Endocrine Abstracts

September 2023 Volume 93
ISSN 1479-6848 (online)

ESE Young Endocrinologists and Scientists (EYES) 2023

8-10 September 2023, Würzburg, Germany

published by bioscientifica

Online version available at
www.endocrine-abstracts.org

Endocrine Abstracts

Volume 93
September 2023

ESE Young Endocrinologists and Scientists (EYES) 2023 and Young Active Research in Endocrinology (YARE) annual meeting 2023

8–10 September 2023, Würzburg, Germany

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ESE Young Endocrinologists and Scientists (EYES) 2023

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OC1

Generation and characterization of CYP21A2-I173N MICE: A humanized mutant animal model for 21-hydroxylase deficiency

Shamini Ramkumar Thirumalasetty[1], Tina Schubert[1], Ronald Naumann[2], Ilka Reichardt[3], Marie-Luise Rohm[4], Dana Landgraf[1], Mirko Peitzsch[4], Mihail Sarov[3], Nicole Reisch[5], Angela Huebner[1] & Katrin Koehler[1]
[1]Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Division of Paediatric Endocrinology and Diabetes, Dresden, Germany; [2]Max Planck Institute of Molecular Cell Biology and Genetics, Transgenic Core Facility, Dresden, Germany; [3]Max Planck Institute of Molecular Cell Biology and Genetics, Genome Engineering Facility, Dresden, Germany; [4]Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden,, Institute of Clinical Chemistry and Laboratory Medicine, Dresden, Germany; [5]Ludwig-Maximilians-Universität München, Medizinische Klinik und Poliklinik IV, Munich, Germany.

Background
Congenital Adrenal Hyperplasia (CAH) is a group of inherited disorders affecting adrenal steroidogenesis. The main form, 21-hydroxylase deficiency (21-OHD), results from mutations in the *CYP21A2* gene. Patients experience hormone deficiencies, and excessive androgens which lead to various symptoms such as hypoglycemia, salt wasting, virilization, and early puberty. Therapy demands high glucocorticoid doses, causing significant side-effects. While new treatment approaches are emerging, there is a lack of a viable animal model for pre-clinical testing.
Objective
Development of a novel mouse model with the human *CYP21A2* gene, carrying the mutation, p.I173N. A common mutation responsible for the simple virilizing form of CAH, which can also be detected in patients with the salt-wasting variant of the disease.
Methods
CRISPR-Cas9-mediated genome editing to replace the mouse *Cyp21a1* gene with the human *CYP21A2* gene and furthermore, to integrate the point mutation p.I173N. Heterozygote dams required dexamethasone treatment during pregnancy and until weaning. Oestrous stage was evaluated from vaginal smears at ten weeks. Mouse plasma at 20-weeks was used to study steroid hormone concentrations using LC–MS/MS. Gene-expression and histological analysis were performed using organs snap-frozen in liquid nitrogen or fixed in paraffin.
Results
At 20 weeks, homozygous mice exhibited hyperplastic adrenals and expressed the human *CYP21A2* gene instead of the mouse *Cyp21a1* gene. Reduced corticosterone and 11-deoxycorticosterone levels were measured in homozygotes. Progesterone levels were significantly higher ($P<0.01$) in homozygous mice. Homozygous mice presented with reduced concentrations of catecholamines. Male mutants exhibited normal fertility, while females were not fertile. The number of ovarian follicles were not reduced but their size was smaller and more peripheral in the persistent diestrus phase.
Conclusions
In summary, our study demonstrates that the *CYP21A2* humanized mutant mice serve as a valuable model to evaluate innovative treatment approaches and will play a crucial role in amalgamating fundamental research and clinical implementation.

DOI: 10.1530/endoabs.93.OC1

OC2

Morbidity in patients with chronic adrenal insufficiency – cardiovascular risk factors and hospitalization rate compared to population based controls

Irina Chifu[1], Marcus Quinkler[2], Barbara Altieri[3], Anke Hannemann[4], Henry Völzke[5], Katharina Lang[6], Nicole Reisch[7], Christina Pamporaki[8], Holger S. Willenberg[9], Felix Beuschlein[10], Stephanie Burger-Stritt[11] & Stefanie Hahner[12]
[1]University Hospital Wuerzburg, Department of Internal Medicine I, Endocrinology and Diabetes, Würzburg, Germany; [2]Endokrinologie in Charlottenburg, Endocrinology in Charlottenburg, Berlin, Germany, Endokrinologie Praxis am Stuttgarter Platz, Berlin, Germany; [3]Department of Internal Medicine I, Department of Internal Medicine I, Division of Endocrinology & Diabetes, University Hospital Wuerzburg, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, Würzburg, Germany; [4]University Medicine Greifswald, Institute of Clinical Chemistry and Laboratory Medicine, Greifswald, Germany; [5]Universitätsmedizin Greifswald, Institut Für Community Medicine, Ship/Klinisch-Epidemiologische Forschung, Greifswald, Germany; [6]Institute of Metabolism and Systems Research, University of Birmingham, Institute of Metabolism and Systems Research, University of Birmingham, Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK; [7]Klinikum der Universität München, Medizinische Klinik IV, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU München, Munich, Germany, München, Germany; [8]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Endocrinology, Dresden, Germany; [9]Division of Endocrinology and Metabolism, Rostock University Medical Center, University of Rostock, Rostock, Germany; [10]Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, München, Germany, Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, Universitätsspital Zürich, Zürich, Switzerland, Zürich, Switzerland; [11]University Hospital of Wuerzburg, Endocrinology and Diabetes Unit, Department of Medicine I, Würzburg, Sweden; [12]University Hospital Würzburg, Endocrinology and Diabetology, Division of Endocrinology and Diabetes, Würzburg, Germany.

Objective
Patients with adrenal insufficiency (AI) have been found to have increased cardiovascular morbidity, partly associated with nonphysiologic glucocorticoid replacement.
Design
We included two separate cohorts (cohort 1 and 2) of patients with chronic primary and secondary AI under standard replacement therapy and compared them to two age- and sex-matched population-based studies (SHIP-TREND/DEGS). Patient cohort 1 comprised 389 individuals assessed by questionnaires, cohort 2 included 197 patients participating in a longitudinal patient registry. Odds ratios with 95% CI for hypertension, hyperlipidaemia/HLP, type 2 diabetes/T2DM, obesity and hospitalization with adjustment for confounders were evaluated by logistic regression
Results
Patient cohort 1 had significantly lower ORs for obesity (0.5 (0.3–0.6), $P<0.001$) and hypertension (0.4 (0.3–0.6), $P<0.001$) compared to SHIP-TREND and for obesity (0.6 (0.5–0.9), $P=0.003$), hypertension (0.4 (0.3–0.6), $P<0.001$) and HLP (0.5 (0.4–0.7), $P<0.001$) compared to DEGS. In cohort 2, ORs were significantly lower for HLP compared to both SHIP-TREND (0.3 (0.2–0.6), $P<0.001$) and DEGS (0.3 (0.2–0.5), $P<0.001$) and for hypertension (0.7 (0.5–0.9), $P=0.04$) compared to SHIP-TREND. In patients with SAI from cohort 2, ORs for hypertension (2.5 (1.4–4.5), $P=0.002$) and obesity (1.9 (1.1–3.1), $P=0.02$) were significantly higher compared to DEGS, whereas ORs for HLP were significantly lower compared to both SHIP (0.3 (0.1–0.7), $P=0.006$) and DEGS (0.3 (0.1–0.8), $P=0.008$). ORs for hospitalization were significantly higher in both patient cohorts.
Conclusion
In most of our AI patients treated with conventional glucocorticoid doses, the risk for T2DM, obesity, hypertension, and HLP was not increased. The number of hospitalizations was significantly higher in AI patients compared to controls, which might reflect increased susceptibility but also a more proactive management of concomitant diseases by physicians and patients.

DOI: 10.1530/endoabs.93.OC2

OC3

Preoperative 1 mg dexamethasone suppression test predicts hypothalamus–pituitary–adrenal axis recovery: A one-year retrospective study of adrenal incidentalomas undergoing unilateral adrenalectomy

Ilaria Bonaventura[1], Alessandra Tomaselli[2], Francesco Angelini[2], Davide Ferrari[2], Dario De Alcubierre[3], Valentina Sada[2], Marianna Minnetti[2], Valeria Hasenmajer[2], Alessia Cozzolino[2], Emilia Sbardella[2], Andrea Isidori[2] & Riccardo Pofi[4]
[1]Sapienza University of Rome, Experimental Medicine, Rome, Italy; [2]Sapienza University of Rome, Italy; [3]Claude Bernard Lyon 1 University, France; [4]Ocdem, Nihr Oxford Biomedical Research Centre, University of Oxford, UK.

Background
The evaluation of postoperative adrenal insufficiency (PAI) and hypothalamus–pituitary–adrenal (HPA) axis recovery in patients with adrenal incidentaloma (AI) undergoing unilateral adrenalectomy remains limited.
Objectives
We aimed to identify predictive factors for PAI development and evaluate HPA axis recovery in AI patients undergoing unilateral adrenalectomy.
Methods
We retrospectively analysed adrenal function in 32 consecutive AI patients with histologically confirmed adrenal cortex adenomas who underwent unilateral

adrenalectomy between 2019 and 2023. Before surgery, adrenal function was evaluated through ACTH, urinary free cortisol and serum cortisol after 1 mg dexamethasone suppression test (1 mg-DST). ACTH and serum cortisol or Short Synacthen Test were performed at 6 days, 6 weeks, 6 months, and one year postoperatively.
Results
Six days post-adrenalectomy, 18.8% of patients had normal adrenal function. Of those having PAI, 43.8% recovered at 6 weeks. Those patients recovering had lower preoperative 1 mg-DST compared to those still experiencing PAI at 6 weeks (median 1 mg-DST 69.5 nmol/l [95%CI 45.0–98.7] *vs* 260.0 nmol/l [95%CI 113.0–288.5], $P < 0.01$). A 1 mg-DST level $\leq$ 131 nmol/l predicted recovery with 89.5% sensitivity and 72.7% specificity and those patients below this threshold had a median HPA axis recovery time of 6 weeks, compared to 48 weeks for those above. ACTH levels rose postoperatively in all patients ($P < 0.001$) but did not predict HPA axis recovery.
Conclusions
The 1 mg-DST was found to be the best predictor of HPA axis recovery, indicating the importance of hypercortisolism severity in influencing PAI duration. Notably, pre and postoperative ACTH levels were not predictive of HPA axis recovery, suggesting they may not be regarded as beneficial in this context.

