Endocrine Abstracts

September 2022 Volume 83
ISSN 1479-6848 (online)

European Society of Endocrinology

ESE Young Endocrinologists and Scientists (EYES) 2022

2-4 September 2022, Zagreb, Croatia

eyes
ESE young endocrinologists and scientists **looking forward**

published by bioscientifica

Online version available at
www.endocrine-abstracts.org

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AO1

Steroidomic approach for the characterization of patients with non-alcoholic fatty liver disease

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Introduction
The onset and progression of liver damage in non-alcoholic fatty liver disease (NAFLD) is tightly associated with metabolic derangements. Steroids may affect lipid metabolism but their alterations in the setting of NAFLD remain to be fully explored.
Patients and Methods
We analyzed data from 267 patients with biopsy-proven NAFLD and 112 controls (CT). A panel of 26 steroids (including glucocorticoids, mineralocorticoids, androgens, and progestogens as well as representative glucuro- and sulphoconjugated metabolites) were measured on plasma samples by liquid chromatography coupled to mass spectrometry (LC-MS/MS). Severe hepatic fibrosis was defined by $F \geq 3$, according to the Kleiner score.
Results
Compared to CT, NAFLD patients were older (median age 51vs43, $P < 0.001$) and were characterized by a higher rate of MS (47%vs2%, $P < 0.001$). More than a half of steroids were deregulated in patients compared to CT. Circulating levels of 16 compounds showed a significant stepwise decrease according to the degree of hepatic fibrosis. At univariate analysis, testosterone, and its derivatives, androsterone metabolites, etiocholanolone metabolites and glicoandrogens metabolites were differentially expressed in patients with severe fibrosis compared to those with absent/moderate fibrosis. After multivariable logistic regression analysis adjusted for age, gender and type 2 diabetes, epitestosterone sulphate, 5α-androstan-3α,17β-diol-3-glucuronide and androsterone sulphate levels were significantly associated with $F \geq 3$. The diagnostic accuracy of the model for the identification of $F \geq 3$ was 0.83 with a sensitivity and specificity of 75% and 80%. No statistical differences were found between the accuracy of the multivariable model and the fibroscan (AUC 0.83) in the diagnosis of severe fibrosis, while the model combining clinical variable, significant steroids and fibroscan demonstrated a high accuracy for predicting severe fibrosis (AUC 0.90).
Conclusions
In NAFLD patients, alterations in androgens and their glucuro- and sulphoconjugated metabolites levels could be expression of compromised 1) liver steroidogenesis or 2) liver steroid homeostasis regulation and are strongly associated with severe fibrosis.

DOI: 10.1530/endoabs.83.AO1

AO2

Combining steroid and global metabolome profiling by mass spectrometry with machine learning to investigate metabolic risk in benign adrenal tumours with mild autonomous cortisol secretion

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Background
Benign adrenal tumours are discovered in 3-10% of adults and can be non-functioning (NFAT) or associated with adrenal hormone excess, most frequently mild autonomous cortisol secretion (MACS) defined by the failure to suppress cortisol after 1 mg dexamethasone overnight but lack of distinct signs of Cushing's syndrome (CS). We found that MACS increases the prevalence and severity of type 2 diabetes and hypertension and primarily affects women (Ann Int Med. 2022 Doi:10.7326/M21-1737).
Objectives
We prospectively recruited 1305 patients with benign adrenal tumours to assess their steroid and global metabolomes and determine links to type 2 diabetes and hypertension.
Methods
We analysed 24-h urine samples from 1305 patients (649 NFAT, 591 MACS, 65 CS) using a 17-steroid liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. We also performed untargeted serum metabolome analysis in a representative sub-cohort of 290 patients (104 NFAT, 140 MACS, 47 CS) employing HILIC and C18-lipidomics LC-MS assays. The data were analysed by two supervised machine learning approaches, generalized matrix learning vector quantization and ordinal regression, to identify the most relevant metabolic changes.
Results
Urine steroid metabolome analysis revealed increased glucocorticoid metabolite excretion from NFAT over MACS to CS, whereas androgen metabolite excretion decreased. Similarly, increased glucocorticoid metabolites were observed in patients with type 2 diabetes and hypertension. Lipidome analysis revealed gradual progression towards lipotoxicity with increasing cortisol excess. Patients with type 2 diabetes showed additional changes in acylcarnitines, bioactive lipids, and triacylglycerides.
Conclusions
We provide mechanistic insights into the metabolic consequences of cortisol excess. Increased cortisol was linked to a change in the lipidome towards lipotoxicity. Patients with type 2 diabetes and hypertension had increased glucocorticoid output and more adverse changes in the lipidome, indicative of a causative contribution of cortisol excess to their higher cardiometabolic burden. Observed changes may hold promise for risk stratification in MACS, a highly relevant and previously largely overlooked metabolic risk condition.

DOI: 10.1530/endoabs.83.AO2

AO3

Looking for fingerprints of increased susceptibility to adrenal crises

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Background
Adrenal crises (AC) still occur even in educated patients with adrenal insufficiency. Identifying predisposing factors can improve risk assessment and facilitate prevention in this patient population.
Objectives
Investigating clinical and biochemical fingerprints of increased susceptibility to AC.
Material and methods
Our study population included 71 patients with adrenal insufficiency, classified in high and low risk according to the frequency of experienced AC per patient-years. Besides classical clinical and biochemical data, following parameters were assessed: morning serum cortisol prior to as well as 60 and 120 min following the morning glucocorticoid replacement dose, 24h urinary cortisol, salivary cortisol day profile, hair cortisol, plasma and urinary catecholamines and polymorphisms (SNP) of the glucocorticoid- and mineralocorticoid receptor, HSD11B1 and HSD11B2 enzymes and FKBP5 co-chaperone.
Results
52% of the patients were classified as having a high risk for AC. This group received higher glucocorticoid replacement doses (15.2 (4.2-26.4) vs. 11.5 (7-20) mg hydrocortisone-equivalent /m^2, $P = 0.01$) and had higher hair cortisol (0.05 (0.006-1.3) vs. 0.03 (0.004-0.3) pg/mg, $P = 0.02$) and higher plasma metanephrine (MN) levels (23 (6-110) vs 15 (3-59) ng/l, $P = 0.04$) compared to the low risk group. Hair cortisol and plasma MN concentrations significantly correlated with both glucocorticoid replacement dose and AC-frequency in the whole cohort. AC occured more often in carriers of the CC genotype for HSD11B1 SNP rs2235543 (CC vs TC + TT, 97% vs 3%, $P = 0.02$).
Conclusion
The higher glucocorticoid replacement dose seen in high risk patients fits to previous observations and most probably reflects dose adjustments to AC events but may also be regarded as an indicator of increased vulnerability. The higher doses correlate with accumulation of cortisol in the hair follicle. Higher metanephrine levels may be due to increased conversion of normetanephrine to metanephrine. The high risk for frequent AC associated with HSD11B1 SNP rs2235543 implies a certain genetic susceptibility.

DOI: 10.1530/endoabs.83.AO3

AO4

Effects of Fibroblast factor 21 to adrenal renewal after chronic hypercortisolism

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Cushing's syndrome (CS) is a hormonal disorder characterized by chronic high levels of circulating cortisol. Patients treated for CS develop chronic adrenal insufficiency (AI) and hypothalamus-pituitary-adrenal (HPA) axis dysfunction. Long-term treatment with glucocorticoids (GC) is mandatory to overcome AI. Fibroblast growth factor (FGF) -21, a key regulator of metabolism, has a bidirectional relationship with GC that bypasses the negative feedback of the HPA axis. In this study, we aimed to investigate the potential effects of FGF21 treatment in the adrenal gland in a mouse model with AI post chronic hypercortisolism. Male mice received corticosterone (CORT) or vehicle (VEH) in the drinking water for 5wks, followed by a 3d tapering period. After this period, the animals developed AI post-CS and were injected daily with recombinant FGF21 for 7d. Plasma circadian and stimulated CORT and ACTH levels were assessed by immunoassay. Adrenal proliferation was determined by Ki67 staining. Genes from the liver and adrenal gland were determined by qPCR. During active Cushing, CORT-treated mice displayed a decreased fasting plasma glucose compared to VEH due to basal hyperinsulinemia that maintains even during the glucose tolerance test. After treatment, AI-FGF21group were challenged with FGF21, and at 3h they presented a lower ACTH/CORT ratio than the AI-VEH group meaning that their adrenals are more responsive to ACTH. As expected, during the nocturnal circadian cycle and hypoglycemia, AI-groups had decreased plasma CORT levels than CTL groups. Interestingly, AI-FGF21 mice display higher CORT plasma levels with higher Fgf21 liver expression during the circadian cycle than AI-VEH mice. Moreover, the number of proliferating cortical adrenal cells, identified by Ki67 staining, was higher in the AI groups than in CTL groups, although there was no difference between the AI groups. In line with this result, AI groups maintained upregulated stem/progenitor markers compared with their respective treatment CTL groups. Interestingly, in hypoglycemic conditions, AI-FGF21 mice presented higher adrenal Sonic hedgehog (Shh) expression levels than CTL-FGF21 and AI-VEH mice. Our data describe that FGF21 contributes to maintaining a sustained CORT secretion and suggests that FGF21 accelerates and supports the adrenocortical cell renewal during AI.

DOI: 10.1530/endoabs.83.AO4

AO5

Bilateral primary aldosteronism prediction by Integer scoring system

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Background
Adrenal venous sampling (AVS) is the gold standard to differentiate patients with unilateral primary aldosteronism (UPA) from those with bilateral disease (BPA).
Objective
The aim of this study was to evaluate the efficiency of using the online Integer scoring system in predicting BPA, as a possible surrogate for AVS.
Methods
We performed a retrospective analysis of 105 patients (66 female, median age at diagnosis 53 years (20-75)) treated for primary aldosteronism (PA) in our center between 2015 and 2022. AVS was bilaterally successful in 86 (82 %) patients. According to AVS 58 (55 %) patients were diagnosed as UPA, 37 (35 %) as BPA and in 10 (10 %) the result was inconclusive. The Integer score was calculated in 86 patients, 52 (60 %) diagnosed with UPA and 34 (40 %) with BPA according to AVS. It was based on serum potassium level, sex, imaging finding on CT, baseline plasma aldosterone concentration and baseline aldosterone to renin ratio. The result between 8 and 12 was considered as predictive for BPA.
Results
Of 34 patients diagnosed with BPA using the AVS, the Integer score was diagnostic in 9 of them, giving a positive predictive value of only 26 %. In 50 of 52 patients diagnosed with UPA using the AVS, the Integer score was less than 8, giving a negative predictive value of 96 %. The sensitivity of this scoring system was 82 % and specificity only 67 %.
Conclusion
Our results suggest that Integer scoring system is not applicable for PA subtype prediction in our center and that each center should determine their own score. To the extent that each center does not have a scoring system, AVS remains the only diagnostic method for subtyping PA.

DOI: 10.1530/endoabs.83.AO5

AO6

Adrenal venous sampling in tertiary centre from 2015 to 2022

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Background
Adrenal venous sampling (AVS) is considered the gold standard for differentiating an aldosterone- producing adenoma (aPA) from bilateral adrenal hyperplasia (BAH).
Objective
The aim of this study is to present our experience with this method in our hospital.
Methods
We performed a retrospective analysis of 105 patients who underwent the AVS protocol at our centre between 2015 and 2022 for PA.
Results
AVS was performed 115 times in 105 patients, and in 20 patients AVS was performed 2 times. AVS was successful in 86 patients (82%). Among them, 66 patients were female (63%) and median age of all our patients was 53 years (20-75). In 62 patients (65%), the potassium level was lower than 3.6 mmol/l. The main reason for work-up was hypokalaemia in 37 patients (35%). AVS result and CT scan were compatible in 59 patients (60%). According to AVS, APA was diagnosed in 58 (55%) patients, BAH in 37 (35%) patients and in 10 (10%) patients the diagnosis was inocclusive. Surgery was performed in 46 (44%) patients and 58 (56%) patients were treated with medication. Complete biochemical remission was seen in 20 (84%) patients and partial biochemical remission in 2 (8%) patients. 2 (8%) patients had subclinical Cushing's syndrome and did not show biochemical remission. Complete clinical remission was seen in 13 (38%) patients, partial clinical remission in 18 (53%) and 3 (9%) patients had no clinical remission. AVS was more successful in the last 4 years than in the years before (83% vs. 69%).
Conclusion
Our results show a high rate of successfully performed AVS. Prolonged hypertension could be one of the reasons for partial biochemical remission.

DOI: 10.1530/endoabs.83.AO6

Poster

AP1

Prader-Willi syndrome proteins NDN and MAGEL2 are implicated in HPA axis regulation

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Background
The adrenal gland produces corticosteroids essential for hydromineral and metabolic homeostasis. It is organised, in mice, in two concentric layers. The zona glomerulosa (zG) and fasciculate (zF), renewed from progenitors located in the capsular periphery. Centripetal renewal and maintenance of cortical zonation are dependant of a balance between WNT/β-catenin and ACTH/PKA signalling pathways. They provide recruitment and consecutive differentiation of progenitors into zG and zF. In the adrenal cortex, zG to zF blockage caused by loss of Senp2 is associated with over expression of Prader-Willi imprinted genes Ndn and Magel2. This is similar to the loss of SENP2 in brown preadipocytes, where Ndn is upregulated and prevent brown adipocyte differentiation. Ndn and Magel2 are implicated in Prader Willi syndrome, a complex genetic disorder affecting multiple endocrine organ and possibly the hypothalamus-pituitary-adrenal axis (HPA).

Objectives
Evaluate the contribution of NDN and MAGEL2 in HPA physiology and response to stress.
Methods
We investigated NDN expression in the adrenal and under several genetic and pharmacologic stimulations. We then submitted Ndn-/- Magel2-/- mice to mild stress and explored the HPA physiology through measurement of peptides and steroid hormones.
Results
We found expression of NDN restricted to the zG in the adrenal and negatively regulated by ACTH via PKA signalling. We show that even though NDN and MAGEL2 loss does not lead to morphological changes, their deletion induces blunted stress response and leads to accumulation of ACTH precursor Pomc in the pituitary.
Conclusion
We can conclude that NDN and MAGEL2 are important actors of proper response to stress. Conditional models targeting the pituitary will lead to better understanding of the mechanisms at stake.

DOI: 10.1530/endoabs.83.AP1

AP2

Autoimmune polyglandular syndrome type 1 in siblings: assembling the jigsaw puzzle

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Background
Autoimmune polyglandular syndrome type 1 (APS-1) is a rare autosomal recessive, monogenic disease, that could be presented as a group of various symptoms, but clinical diagnosis requires existence of minimum two of three leading disorders: chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenocortical insufficiency.
Case Presentation
We report the clinical cases of two siblings with APS-1, one 28-year-old male and one 25-year-old female. He is presenting at the age of 3.5 years with Addison's disease, as well as with hypoparathyroidism at the age of 4 years. Meanwhile, at the age of 4 years, onychomycosis, enamel dysplasia and diffuse alopecia were presented in the female, along with hypoparathyroidism. Furthermore, at the age of 11 years, the diagnosis of Addison's disease was made in the female, and at the age of 13.5 years Hashimoto's thyroiditis was diagnosed. The onset of menarche was at the 14 years, but she further developed hypogonadism as a manifestation of the autoimmune oophoritis. Hormonal replacement therapy was initiated for both siblings, including hydrocortisone and fludrocortisone, as well as levothyroxine and levonorgestrel-ethynyl estradiol to the female. Because of hypoparathyroidism, alfacalcidol with calcium supplement were established for both siblings. Since hypercalciuria was confirmed with recurrences of deep hypocalcemia episodes in the female, hydrochlorothiazide was also introduced into the therapy. Moreover, gastrointestinal endoscopy showed chronic atrophic pangastritis with active Helicobacter pylori (H. pylori) infection and chronic duodenitis, enteritis and colitis. H. pylori first-line eradication therapy was initiated. Values of fecal calprotectin, anti-transglutaminase antibodies IgA, fecal PMN-elastase and bile acids were unremarkable. Genetic testing detected a homozygous c.769C > T (R257X (p.Arg257X)) AIRE mutation in both siblings.
Conclusions
Although this is a rare disease, clinicians should be aware of it, especially in people under 30 years of age with more than one endocrine disorder, because timely diagnosis avoids its life-threatening conditions.

DOI: 10.1530/endoabs.83.AP2

AP3

Recurrent paraganglioma in patient with aneurysmal disease

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Background
Duration of postoperative follow-up in patients with pheochromocytoma/paraganglioma (PPGL) is still not clearly specified. It is estimated that 5-year risk of a new events (metastatic/recurrent disease) after surgery is 27% in young patients, 25% in those with paraganglioma and around 10% in older patients and those with pheochromocytoma. Arterial aneurysms (AA) accompanying PPGL are described as complication/comorbidity that affects prognosis in these patients.
Case Presentation
A 72-year old male patient with five-year history of: hypertensive crises (max 220/130 mmHg), bradycardia to tachycardia (HR 45-120/min), orthostatic hypotension, night sweating and de novo diabetes mellitus, was presented at our Clinic. He had right-side adrenalectomy 18 years before (high risk procedure due to multiple AA), after the same clinical presentation and was diagnosed with composite tumour paraganglioma-ganglioneuroma (PASS 3). In present, catecholamine hypersecretion was confirmed in 24h urine samples - high noradrenaline (6600-12000 nmol/24h) and normetanephrine (11.55-24.40 umol/24h), together with high chromogranine A 974 ng/ml. CT found retroperitoneal interaortocaval tumour 47.9x35.6mm, MIBG scintigraphy was negative, FDG/PET CT showed retroperitoneal mass (SUVmax 35.6) and nodules in mediastinum and left lung (SUVmax 3.9 and 4.8 respectively). Retroperitoneal tumour extirpation was managed, with perioperative complication - left kidney failure, due to a thrombosis of aneurysmatic left renal artery. Pathohistological diagnosis was paraganglioma (PASS 2, Ki67 5.6%). Resolution of all features was observed after surgery, adrenal medulla metabolites were in reference range and lung nodules were CT described as fibrosis. Genetic analyses on MEN2, SDH and VHL are still ongoing.
Conclusions
Current guidelines suggest that patients with PPGL should be followed for at least 10 years after surgery and with extra-adrenal tumour or genetic PPGL should be followed lifelong. Abdominal AA (aorta, renal artery) carry on an additional effect on morbidity and mortality of patients and should be monitored closely and multidisciplinary.

DOI: 10.1530/endoabs.83.AP3

AP4

Malignant PPGLs - diagnosis and treatment challenges in a developing country-case series presentation

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Introduction
Malignant pheochromocytomas and paragangliomas (PPGLs) are rare, and knowledge of the natural history is limited.
Material Methods
Data of 7 (7.6%) (out of 109) patients with malignant PPGLs referred to a Tertiary Centre of Endocrinology from Bucharest, Romania, were retrospectively collected. Follow-up ranged from 2004 to 2022. Demographic data, genetic status, site and size of primary tumor, biochemical activity, metastasis time (synchronous/metachronous), therapeutic approach and outcome were analysed.
Results
Six women and 1 man were included in our analysis. Follow-up duration was 14 $\pm$ 7.2 years. Mean age at diagnosis was 50.2 $\pm$ 14.3 y.o. One patient had RET pathogenic variant, one had Carney-Stratakis Syndrome. For the rest of the patients, we were unable to perform genetic test. Four patients had right PHEO, 2 had bilateral PHEO and 1 had retroperitoneal PGL as the primary tumor. Mean tumor dimensions were 4.3 $\pm$ 2.1 cm. The secreting pattern was noradrenergic in 5 patients and adrenergic in 2 of them. Three patients had metachronous metastatic disease (at 10, 8 and 1 years from the first diagnosis). The rest of four had synchronous metastatic disease. All the patients underwent surgery of the primary tumour. Furthermore, one of them had only MIBG therapy, one had MIBG therapy plus PRRT, one had MIBG plus systemic chemotherapy, one patient had surgery plus chemotherapy and of the rest of three had only surgery. As outcome, two patients with surgery only and the patient with surgery plus chemotherapy were lost to follow-up (probably due to exitus), one patient with surgery only is disease free; the patient with MIBG has biochemical inactive disease, the patient with MIBG+PRRT has biochemical active disease, but without any clinical signs and the patient with MIBG and chemotherapy has active disease.

