregnancy). Sixty-seven women (45.5%) had a vaginal birth and 80 (54.5%) had a cesarean section (newborn mean weight was 3201.4 ± 494.9 g).

Results: Treatment with LT4 began at 18.7 ± 8.6 weeks of gestation. Statistical evaluation was done with analysis of covariance.

Results: On treatment initiation, mean TSH value was 4.48 ± 2.58 mIU/mL and a mean LT4 dose of 71.5 ± 20.4 μg/day was given. Twenty-five (17%) women had positive thyroid antibodies, 24 women (16.3%) had positive thyroid ultrasound findings and 40 women (27.2%) developed gestational diabetes. Before delivery, the mean TSH value was 1.66 ± 1.15 mIU/mL and the mean LT4 dose was at 78.9 ± 24.2 μg/day. In thirty women, LT4 was discontinued after delivery. In the remaining 117 women the mean LT4 dose was decreased at 45.1 ± 29.3 μg/day. Mean TSH value on the first postpartum visit was 1.84 ± 1.8 μIU/mL. After the first postpartum FU visit, LT4 was discontinued in another 40 women. At the time of the second FU visit (after 6 months), LT4 had been discontinued in 64 (45.5%) women. After one year, in 13/64 patients (20.3%) who stopped LT4 in the postpartum period and were available for FU, treatment was reinstated due to hypothyroidism relapse (mean TSH value of 6.72 μIU/mL). This was unrelated to age, gestational age, body weight gain, initial dosage, thyroid antibodies positivity and presence of gestational diabetes (all p > 0.1).

Conclusions: Since a considerable number of pregnant women who were started levothyroxine treatment during pregnancy were able to discontinue it postpartum, our study underlines the need to reassess thyroid function in the next 6 to 12 months.

IODINE DEFICIENCY DISORDERS AND ADVERSE PREGNANCY OUTCOME IN HIMALAYAN MOUNTAIN POPULATION

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Background: The micro-nutrient Iodine is an integral part of the thyroid hormone molecule. Since thyroid hormones are importantly involved in the developmental and reproductive processes, deficiency of iodine in the environment can produce adverse effects. Himalayan mountains are known to be
deficient in iodine, and, Universal Salt Liodisation program (USI) of Govt of India was launched in 1986. In this paper attempt was made to assess salt usage pattern, prevalence of iodine deficiency disorders (IDD) and adverse pregnancy outcomes in populations residing in remote Himalayan region with a view to study the impact of Indian salt iodisation program.

Objective: Assessment of prevalence of iodine deficiency disorders (IDD) and adverse pregnancy outcomes in villages of Himalayan Goitre Belt.

Methods: Eight villages (n = 4,785) were surveyed in rural area of district Dehradun of Uttarakhand State. Periodic Health camps and door to door surveys were conducted in association with Health Directorate. Questionnaire based survey on iodine deficiency disorders (IDD) and adverse pregnancy outcomes were made in normal healthy women after informed consent and due approval of Ethical Committee. Another survey on pregnancy outcome was conducted in subset rural population of Agastyumuni district Radagprayag of Uttarakhand.

Results: Indicate an overall prevalence of goitre 0.11±, 0.24; Strabismus 0.03%; Spastic diplegia 0.041%; deaf/mute 0.116%; cretin (mentally retarded) 0.087%; stunted growth 0.017% of surveyed. Pregnancy outcome from survey I: Miscarriage: 1.33 ± 0.67%, Still birth: 1.88 ± 0.56% from survey II: Miscarriage: 30%, Still birth: 10%. Actual iodized salt consumption in the area commenced only in the last 3–4 years before which the granular un-iodised ‘Gara’ salt was used (obtained twice a year through a widely prevalent barter system in exchange with Amaranthus seeds).