DOI: 10.1530/endoabs.93.OC3

OC4

Constitutional duplication of PRKACA gene is a cause of isolated primary pigmented nodular adrenocortical disease (PPNAD): Results of its systematic search in bilateral nodular adrenal disease

Patricia Vaduva[1], Florian Violon[1], Gérald Raverot[2], Stephanie Espiard[3], Amina Attia[4], Lucas Bouys[1], Karine Perlemoine[1], Albin Chasavang[5], Sylvie Hieronimus[6], Marie Christine Vantyghem[3], Michel Polak[7], Ragazzon Bruno[8], Anne Jouinot[1], Eric Pasmant[5] & Jerome Bertherat[9]
[1]Cochin Institute, Genomic and Signaling of Neuroendocrine Tumors Team, Inserm U1016, Cnrs Umr8104, Paris, France; [2]Groupement Hospitalier Est, Inserm U1052, Lyon I University Université de Lyon, Lyon, France; [3]Lille University Hospital, Department of Endocrinology, Diabetology, Metabolism and Nutrition, Lille, France; [4]Hospital Pitié-Salpêtrière, Thyroid-Endocrine Tumors, Paris, France; [5]Cochin Hospital, Department of Oncogenetics, Paris, France; [6]Nice University Hospital, Department of Endocrinology, Diabetology and Reproductive Medicine, Nice, France; [7]Inserm U1016, Cochin Institute, Université de Paris, Pediatric Endocrinology, Gynecology and Diabetology Unit, Hôpital Universitaire Necker-Enfants Malades, Ap-Hp, Paris, France; [8]Inserm U1016, Institut Cochin, Cnrs Umr8104, Endocrinology Metabolism Diabetes Department, Paris, France; [9]Hospital Cochin, Endocrinology, Cochin Institute, Inserm U1016, Paris, France.

Background
Constitutional duplications of the *PRKACA* gene locus have been described as responsible for adrenal Cushing's disease.
The objective here was to evaluate the results of its systematic screening in bilateral adrenal nodular disease and to specify the associated phenotype.
Methods
Between 2020 and 2023, 440 consecutive index cases with macronodular or micronodular adrenal hyperplasia or Carney Complex (CNC) were genotyped with a targeted NGS panel including the exonic and intronic flanking regions of the *ARMC5*, *MEN1*, *PRKAR1A* (CNC) and *PRKACA* genes. Familial screening was then offered to relatives.
Results
Constitutional duplications of *PRKACA* were identified in 5 index cases and 7 of the 11 screened relatives (sex-ratio =1 male/2 female), supporting the involvement of the *PRKACA* oncogene through a constitutional copy gain mechanism. The whole genome sequencing performed for 4 index cases did not find any other shared pathogenic variant in another gene involved in human pathology in the duplicated region, nor any other alteration in genes implicated in adrenal pathology. All index cases had Primary Pigmented Nodular Adrenocortical Disease (PPNAD) responsible for Cushing's syndrome and ACTH-independent hypercorticism, diagnosed at a median of 20 years (min=9; max=32). They were treated by bilateral adrenalectomy. The adrenals were described as normal on conventional imaging in 3/5 cases, but iodocholesterol scintigraphy showed diffuse bilateral hyperfixation. No other manifestation of the Carney complex was observed apart from PPNAD (median follow-up 11 years), except for testicular calcifications in 1/4 patients.
Conclusions
Constitutional duplication of *PRKACA* is a rare cause of PPNAD. It does not appear to be involved in other forms of adrenal nodular disease, nor is it frequently associated with other manifestations of CNC. Constitutional duplication of *PRKACA* should be searched in the absence of a pathogenic *PRKAR1A* variant for patients with PPNAD.

DOI: 10.1530/endoabs.93.OC4

OC5

Enhanced inflammation and steroidogenesis sensitize adrenal cells to ferroptosis

Agnès Wlodarczyk[1], Uta Lehnert[2], Stefan Bornstein[3] & Waldemar Kanczkowski[4]
[1]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Internal Medicine III, Dresden, Germany; [2]University Hospital Carl Gustav Carus, Department of Internal Medicine III, Dresden, Germany; [3]Univeristy Hospital Carl Gustav Carus, Department of Internal Medicine III, Dresden, Germany; [4]University Hospital Carl Gustac Carus, Department of Internal Medicine III, Dresden, Germany.

Background
Sepsis is a life-threatening inflammatory condition and a leading cause of death in hospitals. It arises when a microbial infection triggers prolonged and uncontrolled systemic inflammation resulting in progressing organ dysfunction. Recent experimental data suggest a possible involvement of ferroptosis – an iron-dependent form of regulated necrosis – in sepsis-mediated damage of many vital organs. However, its role in adrenal gland dysfunction and/or damage during systemic inflammation hasn't been studied so far.
Objectives
The aim of this project is to elucidate whether septic conditions such as enhanced inflammation and steroidogenesis impact ferroptosis activation in the adrenal glands.
Methods
The human adrenocortical cells, NCI-H295R, were either treated with forskolin or inflammatory cytokines (TNFα, IL-6, IFNγ) *in vitro* for 24–48 h. After that time, expression of ferroptosis-relevant genes and proteins was analyzed by qPCR and western blot, respectively. In addition, necrosis induction (via Annexin V and PI staining) as well as lipid peroxidation were analyzed to study ferroptosis induction during those conditions. Potential ferroptosis induction in the adrenals was additionally evaluated *in vivo* using wildtype mice treated with LPS.
Results
The major molecules involved in the suppression (glutathione peroxidase 4; GPX4), and induction (long-chain-fatty-acid-CoA ligase 4; ACSL4) of ferroptosis were strongly expressed in human and mouse adrenal glands, with the adrenal cortex being the major expression site. Enhanced steroidogenesis or treatment with cytokines led to enhanced ACSL4 expression and/or reduction of GPX4 in NCI-H295R cells. Similar results were observed *in vivo*. Furthermore, the same treatments led to an increased necrotic cell death of NCI-H295R cells, as well as induction of phospholipid peroxidation which was mitigated when the cells were treated with the ferroptosis inhibitor Ferrostatin-1.
Conclusions
Altogether, these results suggest that enhanced inflammation and steroidogenesis may sensitize adrenal cells to necrosis. However, additional experiments are required to further verify ferroptosis involvement.

DOI: 10.1530/endoabs.93.OC5

OC6

Outcome of surgical versus conservative management in patients with mild autonomous cortisol secretion

Madalina Elena Iftimie[1], Iulia Burcea[2], Ramona Dobre[2], Ionela Baciu[2], Dan Alexandru Niculescu[3], Cristina Căpățână[2], Simona Găloiu[2], Radian Şerban[2], Nicoleta Baculescu[2], Raluca Trifănescu[2] & Catalina Poiana[4]
[1]'C.I.Parhon' National Institute of Endocrinology, Clinical Endocrinology I, Bucharest, Romania; [2]'Carol Davila' University of Medicine and Pharmacy; 'C.I. Parhon' Institute of Endocrinology, Bucharest, Romania; [3]'C.I.Parhon' National Institute of Endocrinology, Romania; [4]'Carol Davila' University of Medicine and Pharmacy, 'C.I. Parhon' Institute of Endocrinology, Bucharest, Romania.

Background
Adrenal incidentalomas (AI) with mild autonomous cortisol secretion (MACS) are associated with increased morbidity and mortality and constitute a common clinical scenario.

Objective
We assessed the outcome of cardiovascular risk factors associated with MACS after adrenalectomy versus conservative management.
Methods
Retrospective study performed on a cohort of patients evaluated in our clinic between 2018 and 2022 with an AI and an impaired response to 1 mg dexamethasone suppression test (DST), after exclusion of overt hormone excess, mixed hormonal secretion, malignancy and glucocorticoid medication.
Results
Of the 481 patients with AI evaluated, 14.55% had MACS, but only 10.81% were included in the study, with a median follow up of 21 months (9–77.25). 48.08% ($n=25$, aged 58.4±9.42 years, 96% women) underwent surgery and the other 51.92% ($n=27$, aged 59.52±8.05 years, 77.8% women) were managed conservatively. The mean tumor diameter was significantly higher in the surgery group (36.44±12.88 mm vs 23.79±11.3 mm), while bilateral masses were more prevalent in those conservatively treated (51.9% vs 36%). Surgery was performed in cases with higher cortisol values after 1 mg DST (3.54 µg/dl, 2.66–6.23, $P=0.003$) and lower ACTH levels (4.71 pg/ml, 2.51–7.06, $P<0.001$). Surgery was moderately correlated with an improvement in arterial hypertension ($r=0.351$, $P=0.014$), 45.45% of the operated patients requiring less or no hypotensive drugs compared to 11.53% non-operated patients ($P=0.008$). The latter showed a slightly better control of glucidic metabolism ($P=0.077$) and lower triglyceride levels at the last visit ($P=0.026$).
Conclusion
When assessing adrenalectomy as a treatment option for patients with AI and MACS, we need an individualized approach, considering our heterogeneous results and the low-to-moderate-quality evidence available in the literature comparing surgery with the best management of associated comorbid conditions in these patients.

DOI: 10.1530/endoabs.93.OC6

OC7

Clinical prediction model for primary aldosteronism subtyping and special focus on adrenal volumetric assessment: A pilot study

Tugba Barlas[1], Erhan Ilgit[2], Koray Akkan[3], Emetullah Cindil[2], Isil Gultekin[2], Hulya Sodan[4], Muhittin Yalcin[4], Turgay Cerit[4], Sinan Sozen[5], Mujde Akturk[4], Fusun Toruner[4], Ayhan Karakoc[4] & Alev Eroglu Altinova[6]
[1]Gazi University Faculty of Medicine, Endocrinology and Metabolism, Ankara, Turkey; [2]Gazi University Faculty of Medicine, Radiology, Turkey; [3]Gazi University, Radiology, Ankara, Turkey; [4]Gazi University Faculty of Medicine, Endocrinology and Metabolism, Turkey; [5]Gazi University Faculty of Medicine, Urology, Turkey; [6]Gazi University Faculty of Medicine, Endocrinology and Metabolism.