Conclusion
The clinical course of patients with malignant PPGLs is remarkably variable and sometimes independent to treatment. In some situation, patients access to advanced therapeutic approach is limited by the local infrastructure, therefore, patients outcome is not only related to disease characteristics but also to treatment accessibility. Further studies for the PPGLs behaviour to different therapeutic methods are required.

DOI: 10.1530/endoabs.83.AP4

AP5

Is it time for age and sex specific diagnostic criteria for patients with adrenal incidentalomas?

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Background
Recent studies showed that cortisol autonomy is age and sex dependent and highly associated with higher all-cause mortality in patients with adrenal incidentalomas (AI). Dehydroepiandrosterone sulphate (DHEAS) has been recognized as a valuable diagnostic tool in patients with (possible) autonomous cortisol secretion.
Objectives
As DHEAS levels are sex and age specific we aimed to evaluate its value as a diagnostic tool in patients with adrenal incidentalomas.
Methods
We evaluated 306 patients, the mean age was 59.8 $\pm$ 9.6 years, 95 men aged 60.05 $\pm$ 9.59 and 211 women aged 59.74 $\pm$ 9.65 years. Based on average menopause age of 51, we stratified women in two groups: $<$ 51 and $\geq$ 51. For the sake of comparison, we age-matched the male group.
Results
The area under the receiver operating characteristic (AUC-ROC) curve for detection of mild cortisol excess in men was 0.65 (95% CI, 0.539 – 0.760, P = 0.012) with a cutoff value of 2.45 µmol/l. In women the AUC-ROC curve was 0.68 (95% CI, 0.610-0.753, P = 0.000) with a cutoff value of 1.27 µmol/l. However, DHEAS lost its significance as a diagnostic tool in age specific groups in men. Whereas, in women, there was an age specific difference between the groups: in women $<$51 years old the AUC-ROC curve was 0.72 (95% CI, 0.558-0.896, P = 0.022) with a cutoff value of 1.85 µmol/l and in women $\geq$ 51 years old the AUC-ROC curve was 0.67 (95% CI, 0.595-0.752, P = 0.000) with a cutoff value of 1.05 µmol/l.
Conclusion
DHEAS is a reliable sex specific diagnostic tool for detection of mild cortisol excess but in female patients DHEAS is also age specific.

DOI: 10.1530/endoabs.83.AP5

AP6

Interplay of MYC and HIF signaling in pheochromocytomas and paragangliomas: Impact on the differentiation and aggressiveness

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The genetic heterogeneity of pheochromocytomas and paragangliomas (PPGL) offers opportunities to develop individualized treatment approaches for affected patients. Therefore, an improved understanding of the molecular features associated with different tumor phenotypes is required. Hypoxia-inducible factor (HIF) 2α-regulated pathways involving the MYC/MAX complex are directly linked to differentiation and aggressiveness in PPGLs. However, the distinct functions of the two MYC oncogenes, c-MYC and MYCN, in this context remain unclear. We have previously shown that expression of Max in Max-deficient pheochromocytoma cells results in a less aggressive cellular phenotype. Moreover, suppression of c-Myc transcription by JQ1 reduced pro-metastatic behavior, but the involvement of Mycn remained unknown. Expression analysis using TCGA data revealed a significant correlation between c-MYC and MYCN expression in PPGLs. Compared to the normal adrenal, PPGLs showed downregulation of c-MYC, while MYCN expression was increased. Moreover, we found negative correlations between the expression of c-MYC and several differentiation markers including TH, SNAP25, PHOX2B and ASCL1, and the opposite relationship for MYCN. To confirm these findings, we used RNAi to downregulate the expression of c-Myc or Mycn in mouse pheochromocytoma cells with (MPCmCherry-H2A) or without (MPCmCherry-EV) expression of Hif2α. The more aggressive MPCmCherry-H2A cells showed an enhanced expression of Mycn, Snap25, Phox2b and Mash1, while c-Myc was repressed. Knockdown of c-Myc or Mycn revealed no effect on the expression of these proteins, which might be explained by the fact that c-Myc to some extent balances the regulation of Mycn and vice versa. Moreover, MYC downstream signaling is further regulated by several other factors, such as MAX. Further work is needed to fully understand the interaction of HIF and MYC signaling in PPGLs and how we might exploit these molecular differences for more advanced treatment approaches.

DOI: 10.1530/endoabs.83.AP6

Thyroid

Oral

TO1

Does mild form of subclinical hypothyroidism needs treatment?

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Background
Overt hypothyroidisms warrants L-T4 treatment, but treatment in subclinical hypothyroidism (ScH), especially in mild form of ScH (TSH between 4,2-10mU/l and normal free thyroxine) is unknown.
Objectives
To compare the presence of risk factors for atherosclerosis in patients with mild form of ScH to euthyroid subjects.
Methods
Prospectively 67 consecutive patients with newly diagnosed ScH, and 30 healthy subjects were recruited from the outpatient department of University clinic of endocrinology in Skopje, R. of N. Macedonia. Measurement of thyroid hormones, thyroid antibodies, blood pressure, lipids, and carotid intima media thickness (CIMT) were performed in all patients.
Results
Mean TSH value in ScH group was 8.71 $\pm$ 1,9 mU/l. TSH value above 7mU/l was associated and positively correlated with symptoms of hypothyroidism. Prevalence of hypertension in ScH group was higher than the control group (35.4% vs. 13.3%, $P = 0,03$), with a 3.5 times higher risk for hypertension (OR = 3,5 95%CI 1,1 – 11,4). In patients with mild form of SCH statistical significant difference in percentages of patients with arterial hypertension, hypertriglyceridemia, and values of total cholesterol/HDL-C and LDL/HDL above upper reference value were found (33.9 vs. 13.3%, 33.9 vs. 10%, 26.5 vs. 6.9%, 30.6% vs. 10.3%, respectively $P < 0.05$). Mean CIMT was statistically significantly higher in ScH patients than the control group (0.61 $\pm$ 0.1 vs. 0,56 $\pm$ 0,1 mm, $P = 0.03$), but not different between the mild form of ScH and control group ($P = 0.08$). Positive thyroid antibodies in the ScH group have no statistically significant influence on the CIMT.
Conclusions
In a small study, mild form of ScH was associated with higher risk for atherosclerosis, so these patients may benefit with L-T4 treatment.
Key words. Subclinical hypothyroidism, risks factors, atherosclerosis, carotid intima media thickness

DOI: 10.1530/endoabs.83.TO1

TO2

Subacute thyroiditis (SAT) during the COVID-19 pandemic: preliminary data from the "ESE Covid Grant 2021" project

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Background
A possible association between severe acute respiratory syndrome coronavirus (SARS-CoV)-2 pandemic and subacute thyroiditis (SAT) has been reported.
Objectives
To evaluate SAT clinical characteristics, correlating them to virus exposure and/or vaccine and to evaluate thyroid function according to the length of time after symptoms onset.
Methods
We performed a prospective, observational, multi-centre study, considering three Italian centres. Patients with documented SAT diagnosis were enrolled from November 2020 to May 2022 and followed up for 12 months. SARS-CoV-2 infection (i.e. positive rhino-pharyngeal swab obtained within 3 months before SAT onset) and vaccination were recorded. This interim analysis was performed considering the visit performed at diagnosis.
Results
A total of 67 subjects (79.1% F, 20.9% M) were enrolled (age: 49.9 + 12.9 years). The cohort was divided considering the time between symptoms onset and endocrinological evaluation: Group1 included patients who underwent visit within 15 days (44.8%), whereas Group2 those who delayed visit beyond 15 days (55.2%). No difference in inflammation indexes and thyrotoxicosis rate (70.0% vs 70.3%, $P = 0.381$) was found between groups. Hypothyroidism rate was higher in Group2 than in Group1 (8.1% vs 0.0%, $P = 0.004$). The entire cohort was divided according to either SARS-Cov2 infection (13 patients–19.4%) or vaccination (23 patients–34.3%). Thyrotoxicosis rate and inflammation indexes were not significantly different between patients with or without SARS-Cov2 infection and/or vaccination. At multinomial logistic regression analyses, thyrotoxicosis was predicted by erythrocyte sedimentation rate (ESR) elevation ($P < 0.001$), SARS-CoV-2-vaccination ($P = 0.002$) and respiratory symptoms ($P < 0.001$).
Conclusions
Neither SARS-CoV-2 infection nor vaccination affected the clinical SAT presentation. However, SAT-related thyrotoxicosis was predicted by ESR elevation, vaccination, and respiratory symptoms.
DOI: 10.1530/endoabs.83.TO2

TO3

Combined levothyroxine/liothyronine therapy improves quality of life in hypothyroid thyroidectomized patients

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Introduction
Despite normal thyroid stimulating hormone (TSH) serum levels, 10% of hypothyroid patients treated with LT4 complain of hypothyroidism symptoms, likely linked to decreased availability of free triiodothyronine (fT3). Thus, combined levothyroxine/liothyronine (LT4/lT3) therapy was suggested to ensure a more physiological balance in peripheral tissues.
Aim
To evaluate the effectiveness of combined LT4/lT3 therapy in thyroidectomized subjects, considering peripheral markers and quality of life.
Methods
An interim analysis of a prospective, randomized, placebo-controlled, double-blinded clinical trial was performed. Totally thyroidectomized patients treated with LT4 and with TSH levels within reference range in the previous three months were enrolled and randomized in two groups: combined LT4/lT3 therapy (study group) and LT4 + placebo (control group). Lipid profile, sex hormone binding globulin, osteocalcin, C-terminal telopeptide and bone alkaline phosphatase were evaluated as peripheral markers. Quality of life was evaluated by ThyPRO 39 questionnaire.
Results
139 patients (age 55.6 + 12.1 years) were enrolled, 70 in the study and 69 in the control group. Combined LT4/lT3 therapy resulted in more frequent iatrogenic thyrotoxicosis than LT4 monotherapy (9.8% vs 2.2%; $P < 0.05$), requiring more frequent dose adjustments (44.5% vs 22.5%; $P < 0.001$). Peripheral markers neither changed between study and control groups, nor among visits. Combined therapy improved quality of life, measured by a reduction in anxiety ($P = 0.019$), depression ($P = 0.037$), emotional susceptibility ($P = 0.034$) and item 12 ($P = 0.005$) from baseline to visit 3, while no significant differences were detected in controls.
Conclusion
Six months of combined therapy significantly improved quality of life, but did not lead to a change in peripheral tissue markers. However, subjects treated with LT4/lT3 therapy require more dose adjustment and are at higher risk of overtreatment.
DOI: 10.1530/endoabs.83.TO3

TO4

Should we reduce the number of fine-needle aspirations of thyroid nodules?

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Background
Most thyroid nodules are benign, but they can also be associated with thyroid cancer. To be sure how to proceed with an ultrasound suspicious nodule (EU-TIRADS), it is recommended to perform a fine needle aspiration (FNA) biopsy and classify the nodule in the BETHESDA system.
Objectives
The aim of this study was to investigate whether we perform an excessive number of FNA according to the EU-TIRADS classification in order to reduce the number of unnecessary aspirations.
Methods
This retrospective analysis in the Department of Endocrinology, University Hospital Zagreb, included 351 FNA from January 2021 to March 2022. Five endocrinologists performed FNA in patients aged 18 to 83 years (median 53 years), 82% were women. Thyroid nodules were a median of 20 (6-77) mm in size.
Results
Most of the aspirated nodules were classified as EU-TIRADS 3 (48%), 22% as EU-TIRADS 5, 21% as EU-TIRADS 4, and 9% as EU-TIRADS 2. The majority of cytologic findings were BETHESDA 2 (46%) and BETHESDA 1 (40%). In addition, 43% of the EU-TIRADS 5 classified nodules were analysed as BETHESDA 1, only 4% as BETHESDA 5, and 8% as BETHESDA 6. Furthermore, the size of the nodules did not affect the BETHESDA results ($P = 0.530$). There was a significant statistical difference between patient age and BETHESDA findings ($P = 0.027$), the median age of patients classified as BETHESDA 1 was 56 years, while the median age of patients classified as BETHESDA 5 was 38 years. Twenty-two nodules underwent repeat FNA, and none were analysed as BETHESDA 4 or 5.
Conclusion
The high percentage of BETHESDA 1 and 2 findings may indicate that too many FNAs are being performed in our department, so we should redefine and calibrate the indications for performing an FNA and choose to continue to observe more patients rather than perform an FNA.

DOI: 10.1530/endoabs.83.TO4

TO5

Is our recommendation to quit smoking considered in patients with Graves' Disease and Graves' Orbitopathy?

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Background and Objective
Smoking increases the risk of Graves' orbitopathy (GO) in patients with Graves' disease (GD). Therefore, smoking cessation should be recommended to all patients with GD. This study aimed to investigate whether smoking cessation recommendations were taken into account in patients with GD and whether there was a difference in terms of smoking cessation between those with and without GO.
Methods
Smoking status of the cases followed up with GD, who were active smokers when diagnosed, were questioned by telephone visit. The relationship of these data with the presence of GO was evaluated.
Results
74 smokers with GD were included in the study. The mean age of the patients was 48.0 $\pm$10.9 years, and 62.2% were women. All patients were advised to quit smoking by their physicians. While the number of cigarettes was 20 (10-22)/day at the first visit, the current cigarette use was 7 (0-15)/day, ($P < 0.001$). Forty-nine (66.2%) of the patients had GO. It was found that 49% of patients with GO and 36% of those with non-GO quit smoking (p:0.08). The decrease in number of cigarettes/day after the physician's recommendation was significantly higher in patients with GO than patients with non-GO (-95.4% vs. -54.5%), ($P = 0.02$).
Conclusion
Although the importance of smoke cessation was emphasized in all patients with GD, we observed that smoking cessation advice was more followed in the GO group in our study. Explaining in detail that smoking in GD may worsen the course of the disease and impair the quality of life in the possible development of GO, may lead patients to consider smoking cessation recommendations more.
Keywords: Graves disease, Graves orbitopathy, smoking, cigarette, smoke cessation

DOI: 10.1530/endoabs.83.TO5

Poster

TP1

The impact of lockdown on thyroid hormone metabolism in patients on levothyroxine replacement therapy residing in Adjara

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Background
The Covid 19 pandemic has significantly changed people's lives. For patients with chronic diseases, social isolation and distancing have become a provocative factor in metabolic control disorders of varying degrees. Patients avoided hospital visits as much as possible due to fear of infection. Also for the representatives of the medical field, the pandemic has become the basis for new ways of consulting patients (remote, teleconsultation). The aim of the study was to investigate the impact of lockdown on thyroid hormone metabolism in patients on levothyroxine replacement therapy residing in Adjara (The study includes the results of two clinics)
Materials and Methods
A retrospective cohort study identified patients who underwent a dispensary at an endocrinology clinic in 2019 and 2021 due to hypothyroidism and were on replacement therapy with levothyroxine. Demographic data of patients' age, sex, and diagnosis were in the history of the disease. TTH and TT level was also assessed, whether there were mid-term examinations and consultations (via social network/telemedicine service).
Results and Discussion
Data from 54 patients were reviewed as part of the study. Average 18 to 55 years, 18 males and 36 females. Of these, 38 patients were diagnosed with chronic autoimmune thyroiditis, in 16 cases with postoperative hypothyroidism. In 2019, patients 'TTH ranged from 0.9- 3.2 (norm 0.5 to 5.0 mIU / L) TTH- 0.8-1.4 (0.7 to 1.9ng / dL). Patients received levothyroxine 100 mg - 150 mg; During the pandemic period, 32 (59%) patients were examined and their thyroid status was stable (using online services), and in 8 (14.8%) cases, iatrogenic thyrotoxicosis was observed (arbitrary dose increase), 11 (20.3%) cases- hypothyroidism (decrease dose); 3 (5%) In the case of the same dose, despite the lack of control, the thyroid profile was stable.
Conclusion
The results of the study show that social isolation and distancing is a risk factors for decompensation of chronic disease, the use of online services for such patients is innovative and useful for the stability of their condition.

DOI: 10.1530/endoabs.83.TP1

TP2

Unilateral Graves Orbitopathy-case report

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Background
Graves' Orbitopathy (GO) is the most common extra thyroidal feature of autoimmune thyroid disease presentation. It is characterized by development of orbital inflammation that involves both, adipose tissue and extra-ocular muscles. The condition is associated with increased psychological burden and in severe cases may lead to optic nerve damage, causing blindness. While most patients with GO present with bilateral disease, asymmetric or unilateral GO may affect a significant proportion of patients diagnosed with the condition. It has been shown that older age, male sex, active and severe disease are the most significant factors for development of unilateral form of the disease. The pathophysiological mechanisms of unilateral presentation of GO still remains uncertain.

Case presentation
We present a case of 39 years old male patient that presented in ambulatory setting with unilateral proptosis of the right eye that developed during a period of two months before consultation. The patient complained of rare episodes of diplopia during fatigue, occasional lacrimation and itching. He was in good general condition, and did not report any other symptoms usually seen in state of hyper function of the thyroid. Patient was active smoker, obese, with BMI of 38 kg/m2 and was diagnosed with hypertension during his frequent visits in our clinic and was treated accordingly. He had no other prior comorbidities and no prior chronic therapy. Biochemical analysis were in reference range. The thyroid function tests were in addition of thyrotoxicosis with supressed TSH of 0,001(0,27-4,5) uIU/ml, and slightly elevated fT4 of 29,96(9,5-25) pmol/l, with positive antibodies to TSH receptor -10,8 IU/l(0-1,76) and negative A-TPO. Ultrasound of thyroid was without any significant appearance, except of discreetly restructured parenchyma of the gland. The measurement of the anterior projection of the eye with Hertel exophthalmometar showed proptosis of the right eye of 28mm vs normal finding on the left eye of 17mm. Calculated CAS score of the patient was 4. Appointed orbital MRI showed pronounced thickening along the entire length of m.rectus medialis of the right orbit with compression of the optic nerve, as a result of massive inflammatory process of the rear compartment of the orbit Patient was advised cessation of smoking and started with thyroid suppression therapy of 20 mg Methimazole and titrated every three weeks to a low maintenance dose of 2,5 mg. After three months of therapy, an euthyroid state was accomplished with TFT of TSH 0,122mIU/ml, fT4 of 17,27 pmol/l and A-TSHR of 2,68IU/l. Since the severe involvment of the right optic nerve, it was indicated by ophtalmologist, to start with pulsatile corticosteroid therapy. He received cumulative dose of 4, 5 g methylprednisolone, six weekly courses of 500 mg and six weekly courses of 250 mg. After six months of initial start of the therapy, control MRI of the orbit showed complete resolution of the inflammatory process of the right eye. Control exophthalmometry measurement of the right eye proptosis was also improved by 7mm (Hertel 21mm). Patient was continued with low maintenance dose of thyroid suppression therapy and was advised cessation of smoking.
Conclusions
Medical treatment of GO has proven to be most effective during active phase of the disease. Approximately 35% of the patients with GO do not respond to immunosuppressive therapy, so it is a priority to recognise and focus the resources during this period. It has been observed that patient treated with pulsatile corticosteroid therapy for GO have reduced risk of hyperthyroidism relapse, which shows that immunosuppression is important for resolution of the process, especially in younger patients that relapse more often. Clinical activity score has a high predictive value for the outcome of immunosuppressive therapy. Some of the studies indicate that asymmetrical or unilateral GO can be an indicator of greater disease activity and severity and should prompt referral to a tertiary institution of this type of patients. Thyroid-related orbitopathy should be considered as a differential diagnose in all cases involving unilateral or asymmetric exophthalmos.