Conclusion: The striking finding of the observations in Survey I is the low prevalence of IDD and low occurrence of adverse pregnancy outcome in the absence of proper implementation of USI. Result from survey II on pregnancy outcome indicated high incidence of adverse pregnancy outcomes in specific pockets which in the absence of goiter may be related to other factors e.g. strenuous mountain life, lack of adequate facilities in higher Himalaya and genes.

Financial assistance from Department of community medicine, Himalayan Institute of Medical Sciences, SRHU is gratefully acknowledged.

**P3-06-198**

**PRELIMINARY STUDY ON NEURODEVELOPMENTAL PARAMETERS AND CLINICAL MILESTONES IN YOUNG CHILDREN (4-48 MONTHS) IN RURAL HIMALayan Foot Hills**

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Background: Iodine deficiency in the environment is known to cause goiter, impaired growth & development and is the single most common cause of preventable mental retardation and brain damage in the world (WHO ICD 2001). The Himalayan goitre belt is known to be iodine deficient. Surveys have indicated a great majority consuming uniodised salt in the Uttarakhand area. The absent of proper implementation of USI. Result from survey II on pregnancy outcomes were made in normal healthy women after informed consent and due approval of Ethical Committee. Another survey on pregnancy outcome was conducted in subset rural population of Agastyumuni district Radagprayag of Uttarakhand.

Objective: To monitor neurodevelopmental process and clinical milestones in different age groups. A subset of the population was found to have significantly greater proportion of Strabismus, despite the absence of Goiter.

Conclusion: It can be concluded that majority of young (81–91%) born in this area exhibit normal development despite lack of adequate salt iodisation. Also is interesting the prevalence of strabismus (a neurodevelopmental disorders) in the absence of goiter in a subset population of higher Himalaya.

Financial assistance from Department of community medicine, Himalayan Institute of Medical Sciences, SRHU is gratefully acknowledged.

**P3-06-199**

**TRIODOOTHYROACETIC ACID IS A SAFE, WELL TOLERATED AND EFFECTIVE TREATMENT FOR SELECTED PATIENTS WITH RESISTANCE TO THYROID HORMONE BETA**

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Background: Resistance to Thyroid Hormone beta (RTHb) is characterised by elevated thyroid hormone (TH) levels due to resistance in the HPT axis, together with variable tissue refractoriness to hormone action. TH receptor (TR) beta-expressing tissues are relatively TH resistant: TRalpha-expressing tissues remain TH sensitive. Although reports of triiodothyroacetic acid (TRIAC, a TH analogue), treatment exist, efficacy has not been systematically evaluated.

Objectives: To describe clinical, biochemical and metabolic responses to TRIAC in RTHb patients with hyperthyroid features.

Methods: Biochemical indices, sleeping heart rate (SHR), resting energy expenditure (REE), bone mineral density (BMD), and hyperthyroid symptom scores (HSS) were recorded in RTHbeta patients Pre and Post TRIAC treatment.

Results: Five children and three adults were treated with TRIAC (duration 1–12 yrs). TSH levels fell (average 3.61 mIU/L) except in two, concurrently carbimazole-treated, cases. Circulating FT4 levels (average reduction 8.99 pmol/L; 6/8 cases) and REE (average fall 0.015 MJ/kg LBM; 6/8 cases) fell. SHR and BMD were unchanged. Patients reported symptomatic improvement: TSH levels fell (average 3.61 mIU/L) except in two, concurrently carbimazole-treated, cases. Circulating FT4 levels (average reduction 8.99 pmol/L; 6/8 cases) and REE (average fall 0.015 MJ/kg LBM; 6/8 cases) fell. SHR and BMD were unchanged. Patients reported symptomatic improvement, with reduced HSS (Pre: mean 16; Post mean 11). Growth improved in childhood. Except for discontinuation due to headache (n = 1), patients experienced no side effects.

Conclusions: TRIAC lowers TSH, FT4, energy expenditure and alleviates symptoms, without adverse effects on heart rate or bone density in selected RTHb patients with hyperthyroid features.