Background
Adrenal venous sampling (AVS) is the gold standard diagnostic approach for differentiating unilateral from bilateral primary aldosteronism (PA). However, it is a costly, invasive, and operator-dependent procedure with restricted availability.
Objectives
It was aimed to develop a prediction model based on a simple clinical score with prominent parameters from the current literature for the subtype diagnosis of PA. The contribution of adrenal volumetric assessment to PA subtyping was also investigated.
Methods
Thirty-five patients with adequate cannulation in AVS were included. Laboratory data, saline infusion test (SIT), and AVS results of patients with PA were retrospectively evaluated. Volumetric assessment was performed using a magnetic resonance imaging, and the ratio of adrenal volumes was calculated after adjusting for gender- and side-specific mean reference values.
Results
The AVS was consistent with unilateral in 49% and bilateral in 51% of the patients. Hypertension as reason for work-up, highest aldosterone/lowest potassium value >12, the percentage of plasma aldosterone concentration reduction after SIT <43.5%, oral potassium replacement, unilateral disease at pre-AVS imaging, ratio of adjusted adrenal volumes <1.7 pointed to unilateral disease in univariate logistic regression analysis ($P<0.05$). Multivariate logistic regression analysis revealed that adrenal volumetric assessment has an impact on PA subtyping ($P<0.05$). In the prediction model, when each of the six parameters that were significant in the logistic regression analysis was given one point, <4 predicted bilateral, whereas ≥4 predicted unilateral PA (sensitivity 82%, specificity 84%, AUC:0.92, $P<0.001$).
Conclusions
PA subtyping is essential since it changes the therapeutic approach. This pre-AVS prediction model can be a convenient and practical method, and an adjusted adrenal volumetric assessment can make a positive contribution to PA subtyping.

DOI: 10.1530/endoabs.93.OC7

OC8

FKBP5 methylation in adrenal insufficiency: Looking at a new tool for assessing the quality of glucocorticoid replacement?

Irina Chifu[1], Anna Lena Richter[2], Carolin Scheuermann[2], Stephanie Burger-Stritt[3], Juliane Lippert[4], Sabine Herterich[5] & Stefanie Hahner[6]
[1]University Hospital Wuerzburg, Department of Internal Medicine I, Endocrinology and Diabetes, Würzburg, Germany; [2]University Hospital of Würzburg, Division of Endocrinology and Diabetes, Würzburg, Germany; [3]University Hospital of Wuerzburg, Endocrinology and Diabetes Unit, Department of Medicine I, Würzburg, Sweden; [4]Institute of Human Genetics, University of Wuerzburg, Würzburg, Germany; [5]Clinical Chemistry and Laboratory Medicine, Central Laboratory, University Hospital Würzburg, Würzburg, Germany; [6]University Hospital Würzburg, Endocrinology and Diabetology, Division of Endocrinology and Diabetes, Würzburg, Germany.

Introduction
Glucocorticoid (GC) replacement regimens in adrenal insufficiency (AI) only roughly correspond to physiological steroid profiles. Moreover, control of substitution quality is difficult and signs of clinically relevant mild chronic over- or under-replacement might be omitted. FKBP5 regulates GC receptor sensitivity by reducing its affinity to cortisol when bound to the receptor complex. FKBP5 methylation has been inversely correlated with cortisol levels both in healthy controls and in patients with endogenous hypercortisolism.
Methods
We analyzed FKBP5 gene methylation (DNAm) within introns containing GC responsive elements as well as promoter and proximal enhancer regions by bisulfite pyrosequencing in a cohort of 86 patients with primary (PAI, $n=57$) and secondary (SAI, $n=29$) AI. Results were correlated with GC dose, salivary and 24-hour urinary cortisol, prevalence of adrenal crises (AC) per patient-year and 24-hour blood pressure (BP) levels.
Results
GC dose and DNAm were negatively correlated for the majority of the investigated regions (intron 1 rs=−0.45, $P<0.01$, intron 5 rs=−0.35 $P<0.01$, intron 7 rs=−0.23 $P=0.034$, promoter A1 rs=−0.35 $P<0.01$, proximal enhancer A2 rs=−0.38 $P<0.01$). Intronic DNAm correlated negatively with 24-hour urinary cortisol (intron 2, rs=−0.25, $P=0.032$) and positively with bedtime salivary cortisol (intron 7, rs=0.3, $P<0.01$). We observed a positive correlation between the prevalence of AC and intronic DNAm (intron 2 and 5, rs=−0.29 $P<0.01$ for each). Systolic 24-hour and day-time BP, systolic and diastolic night-time BP and noctural dipping correlated negatively with DNAm within several intronic, promoter and proximal enhancer regions. GC replacement was higher, whereas intronic DNAm was lower in PAI compared to SAI (GC: 22 (10–60) vs. 20 (10–37.5) mg $P=0.032$, intron 5: 11% vs 15% $P=0.028$).
Conclusion
FKBP5 methylation analysis might help improve assessment of GC load in AI, as it correlates with replacement doses, cortisol levels and 24-hour BP.

DOI: 10.1530/endoabs.93.OC8

Neuroendocrinology

OC9

Effect of protein supplementation on plasma sodium levels in the syndrome of inappropriate antidiuresis – a monocentric open-label proof-of-concept study – the treasure study

Sophie Monnerat[1], Cihan Atila[2], Fabienne Baur[1], Joyce Santos de Jesus[3], Julie Refardt[4], Michael Dickenmann[5] & Mirjam Christ-Crain[6]
[1]University Hospital Basel, Department of Endocrinology, Diabetology and Metabolism, Basel, Switzerland; [2]University Hospital Basel, 1 Department of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Basel, Switzerland; 2 Department of Clinical Research, University of Basel, Basel, Switzerland;, Department of Endocrinology, Diabetology and Metabolism, Basel, Switzerland; [3]Department of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Basel, Switzerland; [4]Universitätsspital Basel, Department of Clinical Research, University of Basel, Basel, Switzerland, Department of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Basel, Switzerland, Basel, Switzerland; [5]Universitätsspital Basel, Clinic for Transplantation

Immunology and Nephrology, Basel, Switzerland; [6]University Hospital Basel, Department of Clinical Research, University of Basel, Basel, Switzerland, Department of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Basel, Switzerland, Basel, Switzerland.

Background
The syndrome of inappropriate antidiuresis (SIAD) can be treated with oral urea. Proteins are metabolized into urea by the liver. We hypothesized that dietary protein could increase free water clearance through urea-induced osmotic diuresis.
Objectives
To investigate the effect of protein supplementation on plasma sodium levels in chronic SIAD.
Methods
This is a monocentric open-label proof-of-concept trial conducted at the University Hospital of Basel, Switzerland, between 10/2021 and 02/2023. Adult outpatients with chronic SIAD of any etiology were eligible. Patients received 90 g protein daily for 7 days in the form of protein powder dissolved in a maximum of 1l of liquid of choice. After a wash-out period of at least a week, patients received 30 g of oral urea daily for 7 days. The primary endpoint was the increase in sodium levels from baseline to the end of the 7-day protein supplementation.
Results
Seventeen patients were included (14 females, median age 68 [61, 79]). After 7 days of 90 g daily protein supplementation ($n=17$), plasma sodium increased from 131 [129, 133] to 133 [132, 137], i.e., by a median of 3 mmol/l [0, 5] ($P=0.01$). Plasma urea increased by 3 mmol/l [1.7, 4.9] ($P<0.01$) and urine urea to creatinine ratio by 21.2 mmol/mmol [6.2, 29.1] ($P<0.01$). After 7 days of 30 g oral urea ($n=10$), plasma sodium increased from 132 [130, 133] to 134 [131, 136], i.e., by a median of 2 mmol/l [1, 3] ($P=0.06$). Plasma urea increased by 5.8 mmol/l [2.7, 9.2] ($P<0.01$) and urine urea to creatinine ratio by 31.0 mmol/mmol [18.7, 45.1] ($P<0.01$).
Conclusions
Our findings suggest that protein supplementation with protein powder increases plasma sodium levels in patients with chronic SIAD through protein-induced ureagenesis and osmotic diuresis.

DOI: 10.1530/endoabs.93.OC9

OC10

Effects of glucagon-like peptide-1 receptor agonists on copeptin in healthy volunteers and patients with primary polydipsia

Svenja Leibnitz, Mirjam Christ-Crain & Bettina Winzeler
University Hospital of Basel, Department of Endocrinology, Basel, Switzerland.

Background
Today, GLP-1 receptor agonists have great clinical importance in the treatment of type 2 diabetes and obesity. Furthermore, GLP-1 seems to play a significant role in sodium and water homeostasis. Recent findings investigating long-term effects of treatment with GLP-1 receptor agonists showed a reduction of fluid intake irrespective of food consumption. To our knowledge, data regarding physiological mechanisms that could explain these observations are inconclusive. Furthermore, no effect of GLP-1 on Vasopressin has been observed to date.
Objectives
The aim of this secondary analysis was to investigate changes of Copeptin levels in euvolemic participants treated with dulaglutide versus placebo. We hypothesize that dulaglutide effects a stimulation in Vasopressin due to reduced water intake, lowered blood pressure and nausea which are known side effects of GLP-1 receptor agonists.
Methods
A secondary analysis of randomized, double-blind, placebo-controlled, crossover-trials in 20 healthy participants (GATE trial) and 34 patients with primary polydipsia (GOLD trial) was performed at the University Hospital of Basel. In both studies participants received either Dulaglutide (Trulicity®) 1.5 mg or placebo, in random order, subcutaneously once weekly over a three-week treatment phase. After a wash-out period of at least three weeks, patients received the complementary intervention. The primary objective was to investigate the effect of a three-week treatment with Dulaglutide on Copeptin levels in euvolemic adults.
Results
All 54 participants of the two cross-over trials were included. Median age was 27 (IQR 24 to 37) years and 63% were female. After a three-week treatment phase, Dulaglutide showed a significant suppression of Copeptin in both trials ($P=0.04$) compared to placebo [GOLD: treatment effect: −0.67pmol/l versus GATE: treatment effect: −1 pmol/l].
Conclusion
This analysis will provide further information on the direct effects of GLP-1 on Vasopressin and could reveal physiological mechanisms that explain the role of GLP-1 in sodium and water balance.