DOI: 10.1530/endoabs.83.TP2

TP3

Possible factors of hypercalcitoninemia in a benign nodular thyroid disease

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Background
Calcitonin (CT) is a specific marker of Medullary Thyroid Carcinoma (MTC). However, its routine measurement in the assessment of nodular thyroid disease (NTD) remains controversial because MTC is rare and CT may have false positive results.
Objective
To evaluate the frequency of hypercalcitoninemia (hyperCT) among patients with benign NTD and to disclose possible underlying factors.
Methods
Retrospective study including patients investigated for NTD between 2018 and 2021. HyperCt was defined as CT $>$ 14.5 pg/ml, according to our hospital cut-off. Patients either with familial history of/or with MTC, MEN2 or CT $>$ 100 pg/mL were excluded.
Results
Hypercalcitoninemia was documented in 75 cases out of 3209 CT requests (2,3%) corresponding to 75 individuals: 89.3% men, mean age 64.6 $\pm$ 12.5 years (min 21 – max 88). Median CT value was 19.9 (min 15- max 78) pg/mL. Median CT was 17.3 and 20.5 pg/mL respectively in women and men (P = 0.28). In 62 individuals (82,7%), at least one factor likely to contribute for the CT increase was identified: Hashimoto's thyroiditis - n=2, smoking - n=8, treatment with proton pump inhibitors (PPI) - n=19, treatment with beta-blockers (BB) - n=8, treatment with PPI + BB - n=4, treatment with corticosteroids (CCT) - n= 3. A comparative analysis of the CT level based on the presence or absence of each potential influencer was not statistically significant. Eighteen patients had chronic kidney disease (CKD), 7 under haemodialysis. In CKD patients, median CT was 23.6 (min 14.8 – max 72.5 pg/mL). In a linear regression analysis, the presence of CKD influenced the CT result (P = 0.008).
Conclusions
In this series, CKD and the use of PPI and/or BB are the more prevalent causes of non-malignant hypercalcitoninemia.

DOI: 10.1530/endoabs.83.TP3

TP4

Interplay between thyroid, amiodarone and heart - case presentation

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Background
Amiodarone is a commonly used antiarrhythmic drug, but because of its abundance with iodine and a direct toxic effect on the thyroid, it can have side effects like hypo- and hyperthyroidism. There are two types of amiodarone-induced thyrotoxicosis (AIT). We present a case which demonstrates the importance of timely diagnosis and appropriate treatment of amiodarone-induced thyrotoxicosis in patients with serious cardiac comorbidities.
Case Presentation
A 74-year-old male with a history of multinodular goiter, hypertension, paroxysmal atrial fibrillation, implanted mechanical aortic valve because of aortic regurgitation, left ventricular hypertrophy, and reduced ejection fraction was referred to our clinic because of hyperthyroidism. Four months prior to this visit, amiodarone was discontinued by his cardiologist after five years of use. At that time, the patient had a thyroid stimulating hormone (TSH) level below the lower reference limit and no hypermetabolic symptoms. No thyrostatic treatment was initiated nor was he referred to an endocrinologist. Two months later, the patient developed symptoms of hyperthyroidism; TSH was suppressed. His primary care physician started him on 10 mg of thiamazole daily. After two more months, the patient's state worsened. He was referred to an otorhinolaryngologist. Urgent restoration of stable clinical state was needed because the patient had cardiac decompensation and overt hyperthyroidism with suppressed TSH and high free thyroxine (FT4) level, as well as prolonged prothrombin time due to coumarin use. After cardiac recompensation, normalization of the coagulogram, and reduction of the FT4 level under full thiamazole dose (which stayed slightly above the upper reference limit), thyroidectomy was performed. Significant clinical and laboratory improvement followed.
Conclusions
AIT has been associated with increased morbidity and mortality, especially in older patients with impaired left ventricular function. The importance of rapid recovery and stable maintenance of euthyroidism should be emphasized to both endocrinologists and non-endocrinologists.

DOI: 10.1530/endoabs.83.TP4

TP5

Autoimmune hyperthyroidism relapse with active severe Graves' orbitopathy during second trimester of pregnancy, and thyrotoxicity development in offspring

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Background
Graves' disease exacerbations during pregnancy usually occur in the first trimester with very rare cases of disease manifestation or relapse in second/third trimester. Up to five percent of neonates that are born to women with diffuse toxic goiter develop symptoms of hyperthyroidism because of transplacental transfer of TSH-receptor autoantibodies.
Case presentation
Female, born in year 1990, with a history of symptomatic autoimmune hyperthyroidism first diagnosed in 2017. At the time she received thyrostatic therapy with Carbimazole with good results and stable remission during first pregnancy and delivery in February 2021. Relapse of autoimmune hyperthyroidism occured in January 2022, when the patient developed active severe Graves'

orbitopathy in the 26th week of her second pregnancy. Outpatient therapy with Thiamazole 10 mg twice daily, and Anaprilin 20 mg twice daily was initiated. Due to active severe Graves' orbitopathy, the patient received a course of intravenous Methylprednisolone 500 mg once weekly for 5 weeks, but the treatment was discontinued due to arterial hypertension and malaise. The pregnancy ended in spontaneous vaginal delivery in week 35^{+6} with the newborn exhibiting symptoms of increased appetite, restlessness, and tachypnoea. The newborn was hospitalized at Children's Clinical University Hospital where neonatal thyrotoxicosis was diagnosed. At the time the patient discontinued breast-feeding after two weeks, and the dose of intravenous Methylprednisolone was increased to 500 mg 1x/week, and the dose of Thiamazole was increased to 30 mg daily. In control blood tests free thyroid hormones are normalizing, orbitopathy symptoms are decreasing over time.
Conclusions
Early diagnosis of autoimmune hyperthyroidism and achieving optimal disease compensation for the mother, is important for reducing complications in pregnancy outcomes, and maintaining the health of the mother and newborn.

DOI: 10.1530/endoabs.83.TP5

TP6

Thyroid parameters changes in mother-newborn pairs living in a selenium deficient environment

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Background
Selenium (Se) is a crucial micronutrient for thyroid gland homeostasis. Acting through iodothyronine deiodinases, it regulates thyroid hormones synthesis and by glutathione peroxidases removes harmful free radicals. The Se role in pathogenesis of autoimmune thyroiditis is currently under investigation. Se supplementation decreases antithyroid antibodies during pregnancy, may prevent from postpartum thyroiditis and is approved for treatment of mild Graves' ophthalmopathy.
Objectives
We aimed to determine the impact of Se supply on thyroid parameters and antithyroid antibodies in pregnant females and their newborns.
Methods
115 mother-child pairs without Graves' disease were recruited at term delivery from obstetric department in one Polish centre. The blood was collected before childbirth in mothers and during the third phase of delivery from the newborns' cord blood. Se status was assessed by measuring serum Se, selenoprotein P (SELENOP) concentrations and glutathione peroxidase 3 (GPX3) activity. Thyroid assessment encompasses thyrotropin (TSH), free tetraiodothyronine (fT4), free triiodothyronine (fT3), anti-thyroid peroxidase antibodies (a-TPO), anti-thyroglobulin antibodies (a-Tg) and anti-thyrotropin receptor antibodies (TRAb). All parameters were assessed in mothers and newborns.
Results
Majority of mothers and newborns had poor Se status. Newborns with optimal Se supply had lower median TRAb (IQR) concentrations 0.27 (0.07 - 0.37) IU/l, than in Se-deficient group 0.30 (0.30 - 0.56) IU/l, $p = 0.02$. Similarly, lower TRAb was detected in in Se-sufficient mothers 0.30 (0.27 - 0.70) IU/l, than in Se-deficient 0.63 (0.38 - 0.82) IU/l, with borderline significance ($U = 639.5$, $p = 0.07$). Newborns' TRAb concentrations were negatively correlated with their both Se ($R = -0.27$, $p = 0.011$) and SELENOP ($R = -0.22$, $p = 0.038$) levels. Additionally, mothers' selenoproteins correlated positively with children ft4: Se ($r = 0.27$; $p = 0.01$) and GPX3 ($r = 0.23$; $p = 0.02$).
Conclusions
Proper maternal Se supply may improve newborns' thyroid parameters and potentially decrease the risk of neonate thyrotoxicosis in the first days of life, by reducing newborns' TRAb level. Further studies are required to confirm this hypothesis.

DOI: 10.1530/endoabs.83.TP6

TP7

Therapeutic challenge in patient with ventricular septal defect, atrial fibillation and thyreotoxicosis: Case report

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Ventricular septal defect (VSD) is a congenital heart malformation that has been identified as an abnormal communication between the ventricles. The defect can be found at any part of the septum. A large VSD allows unimpeded left-right shunt with subsequent development of pulmonary hypertension and shunt reversal. The shunt reversal leads to development of Eisenmenger syndrome. We present the case of 40-year-old female with ventricular septal defect with Eisenmenger syndrome and amiodarone induced thyrotoxicosis. At the time when diagnosis was made, transthoracic echocardiogram showed dilated left atrium with mitral regurgitation 1-2+. In the membranous part of the septum there was defect in size 18-19 mm, with a bi-directional shunt dominant right - left shunt. The right atrium and right ventricle were dilated, systolic pressure in right ventricle was 104 mmHg with central venous pressure (CVP) estimated at 15 mmHg, 25 mmHg inferior vena cava, deep inspirium collapse $<50\%$, with impaired systolic function. Right catheterization revealed a great gradient of a difference between medium pulmonary artery pressure (65 mmHg) and the medium pressure at the level of capillaries / arterioles (6 mmHg) which indicates a high resistance at the level of arterioles according to the Eisenmenger syndrome. Patient had had permanent atrial fibrillation as well as episodes of non sustained ventricular tachycardia. At first, amiodarone was induced with satisfying therapeutic response. Since patient had had thyrotoxic crisis, amiodarone was discontinued and implantable cardioverter defibrillator (ICD) was induced. Amiodarone induced thyrotoxicosis occurs in 2-12% patients on chronic amiodarone treatment. Since combination of amiodarone and ICD was the only therapeutic option for this patient, strict control of thyroid status had to be maintained.
Key words: ventricular septal defect, amiodarone, thyrotoxicosis
DOI: 10.1530/endoabs.83.TP7

Endocrine-Related Cancer

Oral

ERCO1

Tumor suppressor role of RBM22 in prostate cancer acting as a dual-factor regulating alternative splicing and transcription of key oncogenic genes

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Background
Prostate cancer (PCa) is one the leading causes of cancer-related deaths among men in developed countries. Therefore, the identification of novel molecular targets for treatment is urgently needed to improve patients' outcomes. In this scenario, our group has recently reported that elements of the cellular machinery controlling alternative-splicing processes might be used as potential novel therapeutic tools for PCa. In this context, although RBM22 has been identified as a key spliceosome component and transcription factor, playing an important role in different cancer-types, its role in PCa remains unknown.
Objectives
To evaluate the potential pathophysiological role of RBM22 in PCa.
Methods
RBM22 levels (mRNA and protein) were evaluated in 4 independent cohorts of patients and two preclinical mouse models (TRAMP/Hi-Myc). The functional (proliferation, migration, tumorsphere- and colony-formation) and molecular (RNA-seq, nCounter PanCancer Pathways Panel) consequences of RBM22 modulation were assessed *in vitro* (LNCaP, 22Rv1, and PC-3 cell lines) and *in vivo* (xenograft model).
Results
We found that RBM22 is downregulated (at mRNA and protein-levels) in PCa samples, and its levels are inversely associated with key clinical aggressiveness features (i.e. extraprostatic extension and perineural invasion). Consistently, a gradual reduction of RBM22 from control to prostatic-intraepithelial neoplasia, and then to poorly differentiated PCa was observed in samples from two transgenic PCa mouse models (TRAMP and Hi-Myc). Notably, overexpression of RBM22 in PCa cells decreased aggressiveness features *in vitro*, and tumor growth *in vivo* using a preclinical xenograft mouse model. These actions were associated with the dysregulation of the splicing of numerous genes, alteration of the activity of key oncogenic signalling pathways (e.g. cell-cycle progression), and to the downregulation of critical upstream regulators of cell-cycle (i.e. CDK1, CCND1 and EPAS1).
Conclusion
Altogether, our data demonstrate that RBM22 plays a critical functional role in the pathophysiology of PCa and invites to suggest that targeting negative regulators of RBM22 expression/activity could represent a novel potential therapeutic strategy to tackle this devastating pathology.

DOI: 10.1530/endoabs.83.ERCO1

ERCO2

Ablation of Znrf3 & Trp53 induces metastatic adrenocortical carcinoma in mice

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Background
Adrenocortical carcinoma (ACC) is an aggressive cancer originating from steroidogenic cells within the adrenal cortex. Unfortunately, half of patients present with metastatic spread upon initial diagnosis, and there is no curative therapy for advanced disease. Genomic analysis has identified that the most aggressive subgroup of ACC patients have overlapping alterations in the WNT/β-catenin pathway and the p53/RB signaling pathway.
Objectives
Create a metastatic ACC mouse model based on patient genomic alterations.
Methods
We used SF1-Cre to inactivate both Znrf3, a negative regulator of the WNT/β-catenin pathway, & Trp53, a potent tumor suppressor, in steroidogenic cells of the mouse adrenal cortex. The ROSA26^{mTmG} reporter was included in the breeding scheme to track metastatic dissemination.
Results
By 6 months of age, mice with individual inactivation of Trp53 (PKO) or Znrf3 (ZKO) did not show tumor formation, while the combined inactivation of Trp53 & Znrf3 (DKO) resulted in aggressive carcinomas that metastasize to the lungs at a rate of 40.1%. Consistent with human patients, these tumors show significantly increased expression of established ACC aggressiveness markers Ki67 & EZH2. By subdividing the DKOs based on their ability to form distant metastasis (indolent vs metastatic), we found that metastatic DKOs are nonfunctioning, dedifferentiated tumors that exhibit massive upregulation of WNT/β-catenin signaling. Furthermore, these unique characteristics are maintained at distant secondary locations, suggesting their importance in the tumorigenic process.
Conclusions
These results establish that combined inactivation of Znrf3 & Trp53 in steroidogenic cells provides a habitable environment for the development of metastatic ACC. The timeline and consistent rate of metastasis in this mouse model highlights its importance for the study of metastatic ACC dissemination, immune-tumor interactions, and potential anti-cancer therapies.

DOI: 10.1530/endoabs.83.ERCO2

ERCO3

Hypothalamus-pituitary-adrenal axis recovery after adjuvant mitotane treatment in patients with adrenocortical carcinoma - a retrospective study

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Introduction
Mitotane is an adrenolytic drug which is used in patients with adrenocortical carcinoma (ACC) and leads to adrenal insufficiency (AI). The aim of this study was to evaluate the time to recovery of the hypothalamus-pituitary-adrenal (HPA) axis after adjuvant mitotane treatment and to determine possible predictive factors.
Materials and Methods
In this retrospective study, we included 19 patients with ACC, ENSAT stage I- III, who were treated with mitotane in an adjuvant setting, during a median time of 24 months (3-47). Patients in whom less than 6 months had elapsed after mitotane discontinuation were excluded. HPA recovery was defined by morning cortisol level of $\geq$350 nmol/l or a cortisol level in the Synacthen test of $\geq$440 nmol/l. Partial HPA axis recovery was defined by morning cortisol level of 250-350 nmol/l without an adequate ($\geq$440 nmol/l) increase in cortisol in the Synacthen test. The median follow-up time was 84 months (36-136).
Results
The HPA axis completely recovered in 10 (53%) patients after a median time of 27 months (12-41). In another 3 patients (16%) we noticed a partial HPA axis recovery whereas 6 patients (31%) still had AI after 126 months of follow-up. There was a trend to longer period to HPA axis recovery in patients who developed central hypothyroidism (CH) during mitotane treatment ($P = 0.067$). Of 7 patient who did not develop CH, HPA axis recovered in 5 after a mean time of 18 months after mitotane discontinuation. In contrast, of 12 patients with CH, in 5 HPA axis recovered after mean time of 74 months whereas remaining 7 still had AI after a respective follow-up of 6, 13, 36, 50, 93, 116 and 126 months.
Conclusion
Our study demonstrated that HPA axis do not recover in a considerable number of ACC patients, even after several years of adjuvant mitotane discontinuation. It appears that the development of CH during mitotane treatment might predict delayed HPA axis recovery.

DOI: 10.1530/endoabs.83.ERCO3

ERCO4

Efficacy and safety of radiation therapy in advanced adrenocortical carcinoma (ACC)

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Background
The ESE-ENSAT guidelines emphasize the role of local therapies and suggest radiotherapy (RT) as an individualized treatment in patients with advanced ACC. However, the evidence for this recommendation is very low.
Objectives
The aim of this study was to retrospectively investigate the efficacy and tolerance of RT in advanced ACC.
Methods
We screened all patients in five European reference centers for ACC since 2000 for RT of advanced ACC. Primary endpoint was progression-free survival of the treated lesion (tPFS). Secondary endpoints were best objective response, overall progression-free survival (oPFS, overall survival (OS), toxicity of the treatment, analysis of predictive factors. In addition, we analyzed patients according the equivalent dose in 2 Gy fractions (EQD2) and the biologically effective dose (BED10).
Results
132 tumoral lesions in 80 patients were identified. They were treated with various RT modalities (stereotactic body RT (SBRT) 35-50Gy (n=36), 'non-SBRT' with 50-60 Gy (n=20) or with 20-49 Gy (n=69), 'single dose RT' (SDRT) 12-25Gy (n=7)). Complete response was detected in 6 lesions. 52 metastases showed partial response, 60 were stable and only 14 lesions progressive. In comparison to non-SBRT with 50-60 Gy, tPFS was significantly shorter in non-SBRT with 20-49Gy (multivariate adjusted HR 5.9; 95% CI 1.89-18.9;$P = 0.002$) and in SDRT (HR 4.8; 95% CI 1.13-20.71;$P = 0.033$), but quite similar as to SBRT (HR 1.8; 95% CI 0.54-6.04;$P = 0.34$). The examination with EQD2 and BED10 indicated similar results. Toxicities with grade 3 or higher did not occur.
Conclusions
Our study provides for the first time evidence from a larger cohort that RT is effective in a proportion of patients with advanced ACC. The retrospective nature and the size of the study are major limitations.

DOI: 10.1530/endoabs.83.ERCO4

ERCO5

PD-1, PD-L1 and CTLA-4 immune checkpoint expression – Is there a prognostic impact on adrenocortical carcinoma?

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Adrenocortical carcinoma (ACC) is a very severe endocrine malignancy with poor prognosis. While cancer immunotherapies have revolutionized the treatment of several cancer entities, the results of initial studies of different immune checkpoint inhibitors in ACC were heterogeneous and clinically substantial responses were observed only in a subset of patients. Expression of immune checkpoint molecules - programmed cell death 1 (PD-1), its ligand PD-L1 and cytotoxic T Lymphocytes-associated protein 4 (CTLA-4) - has been shown to predict response in different, but not all cancer entities. Using immunohistochemistry, a cohort of 129 ACCs was examined for PD-1, PD-L1 and CTLA-4 expression. PD-1, PD-L1 and CTLA-4 were present (threshold of $\geq 1\%$ of cells) in 17.4%, 24.4% and 67.8% of samples, respectively, but expression was heterogeneous and in general rather low for PD-1 and PD-L1 (median 3.9% (range 1-15), 19.7% (range 1-90)) and more present for CTLA-4 (median 36.8% (range 1-90)). Interestingly, PD-1 expression was significantly associated with beneficial progression-free (HR: 0.30, 95% CI 0.13-0.72) and overall survival (HR: 0.21, 95% CI 0.53-0.84) independently of established prognostic factors, including ENSAT tumor stage, resection status, Ki67 proliferation index and glucocorticoid excess. In contrast, its ligand PD-L1 and CTLA-4 were not associated with clinical outcome in this ACC cohort. In addition, we analyzed the correlation of PD-1 and PD-L1 with tumor-infiltrating lymphocytes. Whereas PD-L1 correlated significantly with the number of $CD3^+$-, $CD8^+$-, and $FoxP3^+$ T cells ($p = 0.0003$, < 0.0001 and < 0.0001, respectively), PD-1 correlated only with $FoxP3^+$ T cells ($p = 0.020$). When including both PD-1 and different T cell subtypes in the above-mentioned multivariate Cox regression, the presence of $PD1^+$ cells was the strongest predictor of favorable clinical outcome. In conclusion, this study provides several potential explanations for the heterogeneous results of the immune checkpoint therapy in advanced ACC. In addition, PD-1 expression serves as a strong prognostic biomarker that can easily be applied in routine clinical care as part of histo-pathological assessment.