Poster Presentations

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DOI: 10.1159/000491542
**Table 1.** (for Abstract P3-06-199)

<table>
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<th>Gender, Age (yrs)</th>
<th>Mutation</th>
<th>Duration on TRIAC (yrs), current dose (mg/day)</th>
<th>TSH (0.4–4.0mU/l), Pre, Post</th>
<th>FT4 (9–20 pmol/l), Pre, Post</th>
<th>SHR bpm, Pre, Post</th>
<th>Total bone density Z score, Pre, Post, p</th>
<th>REE MJ/kg lean mass, Pre, Post, p</th>
<th>HSS /40, Pre, Post</th>
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<td>* , 0.206</td>
<td>* , 18</td>
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<td>P453T</td>
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<td>15.3, 2.22</td>
<td>28.8, 25.4</td>
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<td>3.12, 2.54</td>
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*Not available.

**P3-06-200**

**SIMILARLY LOW MEDIAN URINARY IODINE CONTRACTION/CREATININE IN EARLY PREGNANCY AND LATE PREGNANCY IN ROMANIAN WOMEN FROM IODINE DEFICIENT AREAS**

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Corina Raducanu Lichiardopoli, Mihai Popescu,
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**Introduction:** Pregnant women are more prone to iodine deficiency due to their higher iodine requirement. Iodine deficiency, especially during first trimester pregnancy, may induce psychoneurological impairment in children.

**Objective:** To assess the median urinary iodine concentration (UIC) in early pregnancy (up to 14 weeks) and late pregnancy (weeks 20 to 42) in women from iodine deficient areas in Romania, after universal salt iodization was implemented in 2004.

**Subjects and Methods:** In 2016–2017 median urinary iodine concentration (UIC), urinary creatinine and UIC/creatinine ratio were evaluated by spectrophotometry (Sandell – Kolthoff method) in the morning urine collected from 631 pregnant women not treated with thyroid hormones. Values from 104 women in early pregnancy were compared with those in other 266 women in late pregnancy from the same iodine deficient counties. The study was approved by the local Ethics Committee.

**Results:** Median UIC in the whole group of pregnant women was 116.1 μg/L, reflecting mild iodine deficiency. Median UIC and UIC/creatinine ratio were 87.4 μg/L and 101.3 μg/g in women with early pregnancy and 108.6 μg/L and 102.0 μg/g (p = NS) in women with late pregnancy (mostly 3rd trimester). Of note, iodine containing supplements (usually with 150 mcg iodine) were used by only 12.5% of women in early pregnancy, compared to 48.5% in late pregnancy (p < 0.0001). In women not taking iodine-containing supplements, median UIC and UIC/creatinine were 84.4 μg/L and 93.9 μg/g in early pregnancy women compared with 109.4 μg/L and 93.5 μg/g (p = NS) in late-pregnancy women.

**Conclusions:** Mild iodine deficiency is still prevalent in pregnant women after more than 10 years since the universal salt iodization in Romania. Similarly low median UIC/creatinine ratio was found in early pregnancy and late pregnancy in women from iodine deficient areas. Efforts should be made to increase the use of iodine supplements during pregnancy.

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**Thyroid Disease**

**P3-07-201**

**APPLICATION OF A NOVEL HOMOGENEOUS CYCLIC AMP ASSAY IN A BIOASSAY FOR MEASURING TSH RECEPTOR STIMULATING AUTOANTIBODIES**

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George J. Kahaly

**1**Johannes Gutenberg University Medical Center, Mainz, Germany

**Objective:** Stimulating TSH receptor (TSHR) autoantibodies (TSAb) are specific for and cause Graves’ disease. We aimed to evaluate the utility of a novel homogeneous, fluorescent cyclic adenosine monophosphate (cAMP) assay for the detection of TSAb.