DOI: 10.1530/endoabs.93.OC10

OC11

Soluble alpha klotho, a new biomarker of growth hormone action

Júnia Ribeiro de Oliveira Longo Schweizer[1], Katharina Schilbach[2], Anica Pauline Gagliardo[3], Michael Haenelt[4], Annette Peters[5], Barbara Thorand[6] & Martin Bidlingmaier[7]
[1]LMU Klinikum; Med. Klinik und Poliklinik IV / Endokrinologie; Med. Klinik und Poliklinik IV, Endokrinologisches Labor, Innenstadt, Munich, Germany; [2]Med. Klinik & Poliklinik IV, LMU Klinikum, Medizinische Klinik und Poliklinik IV, München, Germany; [3]Medizinische Klinik und Poliklinik IV, LMU Klinikum München, Endokrinologisches Labor, München, Germany; [4]Klinikum der Universität München, Medizinische Klinik und Poliklinik IV, Ludwig Maximillians Universität München; Med. Klinik und Poliklinik IV / Endokrinologie; Medizinische Klinik und Poliklinik IV, Munich, Germany, München, Germany; [5]Epidemiologie Medizinische Fakultät, LMU München, Helmholtz Zentrum München – Deutsches Forschungszentrum für Gesundheit und Umwelt, Germany; [6]Helmholtz Zentrum München, GmbH Deutsches Forschungszentrum für Gesundheit und Umwelt, Germany; [7]LMU Klinikum, Med. Klinik und Poliklinik IV / Endokrinologie, Med. Klinik und Poliklinik IV, Munich, Germany.

Background
Soluble alpha klotho (sαKL) is high in active acromegaly, normalizes after disease control, and therefore is suggested as a new biomarker for growth hormone (GH) excess. However, little is known about the impact of biological variables other than GH.
Methods
Serum sαKL (pg/ml) was measured by ELISA (IBL, Hamburg, Germany). We first evaluated pre-analytical stability, defined a reference interval for sαKL in healthy subjects (A: $n=890$), and compared the concentrations to those in patients with non-functional pituitary tumors (NFPA, B, $n=18$) or prolactinomas (C, $n=66$). Moreover, we evaluated the potential impact of various biological variables on sαKL.
Results
The assay for SαKL exhibits excellent intra/inter-assay CVs ($<10\%$) and linearity (92–107%). Concentrations were not significantly affected by storage at room temperature for 72 hours, or by up to 4 freeze/thaw cycles (recovery $>90\%$). The reference interval (2.5–97.5%) for sαKL is 152–1303 (A: median: 673(IQR: 543–846)). SαKL was not different in NFPA ($P>0.05$), but higher in prolactinoma (902(754–1228); A vs.C, $P<0.0001$). Compared to IGF-I and IGFBP 3, SαKL exhibited a weaker negative correlation with age, BMI, waist-hip-ratio and cholesterol ($r_s=-0.30, -0.13, -0.12, -0,16$, respectively, $P<0.05$ for all). In contrast, a positive correlation was seen with glomerular filtration rate and IGF-I ($r_s=0.11, 0.31$, respectively, $P<0.001$ for all). While IGF-I and IGFBP 3 correlated with fasting glucose, sαKL did not ($P>0.05$), and it did also not vary significantly during oGTT ($P>0.05$). Slight reductions in SαKL were observed after >12h of fasting, and in females on estrogen monotherapy ($P<0.05$).
Conclusion
We stablished a reference range for sαKL, a highly stable biomarker of GH action. It is less affected by many biological variables than IGF-I and IGFBP 3. However, our data suggest it decreases in conditions of hepatic GH-resistance (prolonged fasting, oral estrogen), and is slightly increased by prolactin, most likely due to its somatotropic activity.

DOI: 10.1530/endoabs.93.OC11

OC12

Psychopathological characteristics in patients with arginine vasopressin deficiency (central diabetes insipidus) and primary polydipsia

Julia Beck[1], Cihan Atila[2], Julie Refardt[2], Zoran Erlic[3], Juliana Drummond[4], Beatriz Santana Soares Rocha[4], Felix Beuschlein[3], Bettina Winzeler[2] & Mirjam Christ-Crain[2]
[1]University Hospital Basel, Department of Endocrinology, Diabetology and Metabolism, Basel, Switzerland; [2]University Hospital Basel, Endocrinology, Basel, Switzerland; [3]University Hospital Zürich, Department of Endocrinology, Diabetology and Clinical Nutrition, Zürich, Switzerland; [4]Universidade Federal de Minas Gerais, Departamento de Medicina Interna, Faculdade de Medicina, Belo Horizonte, Brazil.

The differential diagnosis between arginine vasopressin deficiency (AVP-D), known as central diabetes insipidus, and primary polydipsia (PP) is challenging. Psychopathologic findings are often used as a hallmark for diagnosing PP; thus. Yet, psychopathologic characteristics are barely assessed in patients with AVP-D, and to date, no data exist comparing AVP-D and PP with regard to these features. Therefore, in this study, we aimed to compare levels of anxiety, depression, alexithymia, and overall mental health in patients with AVP-D and PP. In total, 82 participants ($n=39$ with AVP-D, $n=28$ with PP, and $n=15$ healthy controls

[HC]) underwent a psychological evaluation with standardized questionnaires. Anxiety levels were assessed using the State-Trait Anxiety Inventory, mood using the Beck's Depression Inventory, alexithymia using the Toronto Alexithymia Scale, and overall physical and mental health using the Short Form 36 Health Survey (SF-36). Higher STAI, BDI, and TAS scores indicate higher anxiety, depression, and alexithymia levels. Higher SF-36 scores indicate better health and less disability. Compared with HC, patients with AVP-D and PP showed increased levels of anxiety (HC 28 points [24, 31] vs. AVP-D 36 points [31, 45], $P<0.01$; vs. PP 38 points [33, 46], $P<0.01$), depression (HC one point [0, 2] vs. AVP-D 7 points [4, 14], $P<0.01$; vs. PP 7 points [3, 13], $P<0.01$), and alexithymia (HC 30 points [29, 37] vs. AVP-D 43 points [35, 54], $P<0.01$; vs. PP 46 points [37, 55], $P<0.01$). Levels of anxiety, depression, and alexithymia showed no difference between patients with AVP-D and PP ($P=0.58$, $P=0.90$, $P=0.50$). This is the first study demonstrating comparable increased levels of anxiety, depression, alexithymia, and overall reduced mental health in patients with AVP-D and PP. Based on these data, psychopathological findings should not be used as a hallmark to differentiate between both conditions.

DOI: 10.1530/endoabs.93.OC12

OC13

Hypogonadotropic hypogonadism in a patient with Allgrove syndrome: A case report

Ana Gheorghe-Milea[1], Eva Rusu[2], Oana Stănoiu-Pînzariu[3] & Carmen Emanuela Georgescu[4]

[1]Iuliu Hatieganu University of Medicine and Pharmacy, Cluj County Emergency Hospital, Endocrinology Clinical Unit, Cluj-Napoca, Romania, Department of Endocrinology, Cluj-Napoca, Romania; [2]Cluj County Emergency Hospital, Endocrinology Clinical Unit, Cluj-Napoca, Romania; [3]Iuliu Hatieganu University of Medicine and Pharmacy, Department of Endocrinology, [4]Iuliu Hatieganu University of Medicine and Pharmacy, Department of Endocrinology, Cluj County Emergency Hospital, Endocrinology Clinical Unit, Cluj-Napoca, Romania.

Background

Triple A (Allgrove) syndrome is a rare genetic disorder with autosomal recessive inheritance, caused by mutations in the AAAS gene on chromosome 12q13. It is characterized by the following triad: ACTH-resistant adrenal insufficiency, alacrimia, and achalasia.

Case presentation

We present the case of a 19-year-old male who was diagnosed with adrenal insufficiency at the age of five following an addisonian crisis with hypoglycemic coma. At the time of the diagnosis, the patient had skin hyperpigmentation, a blood pressure of 80/60 mmHg, hyponatremia, and hyperkalemia, his glycemia was 8 mg/dl, the cortisol level was 2 µg/dl, with an ACTH of 1276 pg/ml. At the age of fifteen, after being evaluated for delayed puberty, the patient was diagnosed with hypogonadotropic hypogonadism and under treatment with testosterone enanthate he achieved complete pubertal development. The following year, he started to experience progressive dysphagia, more severe for liquids than solids, postprandial vomiting, and weight loss. The barium swallow revealed a bird beak appearance of the distal esophagus with a dilated thoracic esophagus. Esophageal manometry confirmed the diagnosis of achalasia type 1 for which the patient underwent peroral endoscopic myotomy. The patient's mother also recalled the absence of tears since his early childhood and the Schirmer test was suggestive of alacrimia. In the presence of these cardinal features, the diagnosis of triple A syndrome was established.

Conclusions

The association of Allgrove syndrome with hypogonadotropic hypogonadism is rare, with only one other case reported in the literature: a two-year-old Tunisian patient, in whom a homozygous splice-donor site mutation (IVS14 + 1G > A) was found in the AAAS gene [1].