DOI: 10.1530/endoabs.83.ERCO5

ERCO6

Outcome of immuncheckpoint inhibitor therapy in adrenocortical carcinoma – A multicenter retrospective study

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Background
Adrenocortical carcinoma is a rare endocrine malignancy with poor prognosis and few treatment options in advanced disease. Immune checkpoint inhibitors (ICI) have been studied in few clinical trials with a limited number of patients in ACC. No real-life data are available so far. In the present study we aimed at evaluating treatment response and safety of ICI treatment in advanced ACC and identifying clinical, biochemical, histological and molecular markers for prediction of treatment response
Methods
Retrospective cohort study of 54 patients with advanced ACC who received ICI outside of clinical trials at six German reference centers between 2016 and 2022. Progression-free (PFS) survival was the primary endpoint, secondary end points were overall survival (OS), objective response rate, and treatment-related adverse events (TRAE).
Results
In 52 patients surviving at least 4 weeks after initiation of ICI, median time to progression was 2.5 months (range 0.2-18) and median overall survival was 4.8 months (range 0.2-56). Objective response rate was 13.5% (CI 6-26) and disease control rate 24% (CI 16-41). 17 TRAE occurred in 15 patients (28 %) including seven grade III TRAE. The occurrence of an adverse event was associated with a significantly longer PFS (5.5 (CI 1.9-9.2) vs. 2.5 (CI 2.0- 3.0 months, $P = 0.001$; Hazard Ratio 0.29 (CI 0.13-0.66)) and OS (28.2 (CI 9.5-46.8) vs. 7 (CI 4.1-10.2) months, $P < 0.05$; Hazard Ratio 0.34 (CI 0.12-0.93)). No significant difference regarding PFS and OS was observed relative to concomitant mitotane treatment, glucocorticoid excess, other histological markers, and TMB.
Conclusions
We demonstrate limited efficacy comparable to other frequently used second line therapies and acceptable safety profile of ICI in a cohort of extensively pretreated ACC patients receiving different ICI treatment regimens. Further studies are needed to identify responders and to elucidate the predictive role of PD-L1 immunohistochemistry.

DOI: 10.1530/endoabs.83.ERCO6

Poster

ERCP1

Synchronous eutopic and ectopic papillary thyroid carcinoma

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Background
Papillary thyroid carcinomas are the most common thyroid malignancies. They are more prevalent in women and have a bimodal age distribution. Thyroglossal duct cyst carcinomas are extremely rare (occurring in only 1% of all thyroglossal duct cysts). The large majority of these carcinomas are of thyroid origin.
Case presentation
A 25-year-old woman with no significant medical history was referred to the Endocrinologist with 1-month complaints of cervical swelling. On cervical ultrasound, a predominantly cystic nodule with 22x27x32 mm was reported in the central lower maxillary region (above the hyoid bone). Its solid component was hyperechoic and hypervascularized. In the isthmus it was reported an EU-TIRADS 5 micronodule (7x6x8mm) with microcalcifications. A fine needle aspiration cytology (FNAC) of the submaxillary mass was performed. Thyroglobulin measurement in the washout fluid was >500 ng/mL and calcitonin was negative. The cytological result was consistent with papillary thyroid carcinoma. FNAC of the thyroid micronodule also reported papillary thyroid carcinoma. The patient underwent total thyroidectomy as well as excision of the thyroglossal duct mass. The pathology report revealed the presence of foci of classic papillary thyroid carcinoma in the thyroglossal duct and in the adjacent thyroid tissue. The tumor extensively invaded the hyoid bone and the adjacent fibromuscular tissues. Two foci of classic capsulated papillary thyroid carcinoma, both infracentimetric (0,7 and 0,6 cm), were identified. Post-surgery radiodine ablation was performed.
Conclusions
The authors describe an unusual presentation of multifocal papillary thyroid carcinoma. Ectopic papillary thyroid carcinomas are extremely rare (1-3%). The involvement of thyroglossal duct cyst is even more uncommon. This case serves to emphasize the importance of thyroid nodules surveillance, especially in young women.

DOI: 10.1530/endoabs.83.ERCP1

ERCP2

A case of primary squamous cell carcinoma of the thyroid gland

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Primary squamous cell carcinoma of the thyroid gland (PSCCT) is a rare neoplasm of the thyroid with a poor prognosis. We present a 70-year-old male patient who presented with a progressively growing mass on the left side of the neck causing shortness of breath. The patient presented with suspicious poorly-differentiated malignancy as a result of the thyroid fine-needle aspiration cytology performed due to the rapidly growing mass. No other primary tumor focus was detected in the neck and thoracic computed tomography (CT) performed, and a mass of 8 cm was observed in the thyroid. The patient underwent total thyroidectomy and left neck dissection. The pathology result was compatible with SCCT, and one suspicious nodule was detected in the lung during the whole body scan. Local radiotherapy and cisplatin treatment were initiated for the patient in the post-op period. Post-radiotherapy imaging manifested an elevated size regarding the nodule in the lung and then, the patient was diagnosed to have metastatic disease, and systemic chemotherapy was initiated as palliative treatment. There are publications showing that survival can be prolonged with complete resection and radiotherapy for the treatment of PSCCT. Therefore, disease management requires a multidisciplinary approach.

DOI: 10.1530/endoabs.83.ERCP2

ERCP3

Raising awareness for primary thyroid angiosarcoma – a rare diagnosis not to be missed

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Background
Primary thyroid angiosarcoma (PTA), previously considered a vascular type of anaplastic thyroid carcinoma (ATC), is a rare, aggressive malignant mesenchymal tumor, with a peak incidence in the seventh decade of life. PTA can present as an ATC, a more frequent type of thyroid malignancy. Differential diagnosis is of major importance, as the management and prognosis differ significantly.
Case report
A 72-year-old woman presented for a 2 month history of progressive obstructive respiratory symptoms. A large cervical mass identified on clinical exam was confirmed by the CT scan, showing a 93/90/76 mm inhomogeneous tumour on the topography of the left thyroid lobe, without metastasis. Thyroid function tests and calcitonin were normal. Surgery was imperative, given the significant respiratory symptoms due to adjacent organs' tumor invasion assessed at surgical inspection. Total thyroidectomy and excision of the invaded infrahyoid muscles were performed, followed by a major improvement of the respiratory status. Histological analysis showed vasoformative high grade proliferation, hemorrhage, tumor necrosis, perienural and angioinvasion, and the residual thyroid gland had the aspect of multinodular goiter. Immunohistochemistry was negative for TTF-1, thyroglobulin and calcitonin and positive for the endothelial cell marker CD31, a hallmark for the diagnosis of angiosarcoma.
Conclusions
According to the literature data, PTA usually emerges in multinodular goitre. Although the large tumour mass invaded most of the thyroid tissue, our patient was euthyroid. The prognosis is poor, and it seems like angioinvasion may worsen the prognosis even more. In order to improve survival, early diagnosis, radical surgery and radiotherapy have proven their efficacy over time. Yet, due to its rarity, there is no gold standard treatment. Hence, patients may benefit from raising awareness and enrich clinical knowledge regarding this rare tumour.

DOI: 10.1530/endoabs.83.ERCP3

ERCP4

Impact of androgen deprivation therapy on the bone and metabolic changes in men treated for localized prostate cancer

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Background
Prostate cancer is the most commonly diagnosed male malignancy. Androgen Deprivation Therapy (ADT) with GnRH agonist is commonly used intreating localized prostate cancer. Side effect of ADT is a loss of bone density resulting inosteopenia or osteoporosis. Research concerningpossible molecular and cellular mechanisms of ADT-induced bone changes are still incomplete. Matrix Gla Protein (MGP) is a vitamin-K-dependent protein which is synthesized in a variety of tissues, including bone tissue. MGP overexpression seems to promote the osteoblast proliferation but its function in ADT-induced osteoporosis is unknown.
Objectives
Aim of the study is to analyze the bone and metabolic changes in men treated with ADT for localized prostate cancer.
Methods
This is a prospective, pilot study of two groups of 10 men with localized prostate cancer. The studygroup received ADT while the control group was clinically observed or treated with radiotherapy. We performed dual-energy X-ray densitometry and blood sampling (hormone, metabolic profile, and bone metabolism parameters) in each patient. In addition, we measured the MGP level. The 1stmeasurement was undertaken at the time of the diagnosis, while the 2nd measurement was done 3 months later.
Results
At baseline, no differences were found in all analyzed parameters between the two groups (densitometry, blood count, sedimentation rate, glucose, creatinine, calcium, phosphorous, PTH, alkaline phosphatase, vitamin D, total testosterone, SHBG, lipide profile, P1NP, CTX, MGP). In the follow-up, we only observedstatistically significant change in the total testosterone level between the study and the control group (0.31 nmol/l vs. 17.99 nmol/l, $P < 0.05$). We found no statistically significant difference in the level of MGP between the study

and the control group in the follow-up period (648.5 pmol/l vs. 801.2 pmol/l, $P = 0.24$).
Conclusions
Most of the analyzed hormone, metabolic, and bone parameters in these two groups did not significantly change over 3 months, except for the level of total testosterone which is due to expectedADT effect. However, we find this period too short to result in a significant bone and metabolicchanges. Longer observation of these patients is mandatory to come to the final conclusion.

DOI: 10.1530/endoabs.83.ERCP4

ERCP5

An exceptional case of a papillary thyroid carcinoma arising within an ovarian teratoma

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Background
Papillary thyroid carcinoma (PTC) arising within an ovarian teratoma is an extremely rare condition that comes with certain difficulties in the preoperative diagnosis and postoperative treatment strategy. It is either asymptomatic (detected incidentally) or with nonspecific symptoms. Currently, no consensus exists on the surgical and postoperative treatment of patients with malignant struma ovarii.
Case presentation
A 26-year-old female presented with dizziness, reoccurring epistaxis and a palpable mass on her right breast, diagnosed by mammography as fibroadenoma. Preoperative pelvic ultrasonography revealed a presence of a 9 cm right ovarian tumor and free fluid filling the pouch of Douglas. She had elevated Ca19-9 levels of 88 IU/ml and normal Ca-125 levels (25.7 IU/ml). The patient underwent a laparoscopic ovarian cystectomy along with fibroadenomectomy. Pathohistological evaluation of the operative material declared as a dermoid cyst confirmed a diagnosis of PTC measuring 2.4 cm in the ovarian teratoma. She was admitted to the Institute of Pathophisiology and Nuclear Medicine for further investigation and management. Her thyroid examinations showed euthyroid condition with normal thyroid and neck morphology on ultrasound and normal thyroglobulin (Tg) levels. The PET – CT scan showed no sites of metastatic spread. The patient was informed about the treatment approaches and was given suppressive doses of Levothyroxine (TSH 0.004 mIU/l were achieved with 150 μg/day) until her final decision.
Conclusions
The management of malignant struma ovarii is based on rare case-report studies. The therapy ranges from radical surgery and radio-chemotherapy, thyroidectomy, radioiodine ablation and levothyroxine TSH suppression, to conservative surgery in younger patients with fertility preservation. Early diagnosis based on modern imaging techniques impacts the clinical decision and management, which produces a better outcome regarding the future prognosis.

DOI: 10.1530/endoabs.83.ERCP5

Calcium and Bone

Oral

CBO1

Hypercalcemia during pregnancy is associated with worse outcomes but not fetal loss

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Background
Incidence of hypercalcaemia during pregnancy is difficult to estimate as routine calcium screening is not recommended. Literature is conflicting if hypercalcemia results in worse maternal and fetal outcomes.
Objectives
Aim of this study is to determine frequency and association of hypercalcaemia in pregnancy with early maternal and fetal outcomes.
Methods
This retrospective cohort study included gestations with expected delivery dates between 2017-19 at a tertiary maternity unit. Baseline demographic, biochemical, and clinical data was retrieved for analysis. Primary outcomes were incidence of hypercalcaemia and fetal loss (miscarriage/stillbirth) during pregnancy. Secondary outcomes included rate of other maternal and fetal outcomes: preterm delivery, emergency C-section, hypertension, blood loss during delivery, neonatal intensive care unit (NICU) admission, and fetal birth weight.
Results
Total number of gestations and livebirths recorded were 33,118 and 20,969, respectively, with median age of 30.1 [IQR 25.6-34.3] years. Two-thirds of pregnancies were in Caucasian women (65.9%) followed by Asians (9.6%), Afro-Caribbean (5%), and others (19.5%). 15.7% (n=5195) of all gestations had calcium tested and incidence of hypercalcemia was 0.81% (n=42). The incidence of fetal loss was 22.5% in the hypercalcaemic group compared to 18.9% in normocalcaemic group ($P = 0.560$). Among other outcomes, incidence of preterm delivery (20.0% v 9.2%;p=0.042), emergency C-section (42.4% v 21.4%;p=0.021), NICU admission (19.4% v 8.2%;p=0.024), and blood loss (1252 v 526 mL;$P < 0.001$) were all higher in the hypercalcemic group, however, incidence of hypertension (0% v 1%;p=0.561) was similar. The median adjusted calcium in the hypercalcemic group was 2.75 mmol/l [IQR 2.65-2.88]. Further analysis showed that incidence of hypocalcaemia in this cohort was 9.61% (n=499), and this also was associated with worse outcomes but not with fetal loss.
Conclusions
Incidence of hypercalcemia in pregnancy is low (0.81%). Abnormal calcium levels are associated with worse maternal and fetal outcomes, but rate of fetal loss is not high.

DOI: 10.1530/endoabs.83.CBO1

CBO2

Evidence of a non-classical phenotype of hypoparathyroidism (HPT) in a cohort of adult patients with β-thalassemia

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Background
β-thalassemia is associated with increased iron overload in endocrine tissues, including parathyroid glands. The occurrence of unbalanced calcium (Ca)-phosphorous (P) metabolism, such as chronic HPT, is higher in these patients compared to the general population. However, data about prevalence and presentation of HPT in this setting are scanty.
Aim
To explore the biochemical characteristics of Ca-P metabolism, particularly the prevalence of hypoparathyroidism, in adult patients with β-thalassemia major and intermedia compared to healthy subjects.
Methods
Single-center, retrospective, case-control study, including 34 patients with β-thalassemia and 57 age-matched controls. The main outcome measures were serum Ca, P, Ca/P ratio, intact parathyroid hormone (PTH), albumin, and creatinine. Primary hypoparathyroidism (pHPT) was defined as hypocalcemia with low/inappropriately normal PTH, whereas subclinical hypoparathyroidism (sHPT) as serum Ca at the lower limit of normal range with low PTH.
Results
Serum P was higher in patients with β-thalassemia compared to controls (3.8±0.6 mg/dL vs 3.5±0.6 mg/dL, $P = 0.008$), whereas no difference was found for serum Ca. The Ca/P ratio was lower in the β-thalassemia compared to controls (2.48±0.42 vs 2.77±0.42, $P = 0.002$), as well as serum PTH (22.4±10.9 pg/mL vs 34.1±14.1 pg/mL, $P < 0.001$). No difference was found for serum albumin between groups. A Ca/P ratio <2.3, that is suggestive for unbalanced Ca-P metabolism, was found in 14 out of 34 patients (41.1%) and in 8 out of 57 controls (14.0%). Focusing on β-thalassemic patients, pHPT was observed in 3 patients (8.8%) and sHPT in 22 (64.7%) without difference between major and intermedia forms.
Conclusions
Despite of a low prevalence of overt pHPT, the non-classical phenotype sHPT is a common finding in patients with β-thalassemia. A periodic evaluation of serum Ca and P should be included in the follow-up of these patients to early detect an unbalanced mineral metabolism.

DOI: 10.1530/endoabs.83.CBO2

CBO3

Bone metabolism and dual-release Hydrocortisone: results from a real-life study

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Background
Patients with adrenal insufficiency (AI) require long-term glucocorticoid (GC) replacement therapy and generally show an increased prevalence of bone metabolism alterations. Only few data are available on bone safety of dual-release Hydrocortisone (DR-HC) therapy.
Objective
To evaluate bone metabolism in primary AI (PAI) and secondary AI (SAI) during long-term therapy with DR-HC.
Methods
We evaluated patients with AI on immediate-release GC therapy, collecting data on bone turnover markers, femoral and lumbar spine bone mineral density (BMD) and trabecular bone score (TBS) before and up to 60 months after the switch to an equivalent dose of DR-HC.
Results
28 patients (15 PAI and 13 SAI, mean age 51±14 years, 15 females, 8 post-menopausal) were included. Mean duration of AI was 95 months (range 12-432). Any other hormonal disorders (i.e. diabetes, hypothyroidism, hypogonadism, GH deficiency) were adequately controlled throughout the study. All patients had normal calcium and phosphorus levels and most were under cholecalciferol therapy (mean Vit D 26 ng/mL at baseline; 95% CI 18 – 33 ng/mL). No patient was under anti-resorptive therapy. At baseline, 18% of patients had BMD values compatible with osteopenia and 11% had a diagnosis of osteoporosis. Compared to baseline, no significant difference was observed in BMD at femur neck, total hip and total lumbar spine at 24 ($P = .293$;$P = .471$;$P = .820$), 36 ($P = .812$;$P = .322$;$P = .890$), 48 ($P = .820$;$P = .925$;$P = .432$) and 60 months ($P = .450$;$P = .792$;$P = .847$) of DR-HC therapy. Similarly, TBS values did not significantly change after 24 ($P = .945$), 36 ($P = .400$), 48 ($P = .582$) and 60 months ($P = .572$). Alkaline phosphatase, C-terminal telopeptide and osteocalcin levels showed no difference in all timepoints (at 60 months:$P = .730$;$P = .412$;$P = .981$).
Conclusions
DR-HC is a safe treatment option in terms of bone health in patients with AI, maintaining stable bone mass, bone quality and bone turnover despite aging.

DOI: 10.1530/endoabs.83.CBO3

CBO4

Markers of cardiometabolic and bone health in postmenopausal women on glucocorticoid replacement therapy due to adrenal insufficiency

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Background
Individuals with adrenal insufficiency (AI) receive life-long glucocorticoid (GC) replacement which often exceeds physiological daily GC production, with negative effects on cardiometabolic and bone health parameters.
Objective
Assessment of cardiometabolic and bone health markers in postmenopausal females with AI in relation to the GC dose.
Methods
We retrospectively collected 114 postmenopausal women with AI (37 with primary AI [PAI], 37 with secondary AI [SAI] and 40 with AI following Cushing's syndrome (CS) treatment [post-CS AI]). HbA1c, lipid, bone markers and bone mineral density (BMD) in lumbar spine (LS) and femoral neck (FN) were evaluated at baseline and after 2 years. Total daily hydrocortisone (TDHC) doses were considered as: low dose (LD; TDHC $\leq$ 15 mg, 21 patients), medium dose (MD; 15 mg $<$ TDHC $\leq$ 25 mg, 50 patients) and high dose (HD; TDHC $>$ 25 mg, 43 patients)
Results
Patients were comparable for age, duration of AI, age of menopause and BMI. More PAI patients were on LD (24% vs 14% and 18% for SAI and post-CS, respectively) and more post-CS AI on HD (45% vs 30% and 38% for PAI and SAI, respectively). TDHC did not differ among groups, but PAI patients received less GC/body surface area (BSA). No statistically significant differences were observed in BMD and LS or FN T-Scores but PAI patients had higher P1NP levels. They also had lower HbA1c, cholesterol and LDL values compared to the other 2 groups. After 2 years, BMD and T-Scores remained comparable for the 3 groups. P1NP values remained higher in PAI patients who also continued to exhibit lower lipid levels compared to the SAI and post-CS AI ones.
Conclusions
PAI patients had increased bone formation and better HbA1c and lipid levels compared to SAI and post-CS patients, at baseline and after two years. This possibly relates to the use of lower GC/BSA doses in PAI patients due to residual adrenal function. Of note, when only the mean TDHC was considered no difference was evident, indicating that a BSA based GC dose calculation may better reflect an individual's exposure to GCs. Although lower GC doses are recommended, many AI patients, especially post-CS, cannot tolerate doses of $<$ 25 mg/day. Our data enforce the need for the lowest possible GC replacement dose in AI patients, however tolerability may hamper this effort, especially in SAI and in post-CS patients.