**Methods:** Chinese hamster ovary (CHO) cell lines that express a wild-type (wt.) or chimeric (Mc4) TSHR were incubated with the adenylyl cyclase activator, forskolin or a human TSAb monoclonal antibody (M22). Intracellular levels of cAMP were measured using a commercially available cAMP assay (Bridge-it® CAMP Designer assay, Medomics, St Louis, MO, USA) that is based on binding of cAMP to a DNA-binding protein and results were compared with a FDA cleared TSAb luciferase bioassay (Thyretain, Quidel, San Diego, CA, USA). The TSAb luciferase bioassay utilizes Chinese hamster ovary cells expressing a chimeric TSHR (Mc4) and cAMP response element (CRE)-dependent firefly luciferase gene.

**Results:** Mc4 and wt. cells were stimulated in a dose-dependent manner (0.006–200 μM) with forskolin concentrations. The linear range in the Mc4 and wt. cells was 0.8–25 μM and 3.1–50 μM, respectively. Levels of cAMP and luciferase in forskolin-treated Mc4 and wt. cells were positively correlated (Spearman’s r = 0.91 and 0.84, both p < 0.001). Incubation of both cell lines with M22 (0.006–50 ng/ml) resulted in dose-dependent cAMP levels with linear ranges for the Mc4 and wt. cells of 0.8–2.5 ng/ml and 0.8–6.3 ng/ml, respectively. Comparison of cAMP and luciferase levels in M22 treated Mc4 and wt. cells also showed a positive correlation (r = 0.88, p < 0.001 and 0.75, p = 0.002). Forskolin and M22 increased cAMP levels in the Mc4 cell...
Objective: TSH-Receptor blocking autoantibodies (TBAb) are prevalent in patients with autoimmune thyroid disease. The analytical performance and clinical validity of a novel TBAb bioassay was assessed.

Methods: Chinese Hamster Ovary cells expressing a chimeric form of the TSH-receptor (Mc4) were grown in multi-well plates for 16 hours at 37°C, 5% CO₂. For the sample preparation, samples were 1:11 diluted in TBAb Working Solution. Patient serum and controls (reference, normal and positive) were measured in duplicate. After three hours incubation, the cells were treated with luciferase substrate / lysis reagent and luciferase expression levels of the cell lysates were measured as relative light units (RLU) in a luminometer. Blocking activity was defined as percentage inhibition of luciferase expression relative to induction with bovine TSH alone. Percent Inhibition (%I) was calculated using the formula as follows: %I = (Reference RLU – Sample RLU) / (Reference RLU) x 100.

Results: The analytical performance was determined with 88 serum samples from healthy euthyroid subjects to calculate the limit of blank (LoB). LoB was calculated by the 95th percentile of the blank distribution using the formula: TBAb LoB = results at position [normal blank measurements (p/100) + 0.5] = [88 x 0.95 + 0.5] = 84th position at which the sample produced 13% Inhibition. The limit of detection (LoD) was calculated as LoD = LoB x 1.645 standard deviation (low concentration samples) = 13% I + 1.645 x 5.6% I = 22% I. Two serum samples from healthy control subjects were spiked with two different concentrations of the human monoclonal K1-70 TBAb (40 and 80 ng/ml) and were utilized for the precision testing. Intra-assay precision for 40 and 80 ng/ml were 45 ± 2.6% I and 71 ± 1.5% I with a very low coefficient of variation (CV %), 5.7% and 2.1%, respectively. The inter-assay precision was 45 ± 7.4% I and 71 ± 4.5% I with a low CV %, 16.4% and 6.3% respectively. No cross-reactivity was noted for the follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH) in the 1st, 2nd, and 3rd trimester corresponding to the 2.5th and 97.5th percentiles were 2.40–3.65, 2.14–3.38, 1.95–3.04 pg/mL, 0.97–1.49, 0.75–1.37, 0.70–1.21 ng/dL, and 0.18–3.54, 0.34–3.76, 0.40–4.27 μIU/mL, respectively. The analytical intra- and inter-assay coefficient of variation (CV) for FT3, FT4 and TSH were 1.9/2.6%, 1.4/2.7% and 1.5/3.5%, respectively. Analysis of mean values for FT3, FT4 and TSH between pregnant subjects and healthy non-pregnant subjects showed significantly difference in all trimester.