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DOI: 10.1530/endoabs.93.OC13

OC14

Comparison of metyrapone, osilodrostat and ketoconazole in the short-term therapy of endogenous Cushing's syndrome: Preliminary results of the Mosketeer study

Mario Detomas[1], Chiara Simeoli[2], Nicola Di Paola[2], Alessandro Mazzarella[2], Rosario Pivonello[2], Filippo Ceccato[3], Giacomo Voltan[3], Carla Scaroni[3], Anna Aulinas, Alicia Santos[4], Susan Webb[4], German Rubinstein[5], Leah Braun[5], Martin Reincke[5], Pasquale Dolce[6], Simone Antonini[7], Andrea Lania[7], Maria Stelmachowska-Banaś[7], Karolina Cylke-Falkowska[8], Marianna Minnetti[9], Andrea M. Isidori[9], Andrea Corsello[10], Aleksandra Gilis-Januszewska[11], Mari Minasyjan[11], Lana Sambula[12], Darko Kastelan[12], Timo Deutschbein[13], Linus Haberbosch[14], Ulrich Dischinger[15], Martin Fassnacht[15] & Barbara Altieri[15]

[1]University Hospital Würzburg; Medizinische Klinik I; Division of Endocrinology and Diabetes, Würzburg, Germany, Department of Internal Medicine I, Division of Endocrinology and Diabetes, Würzburg, Germany; [2]Dipartimento DI Medicina Clinica e Chirurgia, Sezione DI Endocrinologia, Università Federico II DI Napoli, Naples, Italy; [3]Endocrine Disease Unit, University-Hospital of Padova, Padova, Italy; [4]Department of Endocrinology, Hospital S Pau, Barcelona; Iib-Sant Pau, Research Center for Pituitary Diseases, Barcelona; Ciberer Unit 747, Isciii and Department of Medicine, Univ Autonoma Barcelona, Spain; [5]Medizinische Klinik und Poliklinik IV, Klinikum der Universität, Ludwig-Maximilians-Universität München, Munich 80336, Germany; [6]Department of Public Health, University of Naples Federico II, Naples, Italy.; [7]Endocrinology, Diabetology and Medical Andrology Unit, Irccs Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy; [8]Department of Endocrinology, Centre of Postgraduate Medical Education, Warsaw, Poland; [9]Department of Experimental Medicine, Sapienza University of Rome, Viale Regina Elena, 324, 00161, Rome, Italy; [10]Department of Translational Medicine and Surgery, Unit of Endocrinology, Università Cattolica del Sacro Cuore-Fondazione Policlinico Universitario A. Gemelli Irccs, Largo Gemelli 8, I-00168 Rome, Italy; [11]Jagiellonian University Medical College, Department of Endocrinology, Krakow, Poland; [12]University Hospital of Zagreb, Department of Endocrinology, Croatia; [13]Medicover Oldenburg Mvz, Oldenburg, Germany; [14]University Hospital of Berlin (Charite); [15]Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital Würzburg, University of Würzburg, Würzburg, Germany.

Background

Steroid synthesis inhibitors, like metyrapone, osilodrostat, and ketoconazole are used as second-line treatment in all types of endogenous Cushing's syndrome (CS). However, a direct comparison of these three drugs is missing. This study aimed to compare these drugs in the short-term therapy of CS.

Design

Retrospective multicenter study involving 16 centers worldwide.

Methods

Patients with CS treated with metyrapone, osilodrostat or ketoconazole as monotherapy for at least 2 weeks were considered eligible. Main outcomes were changes in 24h urinary free cortisol (24h-UFC) after 2(T1), 4(T2), and 12 weeks(T3) of therapy compared to baseline (T0), evaluated as delta (change) percentage from T0.

Results

Data of 328 patients from 13/16 centers were available. 128(39%) patients were treated with metyrapone, 91(28%) with osilodrostat and 109(33%) with ketoconazole. No difference in terms of CS subtypes ($P=0.6$) and baseline 24h-UFC (median 307µg/24 h, 253 µg/24 h and 294 µg/24 h for metyrapone, osilodrostat and ketoconazole, respectively, $P=0.5$) was identified. Median daily starting doses were 750 (range 250–1000) mg, 4 (1–10) mg and 400 (200–800) mg for metyrapone, osilodrostat and ketoconazole, which increased at T3 for all drugs. Considering the patients with a lower dose (according to the median of each drug), 24 h-UFC decreased at T1 in all treatments (−25% metyrapone, −19% osilodrostat, −22% ketoconazole, $P=0.21$). If patients with higher doses were considered, a more pronounced decrease in 24h-UFC in osilodrostat compared to metyrapone was observed at T1 (−46% vs −22%, $P<0.05$). At T3 20(16%) patients under metyrapone, 8(9%) under osilodrostat and 4 under ketoconazole (4%) were supplemented with potassium($P<0.0001$). At T1, a decrease in number of antihypertensives was identified in 7%of patients under metyrapone, 17%under osilodrostat and 7%under ketoconazole ($P<0.001$).

Conclusion

These preliminary results confirmed the efficacy of all the three drugs in decreasing hypercortisolism. Osilodrostat might act faster in decreasing blood pressure. However, these preliminary results need to be validated in the final cohort.

DOI: 10.1530/endoabs.93.OC14

Adrenal Tumors and Neuroendocrine Tumors

OC15

Targeting the ferroptosis-macrophage crosstalk in adrenocortical carcinoma

Alexandra Triebig[1], Isabel Weigand[2], Sena Atici[3], José Pedro Friedmann Angeli[3] & Matthias Kroiß[4]

[1]LMU University Hospital, LMU Munich, Department of Medicine IV, Munich, Germany; [2]LMU University Hospital, LMU Munich, Department of Internal Medicine IV, Munich, Germany; [3]University of Würzburg, Rudolf-Virchow-Center, Würzburg, Germany; [4]LMU Klinikum, Department of Medicine IV, University Hospital, LMU Munich, Ziemssenstraße 1, 80336 München, Germany, Medizinische Klinik und Poliklinik IV, München, Germany.

Background
Ferroptosis is an emerging form of regulated necrotic cell death characterized by excessive lipid peroxidation. Adrenocortical carcinoma (ACC) cells have been shown to be highly susceptible to ferroptosis caused by active steroid hormone synthesis. While therapeutic activation of ferroptosis has been proposed as a novel treatment strategy, its impact on the tumor immune microenvironment (TIME) remains elusive. Macrophages are an important TIME component and modulate inflammation through phagocytosis and the release of cytokines, however the relationship between tumor cell ferroptosis and macrophages is unclear.
Objectives
Characterization of the mediators and consequences of ferroptosis in ACC cell lines on macrophages.
Methods
Prostaglandin E2 (PGE2) secretion in cell culture supernatants was quantified by LC–MS/MS and ELISA. Human peripheral blood mononuclear cells were isolated with Lymphoprep™ gradient and macrophages differentiated with GM-CSF/M-CSF and polarizing factors. Macrophages were characterized by western blotting, immunofluorescence and metabolic phenotyping. Phagocytosis of ferroptotic ACC cells by macrophages was analyzed by flow cytometry.
Results
Treatment of the ACC cell line NCI-H295R with the ferroptosis inducer RSL3 resulted in increased secretion of the immune modulator PGE2. The release of PGE2 was completely blocked upon inhibition of both ferroptosis with the antioxidant Liproxstatin-1 and cyclooxygenase (COX) with celecoxib or diclofenac. Treatment of isolated macrophages with PGE2 lead to macrophage polarization towards an anti-inflammatory M2-like phenotype, which was characterized by high expression of CD163. Co-culturing of these macrophages with RSL3 treated NCI-H295R cells resulted in efficient clearance of ferroptotic ACC cells.
Conclusion
Ferroptosis induction with RSL3 leads to the release of PGE2, an immune suppressor involved in M2-like polarization. ACC cells undergoing ferroptosis are phagocytosed by M2-like macrophages, which is expected to further maintain an anti-inflammatory TIME.

DOI: 10.1530/endoabs.93.OC15

OC16

Bone fragility in well-differentiated gastroenteropancreatic-neuroendocrine tumors: Results from a retrospective two-centered study

Alessandro Brunetti[1], Simona Jaafar[1], Isabella Chiardi[2], Miriam Cellini[3], Antonio Stefano Salcuni[3], Stella Pigni[1], Elisabetta Lavezzi[1], Andrea Lania[1], Gherardo Mazziotti[1] & Fabio Vescini[3]
[1]Irccs Humanitas Research Hospital, Endocrinology, Diabetology and Andrology Unit, Rozzano (Mi), Italy; [2]Humanitas University, Department of Biomedical Sciences, Pieve Emanuele (Mi), Italy; [3]University-Hospital S. Maria Della Misericordia, Endocrinology and Metabolism Unit, Udine, Italy.

Background
Patients affected by gastroenteropancreatic-neuroendocrine tumors (GEP-NETs) present an increased risk of bone fragility due to several factors, such as bone metastases, vitamin D deficiency, hormonal secretion, medical and surgical treatments. Although patients with well-differentiated GEP-NETs generally present a long life-expectancy, occurrence of fragility fractures could significantly impair quality of life.
Objectives
The study aims to investigate prevalence and risk factors for fragility fractures in patients with well-differentiated, G1-G2, GEP-NET.
Methods
We included 292 patients, 154 men and 138 women, with G1-G2 GEP-NETs admitted in the last year (July 1st, 2022, to July 1st, 2023) in our two hospitals, Humanitas Research Hospital, Milan, and Hospital S. Maria della Misericordia, Udine. Reports about clinical fractures, disease course and treatments were retrospectively collected from patients' clinical charts from time of diagnosis to the last follow-up visit (mean follow-up 60 months). Morphometric fractures were assessed according to Genant classification by reviewing chest-abdomen CT or MRI performed both at diagnosis and during follow-up.
Results
At diagnosis, 6.8% of patients had a history of clinical fractures and 11.5% had morphometric fractures. Vitamin D deficiency (<30 ng/ml) and severe insufficiency (<10 ng/ml) were found in 70% and 17.5% of patients, respectively. Baseline fractures (clinical or morphometric) were significantly more frequent in patients with vitamin D deficiency, than in those with normal values ($P<0.05$). No difference in term of hormonal secretion, disease staging or grading was found between fractured and non-fractured patients. Notably, only 20% of patients underwent anti-resorptive therapy during follow-up and 9.8% developed a new fracture. Risk of new fractures was significantly higher in patients already fractured at diagnosis compared to non-fractured ($P<0.01$), independently from surgical or medical treatments.
Conclusions
Fragility fractures are frequent in GEP-NETs and keep often undiagnosed and untreated. Attention to bone health should be part of the clinical management of these patients.

DOI: 10.1530/endoabs.93.OC16

OC17

Preclinical and clinical evidence of progesterone/megestrol acetate activity in metastatic adrenocortical carcinoma

Mariangela Tamburello[1], Andrea Abate[1], Antonella Turla[2], Marta Laganà[2], Elisa Rossini[1], Constanze Hantel[3,4], Guido Alberto Massimo Tiberio[5], Deborah Cosentini[2], Salvatore Grisanti[2], Alfredo Berruti[2] & Sandra Sigala[1]
[1]Section of Pharmacology, Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy; [2]Oncology Unit, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia and ASST Spedali Civili di Brescia, Brescia, Italy; [3]Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich (USZ) and University of Zurich (UZH), Zürich, Switzerland; [4]Medizinische Klinik und Poliklinik III, University Hospital Carl Gustav Carus Dresden, Dresden, Germany; [5]Surgical Clinic, Department of Clinical and Experimental Sciences, University of Brescia at ASST Spedali Civili di Brescia, Brescia, Italy.