DOI: 10.1530/endoabs.83.CBO4

Poster

CBP1

Severe hypomagnesemia due to chronic diarrhea - a case report

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Background
Hypomagnesemia is an electrolyte disturbance defined by a low serum magnesium level. Causes of hypomagnesemia include inadequate dietary intake, decreased intestinal absorption, and increased renal excretion. The clinical presentation varies depending on the severity of the magnesium deficiency-from asymptomatic cases to patients with mild symptoms, to severe, life-threatening cardiac arrhythmias and seizures.
Case presentation
A 55-year-old man presented to the emergency department (ER) complaining of malaise, headache, paresthesias, and muscle tremors. He had been suffering from chronic diarrhea, chronic pancreatitis, arterial hypertension, type 2 diabetes mellitus diagnosed a year ago, chronic gastritis, and obesity for several years. From 2007 to 2014, four episodes of acute pancreatitis of ethyl etiology were documented. In 2021, he was admitted to ER with similar symptoms. During this observation, he developed generalized epileptic seizures and wide-QRS-complex tachycardia, both of which were due to hypomagnesemia (Mg 0.34mmol/l). On the present visit, clinical examination was unremarkable with negative Trousseau and Chvostek's sign. ECG recording showed normal sinus rhythm with normal QRS duration. Laboratory findings showed electrolyte disturbances- hypokalemia, hypocalcemia and marked hypomagnesemia (K 3.9mmol/l, Ca 1.55mmol/l, Mg below measurable cut-off value) as well as a slight increase in inflammatory markers. Serum levels of phosphate and 25-hydroxyvitamin D were within normal range. Initial treatment-monitoring, intravenous administration of calcium gluconate and magnesium sulfate-was initiated at ER. The patient was transferred to the intensive care unit for further treatment. Five days later, he was discharged from the hospital with the recommendation of oral electrolyte replacement therapy. His electrolyte status and general condition were stable during follow-up.
Conclusions
Hypomagnesemia is more common in hospitalized patients than in the general population, and it is often associated with hypocalcemia and hypokalemia. Early recognition, diagnosis, and treatment that is easily accessible and effective are necessary to avoid complications and ensure a positive outcome.

DOI: 10.1530/endoabs.83.CBP1

CBP2

Densitometry misinterpretation leading to unnecessary denosumab prescription

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Background
Bone mineral density (BMD) measurement is an important tool for fracture risk assessment, but should be used with awareness of its performance and analysis pitfalls.
Case Presentation
A 59-year-old patient underwent her first densitometry as part of a routine medical check-up. She had no previous fractures and no risk factors that could impair bone health. The results showed that her BMD was in the range of low bone mass. Four years later, densitometry was performed again with the same device, but without calibration for the least significant change. Based on the very low T-score of -3.7 at the lumbar spine, osteoporosis was diagnosed and denosumab therapy was initiated. There were no newly acquired comorbidities, and secondary causes of osteoporosis were not investigated. The third densitometry was performed a year later, at the age of 64, before she came to our clinic. This time, a lumbar spine T-score of -2.3 was obtained with a different device. This was again discordant to the second densitometry, as such a rapid improvement after the administered therapy would not be expected. We reviewed all three densitometry reports and found that her second densitometry, which showed osteoporosis, had incorrect vertebral labelling: Th12-L3 were measured instead of L1-L4. Even without taking into account that she had previously received three denosumab doses, the Fracture Risk Assessment Tool was low and estimated 5.1% risk of major osteoporotic and 0.5% risk of hip fractures. It was evident that she did not need osteoporosis treatment. Although the risk of rebound effects after short-term denosumab therapy and low C-telopeptide was low, we gave her a dose of zoledronate seven months after the last denosumab application.
Conclusions
Justified indications for BMD (re)testing, careful analysis of results and interpretation of reports are mandatory to avoid overdiagnosis and misdiagnosis of osteoporosis, which could lead to ineffective, costly, and even damaging consequences.

DOI: 10.1530/endoabs.83.CBP2

CBP3

Case report: denosumab in the management of aneurysmal bone cyst of the sacrum

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Background
Aneurismal bone cysts (ABCs) are rare benign tumours of the bone that, similar to the giant cell tumours (GCTBs) of the bone, contain osteoclast-like giant cells. Standard therapeutic options include different surgical approaches and/or radiotherapy. However, in selected cases, other therapeutic options are needed. Denosumab, a human monoclonal antibody to receptor activator nuclear factor kappa B ligand (RANKL) has been approved for the treatment of giant cells

tumours of the bone. Similar pathophysiology between ABCs and GCTBs suggests its potential beneficial use in complex ABC cases.
Case report
We report a case of sacral aneurismal bone cyst in an 18-year-old female patient. Considering the localization of the lesion and the ensuing risk of surgery and radiotherapy, our patient was treated with denosumab 120 mg subcutaneously monthly for 12 months. After the initiation of the treatment the patient's pain resolved completely. New bone formation was evident on magnetic resonance imaging scans at 6 months and continued to show evidence of improvement at 11 months after initiation of treatment. Adverse events following denosumab were not reported.
Conclusion
Treatment with denosumab resulted in symptomatic and radiological improvement in our patient and could be beneficial in selected ABC cases.
Key words: aneurismal bone cyst, denosumab, sacral lesion

DOI: 10.1530/endoabs.83.CBP3

CBP4

Osteitis fibrosa cystica in primary hyperparathyroidism due to bilateral intrathyroidal parathyroid adenomas - Clinical case

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Background
Primary hyperparathyroidism (PHPT) is often only mildly sympthomatic[1]. Nevertheless, some patients are diagnosed late and severe complications such as osteitis fibrosa cystica can develop.
Case Presentation
A 32 years old female was hospitalized due to pain in the left femoral region after falling from standing height. Radiological investigations revealed left femoral pathologic fracture and bone malignancy was suspected. Further radiologic investigations revealed lytic bone lesions in 7th cervical vertebra, multiple ribs, the left scapula and the left tibia. Thyroid ultrasound showed intermediate malignancy risk (TIRADS 4A) thyroid nodules in both lobes. Cytologic evaluation from fine needle aspiration of the left lobe's nodule showed cells with signs of follicular neoplasia. Later the serum calcium (Ca) and parathyroid hormone (PTH) levels were ordered and both were markedly elevated. Patient was hospitalized in the endocrinology ward and laboratory tests were repeated, revealing a serum PTH level 835.37 pg/ml (15.00-68.00), Ca 3.94 mmol/l (2.15-2.50), phosphorus 0.47 mmol/l (0.81-1.45). Repeated thyroid ultrasound failed to visualize a parathyroid (PT) adenoma. PT scintigraphy was inconclusive, but suspected increased uptake in the right lower PT gland. Selective thyroid vein sampling was performed and demonstrated elevated PTH levels in the right middle thyroid vein. The decision to perform a total thyroidectomy was made. Intraoperative serum PTH was ordered and showed substantial drop once the thyroid was excised. Pathohistological evaluation revealed 2 intrathyroidal PT adenomas with no thyroid nodules present. After surgery the patient developed right sided Horner's syndrome, presumably due to iatrogenic damage of the cervical ganglia.
Conclusions
The case illustrates the importance of serum Ca and PTH screening in the population and in patients with skeletal and renal pathologies, as untreated PHPT can cause severe health consequences.
Reference
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DOI: 10.1530/endoabs.83.CBP4

CBP5

Bilateral neck exploration is as safe as focused parathyroidectomy

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Background
Bilateral neck exploration (BNE) as a routine surgery for PHPT is favored by many experts in endocrine surgery as it may provide the identification of preoperatively undetected multiglandular disease. But for a large cohort of patients BNE remains unnecessary and its possible higher rate of surgical complications is being widely discussed.
Objectives
The aim of the study was to evaluate the complication rates of bilateral neck exploration in comparison with focused parathyroidectomy.
Methods
408 patients who underwent an initial surgery for PHPT at SPBU Hospital in 2020 were included in the study. PTH level on the 1st day after surgery, histological reports, postoperative laryngoscopy and surgery protocols were evaluated. Intraoperative PTH level was not measured. Cases of persistent PHPT, parathyroid carcinomas and cases with more than one histologically confirmed adenoma were excluded. Number of cases included in the study was 389.
Results
Number of groups of BNE and FPTX was 287 and 102 respectively. There was no statistically significant difference in postoperative PTH level (1.6 + 1.00 vs 1.8 + 1.13 pmol/l, *P*-value = 0.183) and operation time (33.9 + 13.8 vs 32.4 + 12.7 min, *P*-value = 0.623. No contralateral vocal cord palsy was reported in the group of BNE.
Conclusions
BNE performed by an experienced endocrine surgeon may be as safe as PTX and also be comparable by the duration of the operation

DOI: 10.1530/endoabs.83.CBP5

CBP6

Hyperemesis gravidarum as a clinical presentation of primary hyperparathyrioidism

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Background
Hyperemesis gravidarum is a rare condition with multiple causes. Diagnosis is based on clinical examination and measurement of urine ketones, serum electrolytes, and renal function. Hyperparathyroidism during pregnancy can rarely be manifested with clinical presentation of hyperemesis gravidarum with substantial maternal and fetal complications. In most cases adequate hydration, with or without forced diuresis, as well as with low calcium content diet is treatment of choice in hyperparathyroidism in pregnancy. In some cases, parathyroidectomy is treatment of choice.
Case presentation
Here we report a case of 31-year-old woman in the 13th gestational week who was admitted at the Obstetrician Clinic with symptoms of nausea and refractory vomiting. Laboratory tests revealed hypercalcemia with hypophosphatemia, elevated parathyroid hormone level, low vitamin D levels and hypercalciuria. After stabilization of the general condition and confirmed fetal viability, the patient was transferred to the Clinic for endocrinology, diabetes and metabolic disorders. Ultrasound of the thyroid and parathyroid glands revealed enlarged left lower parathyroid gland. During hospitalization, the patient was initially treated with abundant parenteral and enteral hydration and nutrition. The applied measures of treatment improved the electrolyte disbalance, serum electrolytes decreased, but were not normalized and the symptoms of nausea and vomiting fluctuated. Eventually, lower left parathyroidectomy was done, and the patient was cured and symptoms free.
Conclusions
Primary hyperparathyroidism diagnosed in pregnancy is rare, occurring in approximately 0.5 to 1.4% of pregnancies. Due to unusual clinical presentation, it may remain unrecognized, and if untreated, causes maternal and fetal complications in up to 80% of cases. Parathyroidectomy is the only definitive treatment and is recommended for symptomatic patients, even in pregnancy.

DOI: 10.1530/endoabs.83.CBP6

Diabetes, Obesity, Metabolism and Nutrition

Oral

DOMNO1

Relation of HLA system genes in patients with type 1 diabetes and other autoimmune diseases

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Background
Type 1 diabetes mellitus (T1DM) is caused by destruction of pancreatic beta cells. Children and adolescents with type 1 diabetes have an increased risk of developing other autoimmune diseases, most commonly autoimmune thyroiditis and celiac disease.
Objectives
To examine the frequency of individual human leukocyte antigen (HLA) alleles in people with T1DM and associated autoimmune (AI) diseases of the thyroid, digestive system, and skin, and to examine differences in gender and age at the time of diagnosis.
Subjects and Methods
Subjects were patients referred to the Clinical Institute of Transfusion Medicine for HLA typing. Data were collected in Clinical hospital center Osijek (HLA typing findings, associated autoimmune diseases of the thyroid gland, digestive system, and skin; age and sex).
Results
The study was conducted on 147 subjects with T1DM (51.7% women, 48,3% men). The AI disease of thyroid were most common (24,5%). Distribution of subjects by age groups differs significantly. The most common HLA alleles in men are HLA-DRB1*03, -DQA1*05, -DQB1*02, and in women HLA-DRB1*03, -DQA1*03, -DQB1*03(DQ8). Subjects with T1DM were more likely to have the DRB1*03-DQA1*05-DQB1*02 haplotype, and female subjects with T1DM were more likely to have the DRB1*08-DQA1*03-DQB1*03(DQ8) haplotype. There is a significant difference in the distribution of subjects with respect to the presence of autoimmune AI thyroid disease vs HLA-DRB1*03/*10,-DRB1*03(DQ8); AI of the digestive system disease relative to HLA-DRB1*01; AI skin disease vs HLA-DRB1*01, -DQB1*05.
Conclusion
Age is associated with an earlier diagnosis of T1DM, while gender is not. Individual HLA alleles have been associated with the earlier onset of T1DM and AI disease. The incidence of T1DM in the population is increasing and a proper understanding of the mechanism of occurrence is crucial to better diagnose and prevent the development of complications.
Key words: diabetes mellitus, type 1; histocompatibility antigens class II; autoimmune diseases

DOI: 10.1530/endoabs.83.DOMNO1

DOMNO2

Placental signalling contributes to adipokine dysregulation and systemic insulin resistance in gestational diabetes mellitus

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Background
Placental signalling has been postulated to drive inflammation, endothelial dysfunction and insulin resistance in gestational diabetes mellitus (GDM).
Objectives
To determine if placental signalling contributes to systemic insulin resistance in GDM.
Methods
Adiponectin, leptin, adipsin and resistin in placental and omental explant culture supernatants (n = 10 GDM and n = 10 control) and maternal plasma (n = 20 GDM and n = 20 control) were quantified using LEGENDplex ELISA. Insulin levels were quantified in maternal plasma (n = 20 GDM and n = 20 control) using ELISA (R&D/Bio-Techne). Insulin signalling pathway proteins were quantified in GDM (n = 8) and control (n = 8) omental tissue lysates by western blotting. Histological staining was used to characterise adipocyte structure and omental tissue fibrosis (picro-sirius red) in GDM (n = 15) and control (n = 15) participants.
Results
Circulating plasma levels of adiponectin are significantly lower in GDM participants vs control (37.85μg/ml ± 20.22μg/ml vs. 49.7μg/ml ± 10.85μg/ml, $P = 0.033$). No significant differences were observed in adipokine release from omentum explant cultures. GDM placental explants had lower leptin release (0.29ng/ml ± 0.21ng/ml vs. 0.81ng/ml ± 0.65ng/ml, $P = 0.046$) and higher adipsin release (37.76ng/ml ± 9.25ng/ml vs. 29.43ng/ml ± 5.31ng/ml, $P = 0.028$) relative to control. Insulin levels were significantly higher in GDM participants (135.3pmol/l ± 151.5pmol/l vs. 39.24pmol/l ± 14.36pmol/l, $P = 0.006$). There was significantly higher expression of phosphorylated IRS1 (Ser307)/IRS1 ($P = 0.039$) in GDM omentum relative to healthy controls. GDM omentum samples had a significantly lower ratio of IRS2/IRS1 relative to healthy control samples ($P = 0.039$). Histological analysis showed that GDM omental tissue has a significantly lower adipocyte count relative to healthy pregnancies (147.8 ± 41.6 vs. 173.1 ± 45.2, $P = 0.038$), independent of participant BMI, with no change in adipocyte size or fibrosis.
Conclusions
In GDM pregnancies, visceral adipose tissue lacks the protective adipocyte hyperplasia, which helps to maintain glycaemic homeostasis. Reduced circulating adiponectin and altered placental adipokine release may drive adipocyte dysfunction and insulin resistance in GDM.

DOI: 10.1530/endoabs.83.DOMNO2

DOMNO3

Type 1 diabetes mellitus in pregnancy: high incidence of large-for-gestational-age neonates despite adequate glycemic control and low glycemic variability

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Background
Pregnancy with type 1 diabetes mellitus (T1DM) carries risks for many adverse outcomes; the most common are large-for-gestational-age neonates (LGA). Proper glycemic control reduces the risk for LGA. However, it occurs in almost 40% of T1DM pregnancies despite of achieving almost normoglycemia. Some studies suggested the contributing role of maternal body mass index (BMI) and glucovariability, but the effect on development of LGA still remains unclear.
Objectives
The aim of this study was to analyse incidence of LGA in planned and well-controlled T1DM pregnancies.
Methods
This prospective study included 42 patients with T1DM who were using continuous glucose monitoring (CGM) from preconception to delivery. Including criteria were preconception counselling, CGM at least 3 months prior to the study, duration of T1DM for at least 1 year, HbA1c < 7.5%, BMI <25 kg/m^2. Excluding criteria were HbA1c >7.5% and maternal weight gain > 20 kg in the 2nd and 3rd trimester. Patients used intermittently scanned CGM and data was analysed once in every trimester. Statistical analysis was performed with IBM SPSS software and data was defined as mean and standard deviation.
Results
In the first, second and third trimester time in range was 54.3±14.3, 62.4± 10.6, 67.5±11.7% respectively. Glucose management indicator was 6.5±0.5, 6.0± 0.4, 5.9±0.4% and %coefficient of variation 41.2±7.5, 38.6±5.9, 34.1±6.5% in the first, second and third trimester, respectively. Neonatal birth weight was 3594.3±632.2 grams, birth weight percentile 72.1±28.6 and 45% of neonates were LGA.
Conclusions
In this study we observed improved glycaemic control and decrease of glycemic variability from the first to the third trimester as a result of structured preconception counselling and strict follow-up. However, there was high incidence of LGA despite adequate glycemic control, low glycemic variability and normal BMI. Further studies for defining LGA aetiology in T1DM pregnancies are needed.

DOI: 10.1530/endoabs.83.DOMNO3

DOMNO4

Screening for diabetic retinopathy by an endocrinologist: a retrospective study

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Background
The increasing prevalence of diabetes mellitus (DM) is leading to a higher number of patients with diabetic retinopathy (DR) being referred to an ophthalmologist. In order to provide better care for patients, the Department of Endocrinology at the University Hospital of Zagreb has started screening of the ocular fundus.
Objectives
The aim was to present the results of screening on DR in a random sample of DM patients and to compare the results analysed by an endocrinologist and an ophthalmologist during the first three months of the project.
Methods
The variables analysed were age, sex, type and duration of DM, insulin therapy, HbA1c, body mass index, renal function, and blood pressure. The Crystalvue non-mydriatic fundus camera was used for ocular fundus analysis. The endocrinologist analysed the photographs first, and then the ophthalmologist analysed via telemedicine.
Results
The total number of patients who underwent screening for DR was 194 (median age 50 years (19-85), 102 were male, 48 had type 1 DM, 132 type 2 DM, and 14 corticosteroid-induced DM. Twenty-six had DR. When comparing outcomes assessed by endocrinologists and ophthalmologists, a total of 21 patients (11 %) had differences in outcomes. Sixteen patients were classified by endocrinologists as false-positive for DR, whereas 5 patients were classified as false-negative for DR. The number of false-positive or false-negative results between months was not statistically significant, but the tendency for results to differ between endocrinologist and ophthalmologist was less from month to month (9 vs. 8 vs. 4).
Conclusion
The results indicate that screening for DR can be performed by an endocrinologist with the assistance of an ophthalmologist at baseline. With a non-mydriatic fundus camera in the endocrinology department, we could reduce the workload of ophthalmologists and assign them only patients with DR to provide faster and better care for DM patients.