Conclusions: This study provides trimester-specific reference ranges of thyroid function tests in Thai pregnant women that differed from those of non-pregnant women. Our results may help in the interpretation of thyroid function in pregnant women to avoid unnecessary treatments.

Conclusions: Measurement of TSAb using a novel cAMP assay provides rapid results comparable to a luciferase-based TSAb bioassay.
Methods: We tested sera/plasma from 14 GD, 19 GO and 13 healthy controls using high-throughput proteomics and miRNA sequencing (Illumina’s HiSeq2000 and Agilent-6550 Funnel quadrupole-time-of-flight mass spectrometry). Euclidean distances based on miRNA and protein quantification were visualized through multidimensional scaling (MDS). The differential expression (DE) of miRNA and proteins among groups was analysed with multinomial regression models. Additionally, miRNA and proteins were used to predict whether individuals belonged to the GD, GO or control groups. Lasso-penalised multinomial regression was used for predictions on 150 resampled datasets. This allowed the estimation, along with the accuracy of prediction, of the relative importance of specific miRNA and proteins.

Results: We detected 3025 miRNAs and 1886 proteins. The MDS plot showed a good separation of the three groups (GD, GO, Controls). Overall prediction accuracy was 0.71 or 0.81 with miRNA or protein data alone and 0.86 (±0.18), with miRNA and proteins combined. Comparing the results from DE and prediction analysis identified 5 miRNAs and 20 proteins as potential biomarkers. These include the novel miRNA Novel-19_15038, and the proteins Zonulin, Alpha-2 macroglobulin, Beta-2 glycoprotein 1 and Fibronectin. Functional analysis of miRNA targets and proteins identified relevant pathways, including bacterial invasion of epithelial cells.

Conclusions: Proteomic and miRNA analyses, combined with robust bioinformatics, identified circulating biomarkers useful in early diagnosis and prognosis of GD and to predict GO disease status; a step towards technology-driven personalised medicine.

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P3-07-206
MODULATION OF SPHINGOSINE-1-PHOSPHATE DEPENDENT T-CELL ATTRACTION AS THERAPEUTIC OPTION FOR GRAVES’ ORBITOPATHY

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Graves’ orbitopathy (GO) is an orbital complication of autoimmune hyperthyroidism caused by stimulating thyrotropin receptor auto-antibodies. GO is characterized by orbital inflammation, expansion of adipose connective tissue and/or muscle dysfunction. Besides the action of auto-antibodies an infiltration of T cells into the orbital tissue is one main feature of the eye disease. Orbital fibroblasts (OFs) which can be activated by auto-antibodies and T-cells are central in orbital inflammation and tissue remodeling. Sphingosine-1-phosphate (SIP) plays an important role in T-cell egress and trafficking. Aim of this study was to elucidate the role of SIP in the development and progression of GO. We found increased SIP levels in orbital fat tissue of GO patients by immunofluorescence. OFs derived from GO tissues expressed elevated levels of SIP by more than 40% compared to healthy OFs in response to CD40 ligation. Analyses of sphingolipid levels and the activities of involved enzymes by different methods like UPLC or mass spectrometry revealed an upregulation of the entire sphingolipid pathway which finally resulted in increased SIP levels. We showed that elevated SIP release upon CD40L stimulation led to an almost twofold enhanced attraction of T-cells towards GO OFs via T-cell migration assays.