Background
Adrenocortical carcinoma (ACC) is a rare cancer for which available systemic treatments, mitotane ± etoposide, doxorubicin and cisplatin (EDP-M), have limited efficacy.
Objectives
Here, we strengthen the effect of progesterone (Pg) on metastatic ACC cell lines, studying whether it could influence growth, invasiveness, and metastasis formation. Additionally, we investigate if the Pg analogue megestrol-acetate administered with EDP-M could improve its tolerability and efficacy in advanced ACC patients.
Methods
NCI-H295R, MUC-1, and TVBF-7 ACC cell lines were used. Apoptosis and cell cycle were analyzed by flow cytometry. Cell migration and invasiveness were studied using transwell assays, and metalloprotease 2 (MMP2) activity by zymography. Cell xenografts in Danio rerio embryos were performed measuring both the tumor areas and the number of embryos with metastasis. Metastatic ACC patients (pts) with low-performance status (PS) were treated with EDP-M+ oral megestrol-acetate (EDP-MM) ($n=24$). Toxicity and efficacy of EDP-MM were compared with EDP-M administered to a control group of 48 patients.
Results
Pg exerted a cytotoxic effect, that was maintained after drug withdrawal, inducing apoptosis and changes in cell cycle distribution in NCI-H295R and MUC-1 cells. Pg significantly reduced the xenograft area of each ACC cell line, and metastasis formation in embryos injected with MUC-1 and TVBF-7, confirming the *in vitro* results. This phenomenon is mediated at least in part by the reduction of MMP2 levels. Treatment with megestrol-acetate was overall well tolerated: 54.2% of EDP-MM pts developed progestin-related toxicities; 16.7% discontinued megestrol-acetate for toxicity. Clinical benefit rate was 75.0% vs 60.4% in EDP-MM and EDP-M pts, respectively. Progression-free survival and overall survival curves were similar in both groups.
Conclusions
Our results support the use of progestins in ACC. The efficacy of megestrol-acetate in reducing ACC progression in patients undergoing EDP-M therapy is now under investigation in the PESETA phase II clinical study.

DOI: 10.1530/endoabs.93.OC17

OC18

Towards an understanding of the microenvironment of ACC: Impact of steroid hormones and driver pathways

Tanja Maier[1], Laura-Sophie Landwehr[2], Silviu Sbiera[2], Marc P. Schauer[2], Paul Schwarzmüller[1], Martin Fassnacht[2] & Matthias Kroiß[1]
[1]Department of Internal Medicine IV, LMU Hospital Munich, Munich, Germany; [2]Department Medicine I,University Hospital of Würzburg, Würzburg, Germany.

Background
Immune checkpoint therapy response rate in adrenocortical carcinoma (ACC) is only ∼15%. Glucocorticoid (GC) secretion is present in ∼60% of tumours, associated with adverse outcome and has been associated with an immunologically cold tumoural microenvironment. On the other hand, activation of the Wnt/ß-Catenin pathway has been suggested to contribute to reduced immune infiltration.
Aims
First, we aim to improve the understanding of cellular responses to glucocorticoid receptor (GCR) activation and antagonism and additionally understand the effect of tumoural steroid excess onto glucocorticoid related genes. Second, we hypothesize that activation of the Wnt/ß-Catenin pathway is associated with less tumor infiltrating immune cells.
Methods
Cultured ACC cell lines NCI-H295R and JIL-2266 were treated with the selective GCR antagonist relacorilant and expression of GCR target genes analyzed by qPCR. Nanostring NCounter was used on FFPE extracted RNAs of hormonally active and inactive tumours. Cell viability was measured by CellTiter GloAssay and protein expression quantified by Western blotting for the glucocorticoid receptor (GR) and the cancer-testis antigen PRAME.
Results
Hormonally active tumours showed a downregulation of immune-related genes and an upregulation of glucocorticoid related genes. Up to 1 μM relacorilant in combination with 400 nM hydrocortisone had no effect on ACC cell viability, but expression of GCR target genes was significantly altered in a cell line specific manner. In NCI-H295R cells, the expression of CYP17A1 was dose-dependently repressed by relacorilant, while genes encoding the IL1 receptor were consistently up-regulated. PRAME was expressed in NCI-H295R and repressed by relacorilant.
Conclusion
Treatment with relacorilant leads to a downregulation of glucocorticoid related genes like CYP17A1 in NCIH295R and an upregulation in immune related genes like IL1R1. This might lead to lower steroid levels and higher immune cell infiltration and contribute to a better response to the immunotherapy.

DOI: 10.1530/endoabs.93.OC18

OC19

FGF/FGFR signaling in adrenocortical tumorigenesis: Novel potential therapeutic targets in adrenocortical carcinoma

Lena Kappenstein[1], Alexander Paul[1], Barbara Altieri[1], Iuliu Sbiera[1], Sigala Sandra[2], Berruti Alfredo[3], Martin Fassnacht[4], Silviu Sbiera[1] & Mariangela Tamburello[5]
[1]Division of Endocrinology, Department of Internal Medicine I, University Hospital, University of Würzburg, Würzburg, Germany; [2]Section of Pharmacology, Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy; [3]Oncology Unit, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia and Asst Spedali Civili DI Brescia, Brescia, Italy; [4]Division of Endocrinology, Department of Internal Medicine I, University Hospital, University of Würzburg, Würzburg, Comprehenssive Cancer Center Mainfranken, University of Würzburg, Würzburg, Germany, Germany; [5]Section of Pharmacology, Department of Molecular and Translational Medicine, University of Brescia, Brescia, Division of Endocrinology, Department of Internal Medicine I, University Hospital, University of Würzburg, Würzburg, Germany, Italy.

Background
Adrenocortical carcinoma (ACC) is one of the most aggressive endocrine malignancies. The Fibroblast Growth Factor/Fibroblast Growth Factor Receptor (FGF/FGFR) pathway plays a role in both embryogenesis and tumorigenesis of adrenal gland. Our group demonstrated that FGFR1-4 were upregulated in ACCs and that their high expression was significantly associated with worse prognosis, suggesting that they are potentially interesting therapeutic targets.
Objectives
To evaluate the effect of FGFR-inhibitors (erdafitinib, rogaratinib and fisogatinib) on different ACC cell lines as single treatment and in combination with most used chemotherapeutic drugs (gemcitabine, etoposide or streptozotocin) to scrutinize possible new treatment options for ACC patients.
Methods
FGFRs expression was evaluated by qRT-PCR on six ACC cell lines. For IC50 assessment, cells were treated with increasing concentrations of each drug for four days and cell viability was evaluated using CellTiter-Glo-Assay. Combination experiments were performed on NCI-H295R and TVBF-7 according to the Chou-Talalay method.
Results
All cell lines exhibited weak levels of FGFR1-IIIb and high levels of FGFR1-IIIc isoform. TVBF-7 showed unique expression pattern with highest levels of FGFR2 IIIb, FGFR2 IIIc and FGFR4. In MUC-1, JIL-2266 and CU-ACC2 cells, lower and variable levels of both FGFR2 isoforms and FGFR4 were found. Erdafitinib and rogaratinib, exerted a concentration-dependent effect in all cell lines with TVBF-7 cells being most sensitive (erdafitinib-IC50 = 0.1 μM, rogaratinib-IC50 = 0.78 μM). Conversely, the FGFR4-inhibitor fisogatinib did not affect cell viability up to 50 μM except on NCI-H295R and JIL-2266. Combination treatment of gemcitabine or streptozotocin with erdafitinib or rogaratinib significantly reduced cell viability, compared to single treatments ($P < 0.05$).
Conclusions
Our preliminary results showed that TVBF-7 cells, with highest expression of FGFRs, were more sensitive to the pan-FGFR-inhibitors and that in all cell lines their effect is enhanced by gemcitabine or streptozotocin supporting the role of FGFR targeting in this rare disease with otherwise dismal outcome.

DOI: 10.1530/endoabs.93.OC19

OC20

ROR-1 specific CAR-T cells with CRISPR/CAS9 mediated glucocorticoid receptor-knockout exert potent antitumor efficacy in advanced adrenocortical carcinoma

Marc Philipp Schauer[1,2], Barbara Altieri[1], Rodrigo A Redondo-Frutos[2], Peter Spieler[2], Tanja Maier[3], Daniel Oppelt[1], Matthias Kroiss[1,3,4], Silviu Sbiera[1], Justus Weber[2#], Martin Fassnacht[1,4#], Laura-Sophie Landwehr[1#] & Michael Hudecek[2#]
[1]Department of Internal Medicine I, Division of Endocrinology & Diabetes, University Hospital, University of Wuerzburg, Wuerzburg, Germany; [2]Department of Internal Medicine II, Chair for Cellular Immunotherapy, University Hospital, University of Wuerzburg, Wuerzburg, Germany; [3]Department of Internal Medicine IV, Division of Endocrinology & Diabetes, LMU Hospital Munich, University of Munich, Munich, Germany; [4]Comprehensive Cancer Center Mainfranken, University of Wuerzburg, Wuerzburg, Germany.
[#] These authors contributed equally

Introduction
Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine malignancy with poor prognosis and limited treatment options. In addition, ACC is characterized by endogenous glucocorticoid (GC) excess in 60% of cases which is hypothesized to be one reason, why first clinical trials evaluating the potency of immune checkpoint blockade showed only modest results. Here, we report the identification of ROR-1 as a candidate target for the treatment of ACC and the preclinical assessment of a next-generation CAR-T cell product.
Methods
ROR-1 expression was evaluated in 5 ACC cell lines and 197 ACC tissues. ROR-1 specific CAR-T cells (ROR-1-CART) were generated and functionally tested in preclinical models of ACC.
Results
Our data show ROR-1 transcripts to be detected over background in 92.7% of ACC samples at mRNA ($n = 62$) and in 91.1% at protein level ($n = 135$). ROR-1 expression was 2-fold higher in ACC as compared to normal adrenal glands ($P = 0.015$) and upregulated 3-fold in metastases as compared to primary tumors ($P = 0.002$). ROR-1-CART recognized and potently eradicated ACC tissues in preclinical models. To additionally investigate the potential of GCs on CAR-T cell functions, we desensitized ROR-1-CART by CRISPR/Cas9-mediated genome editing of the hGR locus and found hGR^{KO}ROR-1-CART to exert identical antitumor efficacy under normal and immunosuppressive conditions (ROR-1-CART: 41.8% vs hGR^{KO}ROR-1-CART: 74.9% specific lysis of NCI-H295R cells, E-T 1:1). Lastly, we compared ROR-1-CART efficacy alone with hGR^{KO} and pharmaceutical blockade of GC effector functions and observed hGR^{KO}ROR-1-CART to be superior to a combined treatment approach due to a corticosteroid inhibitor-related downregulation of ROR-1 on ACC tumor cells.
Conclusion
We show that ROR-1 is commonly and homogenously overexpressed in human ACC specimen. Preliminary results also reveal enhanced efficacy of

hGRKOROR-1-CART in preclinical models of ACC. Full data will be presented at the meeting.