DOI: 10.1530/endoabs.83.DOMNO4

DOMNO5

Retrospective observational study of italian patients with diabetes mellitus in Covid-19 pre-vaccine ERA: a big data approach

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Background
Diabetes mellitus (DM) prevalence in patients with severe acute respiratory coronavirus virus (SARS-CoV-2) infection differs among studies, although pre-existing DM seems to double the risk of critical infection and mortality.
Objectives
To evaluate incidence and mortality risk of SARS-CoV-2 infection in a large diabetic population in Northern Italy in pre-vaccine era.
Methods
Retrospective, observational, big data study including non-vaccinated subjects with type 1 and type 2 DM in the Province of Modena, submitted to at least 1 swab for SARS-CoV-2 between March 2020 and March 2021.
Results
SARS-CoV-2 infection was detected in 2302 of 9553 diabetic patients (24.1%) with death in 8.9% of cases. No difference in SARS-CoV-2 prevalence was detected considering sex, whereas youngest people showed highest SARS-CoV-2 infection rate. DM duration was shorter in infected than uninfected patients ($P < 0.001$), but HbA1c was higher in infected compared to uninfected patients ($P < 0.001$). Accordingly, SARS-CoV-2 was less frequent in patients treated with anti-diabetic drugs compared to those not treated ($P < 0.001$). SARS-CoV-2 infection was predicted by age (OR 1.013, 95%CI:1.008-1.017), DM duration (OR 1.007, 95%CI:1.001-1.013), and HbA1c (OR 1.009, 95%CI:1.002-1.016). COVID-19 mortality was predicted by DM duration (OR 1.010, 95%CI: 1.005-1.015) and HbA1c (OR 1.005, 95%CI:1.002-1.009). At ROC analyses with death as test variable, worse prognosis was predicted by DM duration longer than 10.9 years (AUC = 0.639, 95%CI:0.601–0.676) and age older than 74.4 years (AUC = 0.797, 95%CI:0.767–0.827).
Conclusion
Our study confirms the correlation between SARS-CoV-2 related mortality and DM. Although SARS-CoV-2 infection was more frequent in the younger patients, a poor glycemic control worsens outcomes, especially in older diabetic people with long DM duration. Patients with DM and SARS-CoV-2 should be followed carefully when older than 74 years and with long DM duration.

DOI: 10.1530/endoabs.83.DOMNO5

DOMNO6

Anthropometric and metabolic outcomes after bariatric surgery: a single-centre experience

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Background
According to the World Health Organization, there are approximately 650 million obese adults worldwide. In Croatia almost 2/3 (65%) of adults are overweight (42%) or obese (23%), with a growing tendency both in adults and children. The surgical procedures performed to manage obesity are referred to as metabolic or "bariatric" surgery. Candidates for a bariatric surgical procedure include obese patients with a BMI $\geq$ 40 kg/m^2(obesity class III) or $\geq$ 35 kg/m^2(obesity class II) and the presence of comorbidities related to obesity.
Objectives
To assess the effect of bariatric surgery on anthropometric analysis and metabolic laboratory parameters in adults with obesity in a single-centre in Zagreb, Croatia.
Methods
We retrospectively examined the medical records of patients aged 18 years or older, who were admitted for sleeve gastrectomy procedure to Clinical Hospital Dubrava, Zagreb, Croatia, between October 2015 and March 2022. Clinical and demographic data and comorbidities of interest were recorded. The patients underwent a standard and additional set of blood tests and anthropometric analysis. For 30 patients who were followed-up in the outpatient clinic we investigated long-term outcomes.
Results
A total of 41 patients (82.9% female) with the mean age of 44.80 $\pm$ 9.7 years underwent the surgery. The mean pre-surgery weight was 134.56 $\pm$ 22 kg, with a BMI of 47.57 $\pm$ 7.21 kg/m^2. In the mean period of surgery follow-up (76 days) there was a significant weight loss of 19.07 kg ($P < 0.001$) with a BMI reduction of 5.61 kg/m^2 ($P < 0.001$) and a significant reduction in the mass of body fat (MBF) and the visceral adiposity index (VAI). The median reduction in HbA1c was 0.64% ($P < 0.001$) averagely 76 days after surgery.
Conclusions
Bariatric surgery is associated with a fast and significant improvement of anthropometric and metabolic parameters, being among the most effective management modalities for patients with obesity.

DOI: 10.1530/endoabs.83.DOMNO6

Poster

DOMNP1

Does phase angle analysis in overweight women be a surrogate marker of insulin resistance?

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Background
Phase angle (PA) is defined as the angular displacement between the current and voltage waveforms due to capacitor interference, measured in degrees or radians. [1] The fat-free mass (FFM) is made up of water and electrolytes and is characterized by a low impedance, while the FM (fat mass) is water-free and, therefore, with a high impedance. The larger the FM, the higher the resistance, and this parameter affects the PA. Body mass index (BMI) is the most widely used measure of overweight and obesity, but does not analyze body composition. Several studies evaluated the link between phase angle (PA) and adipokines, fasting glucose, insulin, and HOMA index; however, there has not yet been an established link between phase angle and insulin resistance. The gold standard measure of insulin resistance is the hyper-insulinemic-euglycemic clamp, but this method is time- consuming and costly.
Materials and Methods
A spectral bioelectrical impedance device (BIA) (AKERN 101 BIVA PRO body composition analyzer) was used to estimate resistance (R) and reactance (Xc), and subsequently PA was calculated as arctangent (Xc/R) $\times 180°/\pi$.
Results
BIA scans (N = 85) measured FM% in women of reproductive age (18-49 years) in the outpatient clinic. PA was significantly correlated with FM% (r = 0,794; $P < 0{,}001$)
Conclusions
Although more data are needed to confirm these preliminary findings, the results suggest that phase angle is a valuable non-invasive and easily usable tool to identify risk in the early stages of obesity-related health consequences, PA could be a surrogate marker to detect insulin resistance. Woman with the same BMI had quite different amounts of fat mass and associated cardiometabolic risk. In addition, we will perform correlation analysis to assess the relationship between PA and HOMA2-B, HOMA2-IR, and adipokines as well.
Reference
1. Howe CA, Corrigan RJ, Djalali M, McManaway C, Grbcich A, Aidoo GS. Feasibility of Using Bioelectrical Impedance Analysis for Assessing Youth Weight and Health Status: Preliminary Findings. doi:10.3390/ijerph181910094

DOI: 10.1530/endoabs.83.DOMNP1

DOMNP2

Diabetes-induced changes in brain metabolism: a study of four cases

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Background
Emerging evidence shows that diabetes mellitus causes structural and functional alterations in the brain. Recent studies have shown that diabetes may induce reductions in N-acetyl aspartate (NAA) and glutamate concentrations in the cortical grey matter, but few studies have performed the neurochemical profiling of other brain regions in patients with diabetes. Hence, the aim was to investigate brain metabolites in other brain regions of adults with diabetes.
Case presentation
Brain metabolites, including NAA, creatine (Cr) and choline (Cho), were compared between 2 adult patients with type 1 diabetes (T1D) and 2 adult patients with type 2 diabetes (T2D) using single-voxel magnetic resonance (MR) spectroscopy in the following regions: the lentiform nucleus, centrum semiovale, thalamus and cerebellum. The results of MR spectroscopy were converted to standardized ratios: NAA/Cho, NAA/Cr and Cho/Cr; and were considered abnormal if <1.6, <1.2 and >1.5, respectively. All patients had diabetes for more than 7 years and reached their glycemic targets (A1c or time in range) before the scan. Almost 40% of analyzed brain metabolite ratios were considered abnormal, with fewer ratios considered abnormal in patients with T1D than those with T2D. Interestingly, one patient with T2D had an increased Cho/Cr ratio in all brain regions except the lentiform nucleus where decreased NAA/Cho ratio was noted. Similar changes in brain metabolites typically localised unilaterally in only one brain region were found in patients with T1D. The only unaffected parameter in all patients was the NAA/Cr ratio in centrum semiovale.
Conclusions
Distinct metabolic signatures of different brain regions may indicate subclinical region-specific diabetes-induced brain damage. Future large-scale studies should challenge the role of brain metabolites as biomarkers and potentially reveal the underlying mechanism involved in the pathogenesis of comorbid brain disorders in patients with diabetes.

DOI: 10.1530/endoabs.83.DOMNP2

DOMNP3

Excessive presentation of primary hypertriglyceridemia on skin: a case report

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Background
Eruptive xanthomas, benign skin lesions, are rare and can be a sign of lipid metabolism abnormalities. This is an early indicator of the potential risks of pancreatitis and cardiovascular disease.
Case Presentation
A 57-year man admitted to the hospital due to elevated triglyceride level and poorly compensated type 2 diabetes. Main complaints were dry mouth and nocturia. No complaints of nausea, vomiting, stool changes or pain. There was data of previous episodes of acute pancreatitis and plasmapheresis due to dyslipidemia, as well as positive family history of sudden cardiac death. Upon examination the patient was overweight, with slightly elevated AP and no signs of abdominal tension. Small, raised, firm and painless yellow-red nodules throughout the body were discovered. In laboratory findings the lipid profile revealed a total cholesterol of 15,6 mmol/l, high-density lipoprotein of 0,39 mmol/l, low-density lipoprotein of 0,14 mmol/l and triglycerides of 58,0 mmol/l. The rest of plasmapheresis due to elevated lipids. The biochemical investigation was normal. In the imaging studies there were no signs of pancreatitis. Due to extremely high triglycerides patient received 4 plasmapheresis procedures, after which triglyceride level decreased to 5 mmol/l. Patient was treated with dapagliflozin, metformin, gliclazide, rosuvastatin/ezetimibe, omega fatty-acid, AKEi, CCB and indapamide. The patient was discharged with recommendation to make genetic screening for family hypertriglyceridemia.
Conclusions
Based on the medical history, family history, clinical investigation, the patient should be considered to have congenital familial hypertriglyceridemia, the treatment of which requires strong adherence to avoid secondary complications.

DOI: 10.1530/endoabs.83.DOMNP3

Reproductive and Developmental Endocrinology

Oral

RDO1

Follicle stimulating hormone is efficient in increasing sperm parameters in idiopathic infertility

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Background
Exogenous follicle-stimulating hormone (FSH) administration in male idiopathic infertility showed the most convincing rationale in the face of a clinical efficacy below expectations. It was calculated that 10 to 18 men have to be treated to achieve one pregnancy.
Objectives
To assess the effectiveness of FSH administration in male idiopathic infertility in a clinical setting.
Methods
A retrospective real-world study was carried out, including all consecutive male partners of infertile couples attending the Andrology Unit of Modena (Italy) from June 2015 to May 2022. Medical history, physical and andrological examinations, hormonal and seminal parameters, therapeutic management and pregnancy data were collected. Primary endpoints were semen parameters, while pregnancies were the secondary outcome.
Results
197 on 362 (54.4%) infertile men were treated with FSH (mean age 37.9 $\pm$ 6.1 years). After FSH administration (therapy duration 9.1 $\pm$ 7.1 months), a significant increase in sperm concentration (9.9 $\pm$ 12.2 vs 18.9 $\pm$ 38.9 million/mL, $P = 0.045$) was detected. Also, treatment led to a significant increase in normozoospermia (from 1.0 to 4.8%, $P = 0.044$) and decrease in azoospermia rate (from 9.6 to 6.5%, $P = 0.044$). 43 pregnancies were recorded (30.5%), 22 spontaneous and 21 after assisted reproduction. Dividing the cohort in FSH-responders and non-responders, considering obtaining or not a pregnancy, a higher sperm concentration (15.7 $\pm$ 26.6 vs 22.2 $\pm$ 25.7 million/mL, $P = 0.033$) and progressive sperm motility (18.0 $\pm$ 18.2 vs 27.3 $\pm$ 11.3, $P = 0.044$) were found in pregnancy group.
Conclusion
Our experience suggests that FSH empirically administered to men with idiopathic infertility increases sperm concentration and leads to pregnancy in 1 of 5 patients. Although the expected limits due to a real-world data study, the number of FSH-treated patients required to achieve a pregnancy seems to be lower if compared to previously published data.

DOI: 10.1530/endoabs.83.RDO1

RDO2

Ketogenic state is able to improve testosterone serum levels - a meta-analytic approach

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Background
It is widely demonstrated that obesity and hypogonadism are bi-directionally correlated, since the hypogonadism prevalence is higher in obese population, while weight loss increases testosterone serum levels. Several approaches are available to contrast weight excess, from simple dietary regimens to more complex surgical procedures. Ketogenic diets (KD) fit in this context and their application is growing year after year, aiming to improve the metabolic and weight patterns in obese patients. However, KD influence on testosterone levels is still poorly investigated.
Objectives
To systematically evaluate the potential effect of KD on testosterone levels.
Methods
A literature search was performed until April 2022 including studies investigating testosterone levels before and after KD. Secondary endpoints were body weight, estradiol and sex hormone binding globulin serum levels. Any kind of KD was considered eligible, and no specific criteria for study populations were provided.
Results
Seven studies (including eight trials) were included in the analysis, five using normocaloric KD and three very low calories KD (VLCKD). Only three studies enrolled overweight/obese men. A significant total testosterone increase was recorded after any kind of KD considering 111 patients (2.86 [0.95, 4.77], $P = 0.003$). This increase was more evident considering VLCKD compared to normocaloric KD (6.75 [3.31, 10.20], $P < 0.001$, vs 0.98 [0.08, 1.88], $P = 0.030$). Meta-regression analyses highlighted significant correlations between the post-KD testosterone raise with patients' age (R-squared 36.4, $P < 0.001$) and weight loss (R-squared 73.6, $P < 0.001$).
Conclusions
Comprehensively, KD improved testosterone levels depending on both patients' age and KD-induced weight loss. However, the lack of information in included studies on hormones of the hypothalamic-pituitary-gonadal axis prevents an exhaustive comprehension about mechanisms connecting ketosis and testosterone homeostasis.

DOI: 10.1530/endoabs.83.RDO2

RDO3

Which sperm parameter limits could really guide the clinical decision in assisted reproduction?

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Background
The predictive role of sperm motility and morphology was recently detected in a large sample of more than 20000 assisted reproductive technology (ART) fresh cycles. However, the complete ART procedure consisted in both fresh and frozen-embryos transfers and only a comprehensive evaluation of the entire process could really confirm if these parameters really predict the ART success.
Aim of the study
To identify predictive parameters of ART success, applying a real-world data analysis (RWD) on the entire ART path, combining fresh and frozen cycles.
Materials and Methods
A retrospective RWD analysis was performed, enrolling all couples attending a single ART centre from 2008 to 2021. The analysis included both fresh and frozen cycles, and both *in vitro* fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI) procedures. Primary endpoints were strong ART outcomes, i.e. biochemical and clinical pregnancies and live birth rates (LBR).
Results
Fresh cycles success (considering LBR) was predicted by female age (OR: 1.04 [1.02-1.06]), injected oocytes (0.96 [0.93-0.99]), embryo number (0.79 [0.75-0.83]) and progressive sperm motility (0.98 [0.97-0.99]). On the contrary, frozen cycles outcomes were predicted only by sperm motility (0.97 [0.95-0.99]). This prediction was confirmed in IVF but not in ICSI cycles.
Conclusions
Both female and male's parameters predicted the ART success considering entire path. However, frozen cycles success was predicted only by progressive sperm motility, suggesting that the potential amelioration of this male parameter is relevant to improve ART success. Those couples expected to obtain the highest embryos number after fertilization (low female age and better semen parameters) will have more attempts with frozen cycles and thus would benefit of a potential treatment focused to improve sperm parameters.

DOI: 10.1530/endoabs.83.RDO3

RDO4

Comparison of eunuchoid skeletal proportions in male hypogonadism between men with congenital hypogonadotropic hypogonadism (CHH) and Klinefelter Syndrome (KS)

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Background
Patients with CHH and KS share eunuchoid body proportions of skeleton compared to normal male subjects. On the contrary, testosterone levels at puberty are lower in CHH patients compared to KS patients.
Aim
To compare anthropometric measurements of adult male CHH vs KS patients.
Methods
A prospective, cross-sectional, observational study was conducted. CHH patients were subdivided into 2 subgroups according to the timing of treatment start (testosterone replacement therapy [TRT] or gonadotropins): CHH1) CHH patients who started after 18 years; CHH2) CHH patients who started on time before 18. All KS patients started TRT after 18. Height, weight, sitting height, and arm span were collected by using a digital scale and stadiometer (Seca gmbh&co®); legs length, upper-to-lower segment ratio (U/l), upper-to-height, and upper-to-arm span were calculated.
Results
A total of 47 CHH1,23 CHH2 and 55 KS age-matched patients were enrolled (mean age 35.1 ± 14.6, 31.0 ± 11.2 and 36.4 ± 13.5 years, respectively). CHH1 showed a longer arm span compared to CHH2 ($P < 0.001$) and KS ($P = 0.004$), and a shorter sitting height ($P = 0.001$) compared to KS. Furthermore, legs length was shorter in CHH2 compared to CHH1 ($P < 0.001$) and KS ($P = 0.004$). U/l and upper-to-height ratios were lower in CHH1 compared to CHH2 ($P < 0.001$) and KS ($P < 0.001$). On the contrary, the arm span-to-height ratio was higher in CHH1 compared to CHH2 ($P = 0.004$) and KS ($P < 0.001$).
Conclusions
Comparing adult CHH to KS patients, we observed more fine difference under the same definition of eunuchoid skeleton. CHH1 patients who delayed treatment showed longer arm length and lower U/l compared to CHH2 and KS. This suggests a different mechanism involved in eunuchoid skeleton development between CHH and KS confirming a major role for estrogen/androgen deficiency in the former and a possible role of genetic supernumerary X in the latter, displaying an early disproportional growth.

DOI: 10.1530/endoabs.83.RDO4

RDO5

Vascular erectile dysfunction as a mirror of general health: focus on patients comorbidities

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Background
Erectile dysfunction (ED) is the most frequent sexual disorder. Although psychological ED (pED) is the most frequent form, vascular ED (vED) is associated with 1.25 times greater risk of developing major cardiovascular diseases. Alongside cardiovascular aspect, the evaluation of patients' health, measured by the comorbidities number, in relation to the ED aetiology has never been investigated so far.
Objectives
To explore the potential relationship between the comorbidities number and ED aetiology and severity.
Methods
An interim analysis of all andrological patients attending to the Andrology Unit of Modena (Italy) from 2008 to 2011 was performed. For each patient, anamnesis, physical examination, ED characteristics, hormonal data and ongoing therapies were collected. Patients were grouped according to the ED aetiology. ED was graded using the International Index of Erectile Function (IIEF)-15 score and the number of comorbidities with Chronic Disease Score (CDS).
Results
460 ED patients (mean age 53.7 + 12.4 years) were followed for 10.2 + 6.5 years. 357 patients (77.6%) showed pED, 75 (16.3%) vED, 20 (4.3%) hormonal and 8 (1.7%) neurological ED. As expected, CDS significantly increased during follow-up with the highest score collected at the last visit compared to baseline ($P < 0.001$). CDS was significantly different among ED groups ($P < 0.001$) with lower scores in pED compared to vED. However, CDS was not related to IIEF-15 results ($P = 0.083$) but only to age ($P < 0.001$). At logistic regression analysis, CDS was not able to predict ED diagnosis ($P = 0.126$).
Conclusions
We demonstrated that vED patients show an increased comorbidities number compared to other ED etiolologies, confirming the suggested vED role as a mirror of general health. The CDS inability to predict ED etiology and its absent correlation with ED severity could be masked by the limited number of patients enrolled and it could be instead highlighted increasing the sample size.