This study suggests that increased SIP levels in orbital tissue can contribute to T-cell attraction. Therefore SIP may be a therapeutic target for GO. Studies in a GO mouse model on efficacy of the SIP receptor modulator FTY720 are underway.
Introduction: Graves' disease (GD) is a Th2 autoimmune disease affecting thyroid and peripheral tissues such as orbital fat tissue. miR199a-3p (3p) and miR199a-5p (5p) are putative modulators of angiogenesis, endothelial dysfunction, oxidative stress (OS) and adipogenesis which are common features of GD pathophysiology. Accordingly, we previously showed that miRs 3p/5p and T4 are redundant regulators of the NOS/NO pathway in endothelial cells. We now aim to investigate the expression of both miRs in thyroid and fat tissues as well as in the plasma of GD patients.

Methods: Thyroid and plasma samples were obtained from patients operated for multinodular goiters or for GD, orbital fat samples from blepharoplasty (controls) or thyroid associated orbitopathy (TAO). miRs expression was evaluated following Maxwell extraction, quantitative real-time PCR or in situ hybridization.

Results: Thyroids from GD patients presented a significant reduction of 3p/5p expression. Interestingly, 3p/5p plasmatic circulation is also decreased in GD patients. GD orbital adipocytes also demonstrated a significant down-regulation of these miRs. In addition, 5p in situ hybridization revealed a decrease in GD thyrocytes and GD adipocytes compare to controls whereas endothelial cells seem to express these miRs in the same way.

Conclusion: We have identified a new cluster of miRs differently regulated in the context of GD. A dramatic reduction in miR199a-3p/5p expression in GD-thyroid extracts, GD-plasma and GD-orbital fat are observed in GD tissues. Taken together, our results are in agreement with a potential implication of these miRs as regulators of OS, angiogenesis and the systemic manifestations of GD.

P3-07-208
HIGHLY SELECTIVE TSH-RECEPTOR SMALL MOLECULE ANTAGONIST INHIBITS ACTIVATION BY TSH, ANTIBODIES, SMALL AGONIST, SERA FROM GO PATIENTS AND PATHOGENIC ACTIVATING MUTATIONS
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The thyrotropin receptor (TSHR) is the key stimulatory protein of the thyroid gland. TSHR-stimulating autoimmune antibodies (TSAb) bind like TSH to the large ectodomain of TSHR, which in turn activates the receptor via an internal intramolecular agonistic sequence. Pathological over-activation can be triggered i) by TSAb leading to hyperthyroidism in the thyroid gland (Graves’ disease, GD) and to exophthalmos of the eye (Graves’ orbitopathy, GO) or ii) by constitutively activating mutations (CAM) of the TSHR causing congenital hyperthyroidism. Severe GO is considered as a dilemma due to a clinically therapeutic gap. We recently developed a TSHR antagonist by high-throughput screening, subsequent stereo-selective synthesis and chiral separation. Our enantiopure small molecule S37a inhibits not only the TSHR-activation in HEK-TSHR cells by TSH or by human monoclonal antibody M22. By ex vivo studies we showed that S37a also inhibits TSHR-activating high TRAK containing sera from GO patients.

Here we present new data.

1) We prove the high TSHR selectivity of S37a compared to other published TSHR antagonists. With a radioimmunobassay we determined cAMP accumulation in stably transfected HEK cells expressing TSHR or the highly homologous lutropin (LH) or follitropin (FSH) receptors, whereas the latter were not at all affected by S37a, probably due to the rigid bent shape of S37a that is completely different from other known small molecule TSHR inhibitors.

2) In addition to TSAb inhibition, we here provide evidence for a potential future application of S37a in non-autoimmune hyperthyroidism. We observed for S37a a strong reduction of the elevated constitutive (TSH-independent) cAMP accumulation caused by CAM of TSHR. The constitutive activity of the three naturally occurring CAM 1486F, 1568T or V656F was reduced down to the range of basal wildtype receptor cAMP signalling.

3) S37a also inhibits non-competitively the small molecule agonist C2, which activates TSHR allosterically in the transmembrane domain.