DOI: 10.1530/endoabs.93.OC20

OC21

Identification of adrenocortical masses malignancy through radiomics: A pilot study

Lorenzo Tucci[1], Giulio Vara[2], Ilaria Improta[3], Antonio De Leo[4], Saverio Selva[5], Caterina Balacchi[2], Donatella Santini[6], Cristina Mosconi[2], Valentina Vicennati[3], Uberto Pagotto[7] & Guido Di Dalmazi[8]
[1]Alma Mater Studiorum University of Bologna, Irccs Sant'orsola Polyclinic Endocrinology Unit, Medical and Surgical Sciences, Bologna, Italy; [2]Alma Mater Studiorum University of Bologna, Irccs Sant'orsola Polyclinic Radiology Unit, Italy; [3]Alma Mater Studiorum University of Bologna, Irccs Sant'orsola Polyclinic Endocrinology Unit, Italy; [4]Alma Mater Studiorum University of Bologna, Irccs Sant'orsola Polyclinic Anatomic Pathology Unit, Italy; [5]Irccs Sant'orsola Polyclinic General and Endocrine Surgery Unit, Italy; [6]Irccs Sant'orsola Polyclinic Anatomic Pathology Unit, Italy; [7]St. Orsola General Hospital, Internal Medicin/Endocr Unit, Bologna, Italy; [8]Division of Endocrinology, Dept. of Medical and Surgical Sciences, Division of Endocrinology, Department of Medical and Surgical Sciences, Alma Mater University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy, Bologna, Italy.

Background
Adrenal lipid poor adenoma (LPA) and adrenocortical cancer (ACC) may overlap in computerized tomography (CT). Radiomics recently emerged as new tool for malignant behavior identification.
Aim
To assess radiomics utility for identification of ACC and LPA in adrenocortical masses with unenhanced (UE) CT scan attenuation $\geq$10 Hounsfield Unit (HU).
Methods
We retrospectively enrolled 50 patients, 38 radiologically defined LPA with 6–12 months of radiologic stability or benign histological exam ($n=11$), and 12 ACC with histological exam (2 patients with Weiss score = 3; 4 patient with ki67 $\geq$ 10%). All patients underwent CT with UE scan, arterial (ACE), venous (VCE) and 15' delayed (DCE) contrast enhanced phases, on which radiomics was performed with LIFEx software (©LITO 2022–2023). We performed a two-steps multivariate analysis for each CT phase to evaluate predictors of malignancy (Weiss score $\geq$ 3). Multivariate analysis first-step was completed within single radiomics feature classes, then first-step predictors were altogether employed for multivariate analysis second-step. Second-step predictors were utilized for receiver operating characteristic curve analysis and estimation of positive (PPV) and negative predictive value (NPV).
Results
In UE, surface to volume ratio (SVR) and Run Length Non-Uniformity (RLNU) predicted malignancy (Odds Ratio (OR) = 2.718; 95% Confidence Interval (CI) = 1.56–4.75; $P<0.001$), with 83.3% sensitivity, 94.3% specificity, 83.3% PPV, 94.7% NPV. In ACE, SVR and Feret diameter predicted malignancy [OR = 2.718; 95% CI = 1.57–4.745; $P<0.001$], with 83.3% sensitivity, 92.1% specificity, 76.9% PPV, 94.6% NPV. In VCE, SVR and compacity predicted malignancy [OR = 2.719; 95% CI = 1.54–4.79; $P<0.001$], with 83.3% sensitivity, 92.1% specificity, 76.9% PPV, 94.5% NPV. In DCE, SVR and RLNU predicted malignancy [OR = 2.718; 95% CI = 1.54–4.79; $P<0.001$], with 83.3% sensitivity, 91.9% specificity, 76.9% PPV, 94.5% NPV.
Conclusion
Radiomics seems useful to identify adrenal masses nature, even without CT contrast enhanced phases. SVR and RLNU seem to be powerful predictors of adrenocortical masses malignancy.

DOI: 10.1530/endoabs.93.OC21

Pituitary and Neuroendocrinology

OC22

Comparative evaluation of diagnostic performance of the most commonly used screening tests for pathological hypercortisolism: A single centre analysis

Agathoklis Efthymiadis[1], Helen Loo[2], Brian Shine[3], Jeremy Tomlinson[4], Aparna Pal[2] & Riccardo Pofi[5]
[1]Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University Hospitals NHS Trust, Churchill Hospital, Oxford, Endocrinology, Oxford, UK; [2]Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University Hospitals NHS Trust, Churchill Hospital, Oxford, UK; [3]Department of Clinical Biochemistry, Oxford University Hospitals NHS Foundation Trust, Oxford, UK, UK; [4]Oxford Centre for Diabetes, Endocrinology and Metabolism, Nihr Oxford Biomedical Research Centre, University of Oxford, Churchill Hospital, Oxford, UK., Oxford, UK; [5]Oxford Centre for Diabetes, Endocrinology and Metabolism, Nihr Oxford Biomedical Research Centre, University of Oxford, Churchill Hospital, Oxford, UK.

Background
To date, there is no consensus as to the gold-standard screening test for diagnosing Cushing's Syndrome (CS).
Objectives
This study aimed to: a) compare the ability of late-night salivary cortisol (LNSC) against overnight dexamethasone suppression test (ONDT) and urinary free cortisol (UFC) as screening test for pathological hypercortisolism (PH); b) test the performance of those tests in diagnosing Cushing's disease (CD) or mild autonomous cortisol secretion (MACS); c) refine the screening algorithm by adding clinical symptoms.
Methods
We retrospectively reviewed all consecutive adult patients referred to the Oxford Centre for Diabetes, Endocrinology and Metabolism for evaluation of PH who had LNSC measured from January 2017 to November 2022. A binomial logistic regression (LR) was performed to ascertain the ability of each test in diagnosing PH, and compute receiver-operating-characteristic curve analysis. A stepwise backward LR was run to assess the utility of symptoms to predict PH.
Results
LNSC had the best sensitivity, 100.0% (95%CI 80.5–100.0), specificity, 64.9%, (95%CI 47.5–79.8) in distinguishing CD from the absence of PH (AUC 0.82, 95%CI 0.72–0.93, $P<0.001$). ODST proved to be the best test in differentiating between MACS and absence of PH (AUC of 0.76, 95%CI 0.66–1.00, $P=0.004$) with sensitivity of 100.0% (95%CI 82.4–100.0), specificity of 52.2% (95%CI 30.6–73.2). UFC did not reach statistical significance in diagnosing PH ($P=0.26$). Combining AUCs of pre-test signs, symptoms (hypertension, interscapular fat, facial plethora, striae myopathy, easy bruising) with those of screening tests significantly improved diagnostic performance of LNSC (AUC of 0.83, 95%CI 0.74–0.92, $P<0.001$), ONDST (0.82, 95% CI 0.71–0.93, $P<0.001$).
Conclusions
When diagnosing CD, LNSC performed better than ONDST, whereas the opposite was true for patients with MACS. UFCs had the lowest diagnostic accuracy across all PH subgroups. Assessing pre-test clinical probability through the presence of specific symptoms suggesting PH significantly improved the diagnostic accuracy of screening tests.

DOI: 10.1530/endoabs.93.OC22

OC23

Different molecular forms of pituitary adenomas, explaining behavior and prognosis. A new concept

Ana-Silva Corlan[1], Anca Maria Cimpean[2] & Marius Raica[2]
[1]University of Medicine and Pharmacy Timisoara, Endocrinology, Timisoara, Romania; [2]University of Medicine and Pharmacy Timisoara, Microscopic Morphology/Histology. Angiogenesis Research Center, Timisoara, Romania.

Background
Pituitary adenomas(PAs) comprise 10%–25% of all intracranial tumors, the majority of them being benign. But 35% of all PAs are considered invasive, having a higher recurrence rate than benign ones.
Objectives
We analyzed the expression of different angiogenic growth factors and their receptors in PAs and identified correlations with the hormone profile that could explain their behavior and prognosis.
Methods
Our study included 92 cases: 10 normal pituitary glands harvested at autopsy and 82 cases of PAs, removed through transsphenoidal approach.We used the hematoxylin eosin stain, immunohistochemistry and the *in situ* hybridization technique,the RNA scope,which allowed visualization of single mRNA molecules in individual cells, the latter method representing an original aspect of our study.
Results
We obtained a statistically significant correlation between VEGF expression and hormonal profile in somatotroph and lactotroph adenomas;VEGF expression in somatotroph adenomas was associated with an aggressive phenotype. VEGF165b (the inhibitory fraction of VEGF) showed an increased expression predominantly in acidophil PAs; the increased expression of VEGF165b correlated with VEGF overexpression in only 18% of PAs. PDGF-A showed a positive correlation with

prolactin secretion; PDGF-B showed a positive correlation with growth hormone secretion. Somatotroph and lactotroph adenomas showed increased expression of EG-VEGF with positive correlation with EGFR overexpression, promoting survival of tumor cells. Acidophil PAs, predominantly lactotroph ones, showed a correlation of EG-VEGF overexpression with Ki67 index.HER2 correlated with prolactin secretion and a potential HER2/HER3 heterodimerization could be a marker of aggressivity of prolactinomas. HER2-correlated with bihormonal PAs, possibly indicating an unfavorable prognosis.EGFR correlated with bihormonal PAs,expressing prolactin.
Conclusions
Our results sustain the recently developed scientific theory which implies the existence of different molecular forms of PAs within the same morphopathological forms; these molecular forms explain the differences in behavior and prognosis of PAs and could pave the way for personalized therapy.