DOI: 10.1530/endoabs.83.RDO5

RDO6

The role of thyroid autoimmunity in assisted reproduction outcome-not yet solved puzzle

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Background
Thyroid autoantibodies cross blood-follicle barrier in titer dependent manner and may change oocyte microenvironment with adverse effects on implantation or post-implantation period. Thyroid autoimmunity (TAI) interfers with pregnancy course and newborn anthropometry in pregnancy achieved by assisted reproduction (ART).
Objective
To light upon pregnancy course outcomes and newborn anthropometric characteristics regarding TAI in ART programme.
Methods
The course of clinical pregnancy achieved in 24 women undergoing ART was observed and pregnancy and newborn outcomes compared in two groups divided by the presence of TAI.
Results
In the study population, 33.3% were TAI positive and 66.7% TAI negative women. The special interest was adressed on anti-thyroglobulin antibodies with the important difference in serum, as expected, but in follicular fluid, $P < 0.001$. Number of retrieved oocyte, number of embryos, top quality and embryo transferred were not significantly different between the groups, but higher percentage of good quality oocytes in TAI negative group were noticed (70.9% vs 81.5%, $P = 0.053$), without affecting fertilization and implantation rates. Live birth rate was 96.0%, with preterm birth 16.7% and term birth rate 70.8%. Groups were no different comparing the rate of twin pregnancy, early, late miscarriage and preterm birth. Maternal complications, gestational diabetes mellitus or pregnancy induced hypertension, were present in 23.8% with no difference between the groups. In TAI positive group newborns had higher birth weight ($P = 0.001$) and lenght ($P = 0.008$). No congenital malformations in newborns were noted.
Conclusions
The study pointed out no adverse effects of TAI on ART achieved pregnancy outcomes, regardless the higher percentage of good quality oocytes in the women without TAI, but TAI could affect newborn anthropometry.

DOI: 10.1530/endoabs.83.RDO6

Poster

RDP1

A case of postmenopausal hirsutism

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Introduction
Progressive hirsutism and moderate to severe male-pattern balding in women requires exclusion of an adrenal or ovarian tumor.
Case presentation
A 51-year-old lady presented with excessive hair on her face and lower abdomen of 1 year duration which affected her quality of life. Her menopause started 3 years ago. Her body mass index was 28.6 kg/m^2. She had hair on her upper lip, chin, and lower abdomen; she had a Ferriman–Gallwey score of 10. On

examination the patient was normotensive, with male pattern baldness. A hormone profile revealed a markedly elevated serum testosterone of 3.7 µg/l (< 0.47), androstenedione of 6.1 ng/mL (0.35–2.49 ng/mL) and a free androgen index 67% (0.19-3.63%). Cortisol, prolactin, growth hormone and thyroid function tests, glycemic profile were normal. A CT scan of the abdomen and pelvis revealed a 21 mm right ovarian mass and multiple uterine fibroids with normal adrenal glands. The patient underwent total laparoscopic hysterectomy with bilateral salpingo-oophorectomy. Histology confirmed the presence of a Leydig cell tumour, confined to the right ovary, with no malignant features. Postoperatively her androgen levels normalized and symptoms resolved within 10 weeks.
Conclusion
In postmenopausal women with new onset of hirsutism that is severe or rapidly progressive, the possibility of an androgen-secreting tumor must be suspected and detailed history and physical examination, substantiated by focused biochemical and morphological confirmation is necessary.

DOI: 10.1530/endoabs.83.RDP1

RDP2

Late-discovered mosaic Klinefelter syndrome with severe osteoporosis and obesity

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Background
Bone mineral density measurement sometimes reveals osteoporosis that is a consequence of undiagnosed or neglected long-standing health disorders. These secondary causes of osteoporosis should be carefully investigated, especially in men.
Case Presentation
A 63-year-old male complained of back pain and was referred to endocrinology clinic due to a poor densitometry finding indicating osteoporosis. He presented with severe obesity (body mass index 40.5 kg/m^2), grade IV gynecomastia, Tanner IV genital appearance with descended testes. A spine X-ray detected compressive osteoporotic fractures in four thoracic vertebrae (Genant's grade 1 and 2). Laboratory results showed overt hypergonadotropic hypogonadism, mild normocytic anemia, vitamin D deficiency with plasma glucose and HbA1c in the prediabetes range. Peripheral blood cytogenetic analysis revealed mosaic form of Klinefelter syndrome 47, XXY/46, XY - 19 out of 21 metaphases had XXY trisomy. The patient has been married with no children and has never engaged in infertility evaluation. He had no interest in testosterone treatment for sexual dysfunction and focused only on preventing skeletal difficulties. Severe osteoporosis was treated with teriparatide for two years, followed by risedronate. His lumbar pain improved and no new fractures occurred. During follow-up his hypertension was poorly controlled and he developed diabetes, but declined bariatric surgery.
Conclusions
Bone and metabolic complications in patients with Klinefelter syndrome are mainly related to testosterone deficiency. However, testosterone replacement has not yet been approved for osteoporosis treatment due to lack of evidence that it reduces fracture risk. The benefits of testosterone on cardiometabolic disorders were found, but it is necessary to weigh them against potential risks of this therapy in older patients with established comorbidities. Although effective control of male hypogonadism symptoms is usually reported, patients with Klinefelter syndrome might exhibit psychological, cognitive, and social issues that interfere with timely diagnosis, their preference for masculinization and adoption of a healthy lifestyle.

DOI: 10.1530/endoabs.83.RDP2

RDP3

Pharmacodynamics and safety of human recombinant luteinising hormone (LH) in hypogonadotropic hypogonadal men: a new ongoing multicenter study

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State of the art
In pharmacology, human chorionic gonadotropin (hCG) is considered equivalent to luteinising hormone (LH) since both act on the same receptor. Thus, when testicular function needs to be clinically restored (i.e. in case of hypogonadotropic hypogonadism [HH]), hCG is used instead of LH. However, growing evidences showed LH and hCG activate different molecular pathways and offer different outcomes in women undergoing assisted reproduction. The different action between LH and hCG is still not evaluated in men.
Aim of the study
To assess the pharmacodynamics of recombinant LH in HH men, comparing recombinant LH (Luveris®) to the gold standard approach, i.e. hCG (Gonasi HP®).
Study design
A multicenter, longitudinal, randomized, open label, phase II, 'non-inferiority' clinical trial was designed. Endpoints will be testosterone serum levels and drug safety. 32 men with acquired HH will be enrolled and randomized (1:1) to study group treated with Luveris or to control group treated with Gonasi. In both groups, increasing drug doses will be administered (75, 150, 225, 300 IU daily for LH and 500, 1000, 1500 and 2000 IU two times weekly for hCG). Both treatments will be performed for 8 weeks, during which the patient will be evaluated twice weekly, followed by a 4-week washout period. Testosterone and its metabolite will be evaluated at the end of study using the gold standard mass spectrometry methodology.
Expected Results
We expect to describe for the first time the pharmacodynamics of both LH and hCG chronically administered in men, creating a dose-response curve for both compounds. Moreover the clinical hCG dosage is still empirical, thus we will recognize the best treatment regimen to restore normal testosterone levels in HH, for both LH and hCG treatment. This study is preliminary to further studies assessing LH in hypogonadal and/or infertile patients.
Current study state
The study started in March 2022 and we currently enrolled 3 HH patients.

DOI: 10.1530/endoabs.83.RDP3

RDP4

Testosterone therapy in chronic liver disease

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Background
Several clinical features of chronic liver disease, such as sarcopenia, anaemia, low bone mass and gynecomastia are similar as manifestation of hypogonadism. Decreased testosterone levels are common in patients with severe liver disease and are associated with worse clinical outcomes and mortality.
Case Presentation
A 33-year-old patient was admitted to the hospital due to severe alcoholic hepatitis. He was in poor general condition, icteric, encephalopathic with peripheral edema and mild ascites. Due to high Maddrey score, corticosteroid therapy was initiated, leading to a gradual decrease in bilirubin and liver enzymes but his clinical condition remained poor. The patient lost 23 kg of body mass within 2 months and his body mass index (BMI) was 21 kg/m2. The SARC-F score (Strength-Assistance walking-Rice from a chair-Climb Stairs-Falls) was 4. Laboratory findings suggested hypogonadotropic hypogonadism with very low free testosterone levels (32 pmol/l, ref. range 170 - 660) corrected for albumin and SHBG. Transdermal therapy with 25 mg/day of testosterone gel was initiated. A month later, free testosterone was 151 pmol/l and there was a clinical increase in muscle strength and mobility. Dose of 50 mg/day was continued. Body mass further increased (BMI 24 kg/m2); the patient became fully independent in performing physical tasks while free testosterone reached normal levels (251

pmol/l). Liver parameters improved and no side effects occurred. We decided to continue testosterone therapy until further recovery of liver function.
Conclusion
Due to high incidence of hypogonadism, testosterone levels should be assessed in younger patients with severe liver diseases. The transdermal administration of testosterone therapy avoids hepatic circulation and prevents potential occurrence of hepatotoxic effects. It dramatically improved frailty in our patient and similar results have already been described, but this therapeutic option is still not widely prescribed. Further research on long term risk and benefits of transdermal testosterone therapy in chronic liver diseases is required.

DOI: 10.1530/endoabs.83.RDP4

RDP5

Reliability of patient's auto-report on the regularity of their menstrual cycle

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Background
Menstrual cycle characteristics are essential indicators of a woman's reproductive health. The reliability of auto-reported data assesment of menstrual cycle length has been questioned.
Objectives
The aim was to evaluate the reliability of auto-reported data on menstrual cycle regularity.
Methods
We created an anonymous survey about reproductive health and menstrual cycle characteristics and shared it with women of reproductive age. Patients were first asked to auto-report data on menstrual cycle regularity in the last six months and then answer the same question while using the smartphone application for period tracking.
Results
The study included 195 women, mean age 26.54 $\pm$ 6.955 years and an average body mass index (BMI) of 21.982 $\pm$ 2.98 kg/m^2. 123 women (63.1 %) mean age 27.20 $\pm$ 6.98 years, mean BMI 22.11 $\pm$ 3.188 kg/m^2, answered correctly about their menstrual cycle regularity, and 72 women (36.9 %) mean age 25.42 $\pm$ 6.811 years, mean BMI 22.37 $\pm$ 2.59 kg/m^2, gave the wrong answer. Women who gave the wrong answer were significantly younger (mean age 25.42 $\pm$ 6.811 years, $p = 0.018$) than women who answered correctly. There was no difference in BMI, education, marital status, or comorbidities between the groups.
Conclusions
Our data point to significant unreliability of auto-reported data on menstrual cycle regularity. Patients should be encouraged to use the smartphone applications for period tracking. Also, it is important to raise awareness and education on the importance of menstrual cycle characteristics.

DOI: 10.1530/endoabs.83.RDP5

RDP6

Effects of COVID-19 on menstrual cycle changes in women with polycystic ovary syndrome

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Background
It was shown that women with polycystic ovary syndrome (PCOS) are at an increased risk of COVID-19. However, it is not known whether COVID-19 has any effects on reproductive health of PCOS patients.
Objectives
Aim of the study was to evaluate possible effects of COVID-19 on reproductive health in patients with PCOS.
Methods
An anonymous survey about reproductive health was conducted in PCOS patients and healthy control (HC).
Results
254 women completed the survey. All women reported recording their cycles using a phone application. After exclusion of women who had negative COVID-19 test, incomplete survey data and women in menopause, our cohort consisted of 133 females with confirmed COVID-19 prior to evaluation, 30 with PCOS and 103 HC patients. Mean age of patients was 30.09 $\pm$ 9.76 years and BMI 22.64 $\pm$ 3.5 kg/m2. Patients with PCOS reported significantly higher changes in menstrual cycle characteristics than HC ($P < 0.05$). Most noted changes were missed periods, heavier flow and more painful bleeding. Namely, women with PCOS had significantly shorter duration of menstrual bleeding in comparison with HC ($P < 0.05$). There was no difference in changes in PMS symptoms, frequency of period and menstrual flow between groups.
Conclusion
COVID-19 has significant effects on already vulnerable reproductive health of PCOS patients. The exact mechanism why COVID-19 has these effects remains to be elucidated.

DOI: 10.1530/endoabs.83.RDP6

RDP7

Estrogen withdrawal associated psychosis (EWAP) as a result of hormone replacement treatment discontinuation in a patient with 46, XY gonadal dysgenesis

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Background
Gonadal dysgenesis (GD) is a congenital disorder of sex development resulting in gonadal dysfunction caused by a variety of underlying genetic aberrations. Psychiatric morbidity is more common in women with GD in comparison to the general population but whether this is the result of a hormonal disbalance is unknown. However, psychotic symptoms due to abrupt changes in blood estrogen levels have been commonly reported. The aim is to report the first case of a psychotic episode due to hormone replacement treatment (HRT) discontinuation in a patient with 46, XY GD.
Case presentation
A 20-year-old Caucasian female presented with isolation, suspiciousness, avoidance of communication and insomnia during the last 2 months. The patient displayed paranoia and a lack of insight in her illness. A slow stream of thought process with increased latency and paranoid delusions in thought content were observed. The Minnesota Multiphasic Personality Inventory-2 showed a positive Goldberg Index, indicating psychotic functioning, with paranoia and schizophrenia in the patient profile basis. Soon after birth, the patient has been diagnosed with GD and has been under HRT, which she quit taking 2 months prior because of her fear of developing breast cancer. Estradiol was re-introduced into the treatment, which alleviated symptoms. Cytogenetic analysis revealed a male 46, XY karyotype. Next-generation sequencing of 25 genes related to GD revealed a heterozygous variant of uncertain significance (VUS) in the luteinizing hormone choriogonadotropin receptor gene and a hemizygous VUS on chromosome X in the androgen receptor gene. Both variants were not previously reported in major databases of population genetic variation.
Conclusions
Our findings identify a potential link between discontinuation of estrogen replacement therapy and acute psychosis in the context of GD and stress the importance of proper maintenance of hormonal balance for both the physical and mental health of these patients.

DOI: 10.1530/endoabs.83.RDP7

Pituitary and Neuroendocrinology

Oral

PNO1

Leukocyte telomere length and neuregulin-4 levels in female patients with acromegaly: Relationship between disease activation and body fat distribution

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Background and Objectives
Leukocyte telomere length (LTL) is considered as a marker of cellular aging. Brown adipose tissue in women has been claimed to be associated with long life in women. Neuregulin-4 is a new batokine secreted from brown adipose tissue, and it is thought to play a role in the regulation of glucose, lipid metabolism and energy balance. The aim of the study is to examine LTL and serum Neuregulin-4 levels as well as their relations with disease activity, co-morbidities and body fat distribution.
Materials and Methods
Forty female (23 active, 17 inactive) with acromegaly aged 18-65 years and 39 healthy female volunteers who were similar in terms of age and body mass index were included in the study. LTL was studied by the quantitative Polymerase chain reaction (PCR) method. The ratio of telomere repeat amplification product (T) to single-copy gene product (S) was calculated as the relative T/S ratio. T/S ratio < 1 was accepted as shortened telomere length. Serum Neuregulin-4 levels were studied by ELISA method. Body fat distribution was measured by bioelectrical impedance analysis and VİScan.
Results
There was no difference in median LTL values between acromegaly and control groups ($P = 0.530$). The percentage of $T/S < 1$ in patients with acromegaly (60.0%) was similar to that of the control group (43.6%) ($P = 0.144$). Serum Neuregulin-4 levels were significantly higher in patients with acromegaly than those of the control group (1.06 vs 0.79 ng/ml, $P = 0.037$). There were no significant differences with respect to LTL, percentage of $T/S < 1$ and neuregulin-4 levels between active and controlled acromegaly groups ($p > 0.05$). Neuregulin-4 correlated positively with glucose, triglyceride, and lean body mass in the acromegaly group. Although a significant negative correlation was observed between LTL and Neuregulin-4 in the control group, this relationship was not observed in the acromegaly group.
Conclusion
Our findings indicate that acromegaly is associated with unchanged LTL and high neuregulin-4 levels in female patients. However, the relationship between acromegaly, the aging process, and neuregulin-4 involves complex mechanisms, and further studies are needed.
Keywords: acromegaly, leukocyte telomere length, neuregulin-4.

DOI: 10.1530/endoabs.83.PNO1

PNO2

Real-world use of intravenous hypertonic saline for hyponatraemia: a data-driven refinement of ESE guidelines

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Background
The European Society of Endocrinology (ESE) published guidelines to standardise intravenous hypertonic saline (HTS) for severe symptomatic hyponatraemia in 2014. Two 150 mL boluses of 3.0% HTS are proposed, one after the other, to achieve an initial sodium rise of 5 mmol/l without waiting for an interval sodium result. ESE guidelines were adopted by our University Hospital in 2017. However, high rates of sodium overcorrection were observed, and the guidelines lacked detailed guidance on overcorrection management.
Objectives
To evaluate the 'real-world' safety and efficacy of ESE guidelines for the use of HTS, and to design a bespoke protocol to overcome any identified limitations.
Methods
We conducted a retrospective medical records review of all patients who were administered HTS between 2017-2020 focussing on rates of sodium overcorrection and its management.
Results
In total 112 patients received HTS. Overcorrection rates at 24 hours were 44.9%. There was no reported episode of osmotic demyelination syndrome and HTS administration was not linked to inpatient mortality. 22.6% had overshot the immediate target rise of 5 mmol/l after just one bolus of HTS. Overall, 20% of our cohort received overcorrection treatment but there was heterogeneity in use of overcorrection treatments. Based on these findings, we updated the guideline with a point of care venous blood gas sodium check after the first HTS bolus, and only recommend second bolus if the intended 5 mmol/l rise in sodium has not already been achieved. Further, we adopted use of fixed volume (200 mL) boluses of intravenous dextrose to standardise safe management of sodium overcorrection.
Conclusions
Our data comprise the largest real-world cohort evaluating ESE guidelines. Overcorrection rates were significant prompting a data-driven refinement of ESE guidance for use in our hospital. Our data indicate that a review of ESE guidelines is warranted to amend the current bolus strategy.

DOI: 10.1530/endoabs.83.PNO2

PNO3

Development of novel immunoassays for the pro-opiomelanocortin joining peptide (A surrogate marker of adrenocorticotrophin levels) for use in the diagnosis of Cushing's syndrome

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Background
Excess adrenocorticotrophin (ACTH), most often from a pituitary tumour, results in the overproduction of cortisol and the condition, Cushing's syndrome. Plasma ACTH measurements are used in the diagnosis of Cushing's syndrome but due to the presence of multiple dibasic cleavage sites within its sequence, ACTH is extremely labile and far from an ideal analyte. Processing of ACTH by some ectopic tumours releases high levels of smaller-ACTH like fragments, α-MSH and CLIP, which can interfere with individual antibodies in current immunoassays. Furthermore, cross-reactivity with the precursor, pro-opiomelanocortin (POMC), increases the likelihood of erroneous interpretations and unreliable results.
Objectives
Here we explore the use of another POMC-derived peptide, the 30 amino acid (aa) joining peptide (JP), as a more robust surrogate measure of secreted ACTH levels. As it is not subject to further trypsin-like degradation, the JP is expected to have a much longer half-life than ACTH in plasma.
Methods
Antiserum was raised in sheep against synthetic 30 aa human POMC JP conjugated to keyhole-limpet hemocyanin (KLH). N- and C-terminal specific antibodies were affinity purified and subsequently used to develop ELISAs for the direct measurement of the dimeric endogenous JP in unextracted human plasma.
Results
The sensitivity of the assay was 10 ± 0.5 ng/l ($n = 8$). The mean coefficient of variation was 6.8% within-assay and 5.5% between-assay and is less than 10% between 20 and > 5000 ng/l. Initial experiments show endogenous JP immunoactivity is stable *in vitro* at 18-22°C for at least 24 hrs in plasma and serum. In comparison, the half-life for ACTH in plasma is < 30 mins.
Conclusions
The assay is now being evaluated in normal subjects and patients with Cushing's disease, ectopic Cushing's syndrome and small-cell lung carcinomas. To conclude, the two-site ELISA for POMC JP in unextracted plasma could offer a reliable surrogate assay for clinical purposes.