4) Verifications prior in vivo mouse studies indicate that bTSH-induced activation of mouse TSHR expressed in HEK cells is inhibited with micromolar concentrations of S37a. The murine monoclonal activating TSHR antibody KSA1b is inhibited in a similar manner as human M22.

5) Initial in vivo pharmacokinetic studies in male CD-1 mice revealed a good tolerance and remarkable 53% bioavailability after oral S37a administration.

In summary we demonstrate new data about a highly TSHR-selective inhibitor, which is applicable in vivo in mice and has a potential for further development.

P3-07-209
MINOR IMPACT OF SEX ON AUTOIMMUNE HYPERTHYROIDISM AND ASSOCIATED ORBITOPATHY IN A THYROTROPIN HORMONE RECEPTOR INDUCED MOUSE MODEL
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Background: Graves’ orbitopathy (GO) is the most common extra thyroidal complication of autoimmune hyperthyroidism and occurs predominantly in women but more severe in men. The reason for this effect of gender on GO is unknown. Herein we studied the impact of gender experimentally in an induced mouse model.

Methods: Male and female BALB/c mice were immunized with human TSHR A-subunit encoding plasmid. Mice were daily inspected for eye symptoms. Critical features of GO were evaluated by Magnet Resonance Imaging (MRI) of living mice and/or postmortem by immunohistochemistry, TSHR antibodies were evaluated by TBI assay and CHO bioassay. Total T4 values were measured by ELISA. Thyroids and hearts were assessed histologically. Total disease incidence and outcome was analyzed by Z-score method.

Results: Both sexes developed autoimmune hyperthyroidism characterized by TSHR stimulating autoantibodies, elevated T4 values, hyperplastic thyroids and hearts. Autoimmune mice developed inflammatory eye symptoms and proptosis although males earlier than females. Serial MRI revealed elevated inflammatory infiltration, increased fat volume and glycosaminoglycan deposition in orbits of both sexes but most significant in female mice. Histologically, infiltration of T-cells, extension of brown fat and overall collagen deposition were characteristics of GO in male mice. In contrast, females developed predominantly macrophage infiltration in muscle and connective tissue, and muscle hypertrophy. Apart from sex-dependent variabilities in pathogenesis, Z-score analysis and disease classification revealed minor sex-differences in incidence and total outcome.

Conclusion: Gender solely does not predispose for GO. However, additional risk factors linked to gender most likely genetic variabilities, advanced age and smoking could be major determinants for development of female-bias in autoimmune hyperthyroidism and associated orbitopathy. The mouse model can be useful to dissect the contribution of risk factors to female-bias in GO in future studies.

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Methods: DCFDA was used to quantify ROS production in human primary cultures of thyrocytes incubated with Th1 cytokines (Interleukin-1β and Interferon-γ) to mimic HT. The expression of Peroxiredoxin 1 (PRDX1) known to detoxify H₂O₂ and of superoxide dismutase 1 (SOD1) known to detoxify superoxide anions was analyzed by western blot (WB), immunohistochemistry (IHC) and immunofluorescence (IF) in the human primary cultures of thyrocytes and in thyroid samples from HT patients and in paranodular tissue from multinodular goiter patients (controls).

Results: A significant increase of ROS was observed in human thyrocytes incubated with Th1 cytokines. In the meantime, the expression of PRDX1 and SOD1 was dramatically decreased. The decrease of PRDX1 and SOD1 was also observed in thyroids from HT patients. IHC and IF of HT thyroids sections compared to control revealed a main heterogeneity of follicles. In normal type 1 follicles, PRDX1 was decreased while SOD1 was unchanged. In hyperactive type 2 follicles, PRDX1 was increased but SOD1 was barely expressed and inactive type 3 follicles (unable to form T4) did not express those proteins.

Conclusions: The oxidative stress and the thyroid cell destruction provoked by TH1 cytokines result from a loss of antioxidant defenses and the intracellular accumulation of ROS. This observation could be of importance in the treatment of HT.
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