DOI: 10.1530/endoabs.83.PNO3

PNO4

Cardiovascular parameters and endothelial dysfunction in Cushing's Syndrome following remission: A prospective study

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Background
Cushing's syndrome is a well-known risk factor for endothelial dysfunction, cardiovascular morbidity and mortality.
Objectives
We aimed to prospectively investigate changes in metabolic and cardiovascular parameters and their correlations with markers of endothelial function in patients with endogenous Cushing syndrome following remission.
Methods
Adult patients newly diagnosed with endogenous Cushing's Syndrome (Cushing's disease(CD) or adrenal Cushing's) and a control group matched in terms of age, gender, BMI, lipid, and glucose parameters were enrolled. Metabolic (BMI, body composition analyses, glucose, lipid values) and cardiovascular evaluation studies (echocardiography, 24-hour ambulatory blood pressure monitoring, carotid intima-media thickness(CIMT), flow-mediated dilation(FMD)) were performed and markers associated with endothelial function (asymmetric dimethylarginine(ADMA), interleukin-1β(IL-1β), nitric oxide(NO), endothelin-1(ET-1)) were measured before and one year following remission. Spearman's correlation analysis was used to investigate the association between variables.
Results
Twenty-five patients (CD(n = 9); adrenal Cushing's(n = 16)), mean age 40.60 ± 14.04 years, completed the study. Ten patients had type 2 diabetes mellitus and 13 had hypertension that was well-controlled before surgery. Compared to controls(n = 22) total, daytime and nighttime mean arterial pressures(MAP) and CIMT were higher and FMD lower in patients. Baseline serum IL-1β, NO, ADMA and ET-1 were similar between the groups. Patients' serum ET-1 and IL-1β were negatively correlated with CIMT at baseline (r = -0.465, $P = 0.025$ and r = -0.567, $P = 0.005$, respectively). All patients were in complete remission one year following surgery. After remission, BMI, total cholesterol, LDL, total, daytime, nighttime MAP and CIMT significantly decreased. Serum ET-1 levels significantly increased ($P = 0.011$), while ADMA, IL-1β and NO remained similar one year after remission. Subgroup analysis comparing patients with and without hypertension revealed increase in ADMA and ET-1 levels in the hypertensive group following remission while there was no change in the normotensive group.
Conclusions
There is a significant improvement in metabolic parameters, MAPs, CIMT in patients with Cushing's syndrome at the first year following remission. The unexpected increase in ET-1 needs to be further investigated.

DOI: 10.1530/endoabs.83.PNO4

PNO5

Postoperative basal cortisol level as an indicator of pituitary surgery success in Cushing's disease treatment: a single centre retrospective study

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Background
Pituitary surgery is the primary therapy for Cushing's disease (CD). Basal cortisol level (BCL) is measured postoperatively to evaluate the immediate efficacy of surgical treatment, but no definitive cut-off value has yet been determined as reliable. Our pituitary-dedicated centre uses an arbitrary BCL less than 50 nmol/l as expected early remission marker, identifying all patients with higher BCL as a risk group for early surgical failure.
Objectives
(i) To assess whether BCL is indicative of immediate outcome of pituitary surgery as first-line CD treatment (ii) If (i) is affirmative, to ascertain the optimal BCL cut-off value based on our centre data
Methods
This single centre retrospective study reviewed 42 consecutive patients who underwent pituitary surgery as initial therapy for CD. BCL was measured during the first postoperative week. Surgical success was defined as biochemical remission at 3-month follow-up, whereas surgical failure was defined as persistent CD at 3-month follow-up. ROC curve was used for statistical analysis.
Results
Out of 42 patients, 36 were in remission and 6 had persistent CD at 3-month follow-up. Postoperative BCL ranged 11-2326 nmol/l. According to ROC curve (AUROC:0.926; 95%CI:0.843,1.0;$P = 0.001$), BCL was an excellent indicator of early surgical outcome. A cut-off value of 50 nmol/l we ordinarily used was 100% sensitive and 58.3% specific for determining surgical success, meaning 41.7% of patients perceived as potential immediate surgical failure actually achieved remission. A more appropriate cut-off value of 317 nmol/l (sensitivity 100%, specificity 80.6%) still detected all surgical failures with only 19.4% of successful outcomes having higher BCL.
Conclusions
(i) Postoperative BCL indicates early outcome in pituitary surgery as initial treatment for CD. (ii) Postoperative BCL higher than we previously thought can be found in successful early outcomes, justifying the wait-and-see approach. Further studies on larger samples are required to determine the optimal cut-off value.

DOI: 10.1530/endoabs.83.PNO5

PNO6

Long-term outcomes of treatment of Cushing disease in UHC Zagreb

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Introduction
Cushing disease (CD) is the leading cause of endogenous hypercortisolism, caused by a pituitary tumor that produces ACTH. Treatment modalities include transsphenoidal selective adenomectomy (TSA), pharmacological therapy, radiotherapy (RT), and bilateral adrenalectomy (BA). The goal of our study was to analyze the outcomes of Cushing disease treatment in UHC Zagreb.
Method
This retrospective study comprised 64 patients with CD (51 (80% women), the median age of 39 (16-70 years) treated in the Department of Endocrinology at UHC Zagreb from 2005 to 2022.
Results
After TSA, 53 (83%) of patients achieved remission, but four patients developed relapse during the follow-up (the median time to relapse was 21.5 (5-144) months). Eleven patients who did not achieve remission after TSA and four patients with relapse were introduced to the other treatments: ketoconazole (9 patients), metyrapone (2), gamma-knife RT (3), and BA in two patients, resulting in remission in ten patients. Among patients with the active disease after surgery, one patient died, another one was lost to follow-up, and one patient still has active disease. Furthermore, additional two patients with relapse were lost to follow-up. After all treatment modalities, we accomplished remission in 92% of patients.
Conclusion
The main goals of CD treatment should be the achievement of remission and timely relapse detection. Despite all treatment options, managing patients with CD remains challenging, and patients' motivation for long-term follow-up is an important issue.

DOI: 10.1530/endoabs.83.PNO6

Poster

PNP1

Newly diagnosed diabetes mellitus in an untreated hypopituitary patient

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Congenital hypopituitarism is a rare disease, occurring sporadically in the vast majority of cases, that is found more frequently in males. We are presenting the case of a 19 year old that addressed our clinic because of short stature and lack of development of secondary sexual traits. During the clinical assessment we found his height to be 146 cm, corresponding to -4.78 SDs, Tanner stage of pubertal development 1 and lack of apocrine axillary odor. The patient was inapetent and had progressive weight loss of about 10 kg in the last year. Hormonal tests confirmed that he had panhypopituitarism (the central adrenal insufficiency only becoming obvious shortly after starting levothyroxine replacement therapy). We performed a Synachten-stimulation test in which cortisole failed to stimulate adequately. Hypophyseal imaging showed pituitary hypoplasia - the most frequent neuroradiologic find associated with the disease. The unexpected find in this case, though, was marked hyperglicemia, further evaluation showing that the

patient also had type 1 diabetes mellitus. Initial management consisted of replacement therapy with levothyroxine and hydrocortisone and insuline therapy - with the intent to start growth hormone replacement therapy as soon as possible - with good expected heightening prognostic, given that the patient has delayed bone age. The case stands out through the fact that it illustrates the intricate and particular interdynamic of the two co-occurring diseases - including the "sparing" effect of hypopituitarism on diabetes mellitus through insulinosensitivity and low levels of counterregulatory hyperglycemic hormones. Lastly, the interplaying patophysiology also offers a challenging management of such a case for the physician.

DOI: 10.1530/endoabs.83.PNP1

PNP2

An unusual cause of hypopituitarism with An even more unusual presentation – a case report

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Background
Hypopituitarism is a rare clinical condition which can present as partial or complete absence of pituitary hormones. The most common cause is a sellar or parasellar mass, particularly tumour, and the golden standard for differential diagnosis is magnetic resonance imaging. Intrasellar aneurysm is an unusual cause of hypopituitarism with an estimated incidence of 0,17% of cases.
Case presentation
We report a case of a 72-year-old male who was admitted to the hospital due to symptoms of gastrointestinal disorder accompanied by malnourishment. Due to persistent hyponatremia and spontaneous hypoglycaemia in laboratory findings, the examination of hypothalamic-pituitary-adrenal axis was eventually initiated, and the patient was later diagnosed with unruptured aneurysm of the ophthalmic segment of the right internal carotid artery with extension into the sella, as a cause of panhypopituitarism. A combined endovascular treatment was performed with stent assisted coil embolization of the aneurysm and the patient was prescribed with oral hormone therapy. At the 1-year follow-up visit, pituitary MRI showed complete aneurysm occlusion and partial 'empty' sella with significantly decreased volume of the hypophysis, and no improvement in the pituitary function has been observed.
Conclusions
Aneurysms of the internal carotid artery are a rare, but potential cause of hypopituitarism with a possible delay in diagnosis due to unusual clinical presentation. Endovascular procedure such as coil embolization of the aneurysm could be the treatment of choice in these patients. Persistent hypopituitarism could be expected even after a successful treatment of the aneurysm.

DOI: 10.1530/endoabs.83.PNP2

PNP3

A patient with aggressive prolactinoma

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Prolactinomas are the most common secreting pituitary tumors. Although most respond well to dopamine agonists, some prolactinomas are dopamine-resistant and very aggressive. Here we present a 37-year-old patient with aggressive prolactinoma.
Case report
The 37-year-old patient was referred to the University Hospital Centre Zagreb in March 2020 for bilateral visual field defects and headaches due to prolactinoma. In 2017, he had a transsphenoidal resection of the macroprolactinoma. After the surgery, the tumor remnant was 15 mm. The patient was initially treated with bromocriptine and, from October 2019, with cabergoline five times a week. At the first follow-up in our department, the prolactin level was 730 μg/l; MRI showed a residual adenoma of 35x19x22 mm. After one month, the visual field further deteriorated, and the prolactin level increased to 1270 μg/l. The patient was sent for transcranial surgery. The postoperative prolactin level was 644 μg/l. After discharge, he was treated with cabergoline. In May, he was readmitted for visual field disturbances and a prolactin level of 1955 μg/l. MRI showed tumor progression. The patient underwent further transsphenoidal tumor resection and was referred for concomitant chemoradiotherapy (temozolomide + conventional radiotherapy) followed by nine cycles of temozolomide. In the next seven months, MRI showed regression of the tumor and reduction of prolactin levels to 28 mg/l. From July to November 2021, the prolactin level gradually increased to 705 μg/l. MRI scan again showed tumor progression. He was treated with cabergoline and anastrozole and restarted temozolomide until he was hospitalized due to a COVID-19 infection. In January, another transcranial surgery was performed. The PRL level after the surgery was 1640 mg/l, and an MRI scan showed a residual tumor. Pasireotide therapy was initiated, and he received three applications. The PRL level further increased to 3030 mg/l in April 2022. It was decided to start bevacizumab, but the patient developed sepsis and died before bevacizumab could be started.
Conclusion
This aggressive prolactinoma did not respond to many treatment modalities. Unfortunately, immune checkpoint inhibitors are mainly unattainable due to their cost.

DOI: 10.1530/endoabs.83.PNP3

PNP4

Hypoglicaemia in patient with unrecognized pituitary stalk interruption syndrome

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Introduction
Pituitary stalk interruption syndrome (PSIS) is a rare congenital pituitary malformation characterized by the classical triad: pituitary stalk rupture, absent or ectopic neurohypophysis, and hypoplasia or aplasia of adenohypophysis. The clinical presentation depends on the age of the patient at the time of diagnosis. Patients may also have seizures, hypotension, and mental retardation at presentation. He aim is to describe a patient with an unrecognized pituitary stalk interruption syndrome, who as such was for many years only under the supervision of a neurologist due to epilepsy and mental retardation and without hormone replacement therapy.
Patient presentation
A 25-year-old man was admitted to endocrinology due to hypoglycemia, nausea and vomiting, and after a series of epileptic seizures. He was previously diagnosed with cerebral palsy, mental retardation and epilepsy. Clinical examination at admission verified low growth (height 133.5 cm, weight 35 kg), hypoglycemia and hypotension. Hormonal analyzes have shown hypothyroidism, hypocorticism, hypogonadism, and hyperprolactinemia. Pituitary NMR findings indicated hypoplastic / aplastic adenohypophysis, hypoplastic stalk, and ectopic neurohypophysis. Radiography of the hand estimated bone maturity of the age of 15 years. Testicular ultrasound showed an undescended left testis in the inguinal canal. In accordance with the findings, the patient was introduced hormone replacement therapy with hydrocortisone and levothyroxine, which resulted in satisfactory clinical recovery.
Conclusion
The case of a patient with a late diagnosis of pituitary stalk rupture syndrome and with all the consequences of untreated panhypopituitarism is presented. In any patient who presents with low growth, epileptic seizures and hypoglycemia in adulthood, it is crucial to suspect the endocrine etiology of the changes.

DOI: 10.1530/endoabs.83.PNP4

Environmental Endocrinology

Oral

EEO1

Influence of mercury on thyroid hormone levels in the Serbian population – Benchmark dose approach

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Introduction
It is known that many metals can contribute to thyroid dysfunction. Mercury (Hg) has attracted the attention of researchers because it is widespread in the environment (food, air, soil). However, only several studies deal with the exposure to low doses of Hg, which may reflect the real exposure of the general population.
Aim
This study examined the relationship between measured concentrations of Hg in the blood and levels of free thyroxine (FT4) and thyroid-stimulating hormone (TSH) in the serum of subjects representing the general population of Serbia.
Methods
In a human biomonitoring study conducted as part of the DecodExpo project, 425 blood samples were collected from subjects (207 men and 218 women) at the Clinical Center and the Clinical Hospital Center "Bežanijska kosa" in Belgrade. The Hg concentration was then determined by inductively coupled plasma mass spectrometry. Chemiluminescent immunoassay on a Cobas e411 analyzer was used to measure serum FT4 and TSH levels. The dose-response relationship was determined using the Benchmark dose (BMD) approach and the analysis was performed in PROAST software.
Results
The estimated BMD interval (BMDI) for TSH was broad in men, and 0.494-10.2 μg/l in women. The relatively narrow BMDI obtained for Hg-TSH levels in women indicates high certainty in estimates that a blood Hg concentration of 0.494 μg/l (BMDL) can increase the risk of TSH levels by 10%. The obtained BMDL for women was lower than the median value (3,444 μg/l). Further, for the levels of Hg and FT4, the dose dependence was determined using continuous data and the levels of FT4 hormone decreased with increasing levels of Hg, although the obtained BMDI was wide indicating the high variability of the obtained data.
Conclusion
The obtained results revealed possible effects of Hg environmental levels on thyroid function homeostasis.

DOI: 10.1530/endoabs.83.EEO1

EEO2

Influence of exposure to metaloestrogen – selenium on Leydig cell epigenetic status

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Background
As a trace element selenium (Se) is essential for man and animals, in particular for the maintenance of spermatogenesis and male fertility. A growing number of evidence shows that Se is necessary for testosterone synthesis, and inappropriate concentration, Se can stimulate Leydig cell proliferation. However, Se can also act as a metalloestrogen, which can mimic estrogen and activate the estrogen receptors. In higher concentrations, Se might have an adverse effect on male fertility.
Objectives
The aim of this study was to investigate the effect of selenium on the epigenetic status of mouse Leydig cells.
Methods
Mouse Leydig cells (MA-10) were treated for 24h with sodium selenite (Na2SeO3) in 4 μM and 8 μM concentrations. Immunofluorescence was utilized for the detection of γH2AX and 5-methylocytosine. Western blot was employed to analyze the expression of γH2AX. qRT-PCR was used to evaluate the expression of methyltransferases (Dnmt1, Dnmt3a, Dnmt3b).
Results
Independently of the dose, treatment did not affect the morphology of the cells. However, we found an increase in the number of lipid droplets between treated cells. Immunofluorescence revealed strong immunosignal for 5-methylcytosine in both control and treated cells, with a stronger signal in the 8 μM treated group. qRT-PCR confirmed an increased expression of Dnmt3b in 8 μM cells. Analysis of expression of γH2AX (a marker for double-stranded DNA breaks) revealed an increased amount of DNA brakes in the group treated with 8 μM concentration.
Conclusions
High concentration of Se causes DNA breaks and changes in Leydig cell methylation status, especially in the case of de novo methylation which is mediated by Dnmt3b. This might be an adaptive mechanism of cells in response to the changes in the microenvironment.

DOI: 10.1530/endoabs.83.EEO2

EEO3

Commercially available multivitamin supplements during pregnancy are ineffective for optimal selenium supply for mothers and newborns

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Background
Selenium (Se) sufficiency is beneficial for thyroid metabolism and pregnancy course due to its antioxidant and anti-inflammatory properties. As a part of selenoenzymes, it ameliorates autoimmune thyroid disease (AITD) progression in mothers and provides proper neurogenesis in fetuses. Despite lacking or conflicting recommendations for its supplementation in pregnancy, Se is used in a clinical setting, as a common constituent of multivitamin pregnancy diet supplements.
Objectives
The aim of the study was to evaluate Se supply and real-life supplementation effectiveness in pregnancy, based on Se biomarkers assessment in mothers and their newborns.
Methods
115 mother-child pairs were recruited at term delivery from obstetric department in one Polish centre. By the medical interview Se supplementation during pregnancy was assessed. The blood was collected before childbirth in mothers and during the third phase of delivery from the newborns' cord blood. Se status was assessed by measuring serum Se and selenoprotein P (SELENOP) concentrations and glutathione peroxidase 3 (GPX3) activity.
Results
Se intake was declared by 30% of women, using multi-micronutrient supplements, with a mean Se dosage ($\pm$ SD) of 42 $\pm$ 14 μg/day. The whole group was deficient in Se in 89% (Se $<$70 μg/l) and SELENOP in 77%. Median serum Se (54 vs. 58 μg/l), SELENOP (2.2 vs. 2.3 mg/l), or GPX3 (199 vs. 208.5 U/l) concentrations were slightly but not significantly higher in the supplemented than non-supplemented group. However, in the subgroups of low ($<$ 55 μg/day) and moderate ($\geq$ 55 μg/day) daily Se dosage, median SELENOP was significantly higher in the latter group (1.84 vs. 3.17 mg/l, $p = 0.006$). Additionally, positive correlations of Se ($z = 8.07$, $P < 0.001$), SELENOP ($z = 5.15$, $P < 0.001$) and GPX3 ($z = 7.41$, $P < 0.001$) within mother-newborn pairs were observed.
Conclusions
Se supplementation from pregnancy multivitamin formulas was ineffective in the presented cohort. The mothers' Se supply reflects Se bioavailability for newborns. Considering diversity in geographical Se stores, differences in diet and individual Se level, no common guidelines can be applied worldwide, thus, there is a need of local Se status verification and adjusted recommendations.

DOI: 10.1530/endoabs.83.EEO3

EEO4

Impact of COVID-19 on women's reproductive health

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Background
Reproductive health is an integral part of a women's general health and is influenced by various endogenous and exogenous factors.
Objectives
The aim was to detect the possible effects of COVID-19 on women's reproductive health.
Methods
We created an anonymous survey about reproductive health and shared it with women of reproductive age. Regarding menstrual cycle characteristics all women used the smartphone application for period tracking.
Results
205 women completed the survey. Based on inclusion, exclusion and complete data availability 162 surveys were taken into the final analysis. Mean age was 28.8 $\pm$ 9.5 years. 115 (71%) women reported previously being infected with COVID-19. 94 (81.7%) of these women reported having changes in their menstrual cycle (MC) afterwards ($P < 0.0001$) when compared to non-COVID19 participants. Women under the age of 30 who had a COVID-19 were more likely to have changes in their MC ($P = 0.02$) when compared to women older than 30. 42 (36.5%) women reported having heavier periods ($P < 0.0001$), 22 (19.1%) reported earlier periods ($P = 0.04$) and 23 (20%) women reported more pronounced premenstrual symptoms ($P = 0.015$). 62 (54%) women reported gaining weight during the pandemic, with a median of 4 kg. The main specific stressor was a difficulty accessing healthcare (30/26%) ($P = 0.035$). The age was the most significant predictor of changes in the MC (B = 0.054, 95% CI B = 1.004 - 1.109, $P = 0.034$).
Conclusions
According to our data COVID-19 leads to MC changes, especially in women under 30, such as heavier periods, shorter duration of MC and worsening of PMS. Other possible consequences remain yet to be elucidated.

DOI: 10.1530/endoabs.83.EEO4