DOI: 10.1530/endoabs.93.OC23

OC24

Transcriptome in paraffin samples for the diagnosis and prognosis of pituitary neuroendocrine tumors (PITNETS)

Nesrine Benanteur[1], Chiara Villa[2], Maria Francesca Birtolo[1], Anne Jouinot[1], Daniel De Murat[1], Franck Letourneur[3], Stephan Gaillard[4], Marie-Laure Raffin-Sanson[5], Jean-François Emile[6], Jérôme Bertherat[3], Bertrand Baussard[7] & Guillaume Assié[3]
[1]Institut Cochin U1016 Inserm/Cnrs/Umr-S8104 – Université de Paris, Team 'Genomics and Signaling of Endocrine Tumors', Paris, France; [2]Département de Neuropathologie de la Pitié Salpêtrière Hôpital de la Pitié-Salpêtrière (Assistance Publique des Hopitaux de Paris), Institut Cochin U1016 Inserm/Cnrs/Umr-S8104 – Université de Paris, Paris, France; [3]Institut Cochin U1016 Inserm/Cnrs/Umr-S8104 – Université de Paris, Paris, France; [4]Département de Neurochirurgie – Hôpital de la Pitié-Salpêtrière (Assitance Publique des Hopitaux de Paris), Paris, France; [5]Département D'endocrinologie, Hôpital Ambroise Paré (Assistance Publique des Hopitaux de Paris), Paris, France; [6]Anatomie Pathologie, Hôpital Ambroise Paré (Assistance Publique des Hôpitaux de Paris), Boulogne Billancourt, France; [7]Département de Neurochirurgie – Hôpital de la Pitié-Salpêtrière (Assitance Publique des Hopitaux de Paris), Institut Cochin U1016 Inserm/Cnrs/Umr-S8104 – Université de Paris, Paris, France.

An initial multi-omics analysis of PitNETs has refined histological classifications, and could improve diagnostic and prognostic assessment (Neou, Cancer Cell 2020). Of all omics, transcriptome best discriminates between these different classes. This molecular classification has been built upon frozen samples, which are difficult to use in routine clinical practice.
Aim
Demonstrate the feasibility of measuring the transcriptome in Formalin-Fixed Paraffin-Embedded (FFPE) samples using 3' end RNA sequencing.
Methods
RNA extraction was performed on 198 PitNETs FFPE samples (RNEasy DSP FFPE kits, Qiagen) operated between 2005 and 2022. 3′ transcriptome was sequenced using the 3′RNASeq technique (Lexogen, Illumina). After alignment, counting (STAR), normalization (DESeq2) and dimension reduction (NMF), unsupervised clustering was performed.
Results
The proportion of informative samples reached 98%. The average sequencing depth was 11 million transcripts. With these FFPE samples, we find the clustering established on frozen samples and reflecting lineage, with the different subgroups of corticotroph tumors, prolactinomas, somatotroph tumors mixed with 'Mixed GH-PRL' tumors, gonadotroph tumors mixed with 'null-cell' and thyrotroph tumors. The molecular group can be predicted individually from this transcriptome.
Conclusion
The molecular classification of PitNETs can be predicted from FFPE samples. This opens up the prospect of larger cohorts, enabling prognostic assessment of the transcriptome, stratifying by subtype.

DOI: 10.1530/endoabs.93.OC24

OC25

The genetic background of acromegaly in a tertiary referral centre in Krakow, Poland

Anna Bogusławska[1], Magdalena Godlewska[1], Ewelina Rzepka[1], Marta Korbonits[2], Alicja Hubalewska-Dydejczyk[1] & Aleksandra Gilis-Januszewska[1]
[1]Chair and Department of Endocrinology, Jagiellonian University, Medical College, Cracow, Poland; [2] Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London.

Introduction
Acromegaly is the most genetically determined pituitary disease.
Objectives
We studied the prevalence of syndromic disease and germline mutations (*AIP, MEN1, GNAS, PRKAR1A, CDKN1b)* in a cohort of unselected, consecutive patients with acromegaly.
Materials and methods
A total of 133 patients (79 females, 54 males, age range 16–75 years) with somatotroph pituitary neuroendocrine tumor who were studied at the Jagiellonian University (Krakow), a tertiary referral center, between 2019 and 2022, were enrolled in this study. *AIP* testing was performed in all patients with acromegaly, whereas other genes were tested in young patients (<30 years-old), patients with macroadenoma or with syndromic features. Sanger sequencing was used for the assessment of *AIP, MEN1*, *GNAS, PRKAR1A, CDKN1B* gene variants, and multiplex ligation-dependent probe amplification (MLPA) was used for the assessment of *PRKAR1A* negative results in Sanger sequencing.
Results
Overall, a total of 12.2% (16/131) patients presented clinical manifestations of syndromic disease or gene variants which might be associated with acromegaly. *AIP* variants were identified in 7.7% (8/104), *MEN1* alterations were detected in 3.6% (3/84), McCune-Albright syndrome was clinically diagnosed in one patient (0.75%), one patient was clinically diagnosed with Carney complex (0.75%), and three patients presented MEN1 associated symptoms (acromegaly and hyperparathyroidism) with negative genetic evaluation for *MEN1* and *CDKN1B* (Sanger sequencing). One patient presented Neurofibromatosis type 1 features, two additional patients presented some of Carney complex symptoms. None of patients harbored *PRKAR1A* and *CDKN1B* variants. Further confirmatory genetic analysis are planned in patients with clinical suspicion of syndromic disease and negative Sanger and MLPA testing.
Conclusions
This study is one of the first to show genetic abnormalities among adult patients with acromegaly in Poland. Genetic testing in acromegaly should be considered to personalize and optimize the treatment of patients.

DOI: 10.1530/endoabs.93.OC25

OC26

Whole blood transcriptomic signature of Cushing's syndrome

Maria Francesca Birtolo[1], Roberta Armignacco[1], Nesrine Benanteur[1], Daniel De Murat[1], Laurence Guignat[1], Lionel Groussin[1], Rossella Libé[1], Franck Letourneur[2], Jérôme Bertherat[1], Anne Jouinot[1] & Guillaume Assié[1]
[1]Université Paris Cité, Cnrs Umr8104, Inserm U1016, Institut Cochin, Genomics and Signaling of Endocrine Tumors, Paris, France; [2]Université Paris Cité, Cnrs Umr8104, Inserm U1016, Institut Cochin.

Background
Cushing's syndrome (CS) is associated with high morbidity and presents high interindividual variability. Easily measurable biomarkers, in addition to the hormone assays currently used for diagnosis, could better quantify the individual biological impact of glucocorticoids. The aim of this study is to identify such biomarkers through the analysis of whole blood transcriptome.
Methods
Whole blood transcriptome was evaluated in 57 samples ($n=35$ in the training cohort; $n=22$ in the validation cohort) classified in overt CS, mild CS, eucortisolism and adrenal insufficiency according to the clinical evaluation and 24-h urine-free cortisol. Total RNA was obtained from whole blood samples and sequenced on NovaSeq 6000 platform (Illumina). Both unsupervised (principal component analysis) and supervised (Limma) methods were used to explore transcriptome profile.
Results
the transcriptomic profile discriminates samples with overt Cushing syndrome. Genes most associated with overt Cushing syndrome are enriched in pathways related to immunity, particularly in neutrophil activation. A prediction model of 1500 genes built on the training cohort demonstrated its discriminating value in the validation cohort (accuracy 0.73) and remains significant in multivariate analysis including the neutrophil rate ($P=0.002$). The prediction based on FKBP5 alone, a gene involved in glucocorticoid receptor signaling and one of the most overexpressed in overt Cushing syndrome, is comparable to the predictor based on 1500 genes (accuracy 0.68).
Conclusion
whole blood transcriptome reflects the biological action of glucocorticoids. FKBP5 could be a non-hormonal marker of Cushing syndrome.

DOI: 10.1530/endoabs.93.OC26

OC27

The role of the GH receptor polymorphisms as a prognostic factor of vertebral fractures in acromegalic patients resistant to first-generation SSAs and treated with Pegvisomant or Pasireotide Lar

Flavia Costanza[1], Sabrina Chiloiro[2], Antonella Giampietro[3], Pier Paolo Mattogno[3], Amato Infante[3], Flavia Angelini[3], Liverana Lauretti[3], Alessandro Olivi[3], Alfredo Pontecorvi[3], Francesco Doglietto[3], Laura De Marinis[3] & Antonio Bianchi[3]

[1]Catholic University of the Sacred Heart – Fondazione Policlinico Universitario A. Gemelli Irccs, Endocrinology and Diabetology, Rome, Italy; [2]Department of Endocrinology, Catholic University of the Sacred Heart, Rome, Italy; [3]Catholic University of the Sacred Heart-Fondazione Policlinico Universitario A. Gemelli Irccs.

Background

Acromegaly is associated with skeletal fragility and increased prevalence of vertebral fractures (VF). In recent years several authors tried to investigate predictor markers of bone fragility risk in this endocrine disorder. Two isoforms of GH receptor (GHR) have been described, which differ in the presence or absence of a transcript of exon 3 of the GHR gene. Both isoforms produce a functional receptor, but the exon 3-deleted isoforms (d3-GHR) have greater sensitivity to endogenous and recombinant GH than the full-length isoform (fl-GHR).

Objectives

We conducted a longitudinal, retrospective, observational, single-center study to investigate the role of GHR polymorphisms as prognostic factor of incidental VF (I-VF) in first-generation somatostatin analogs (SSAs)-resistant acromegalic patients and treated with GHR antagonist (Pegvisomant) or second-generation somatostatin analogs (Pasireotide Lar).

Methods

72 patients with acromegaly were included in our study. 28 patients carried d3-GHR isoform, and 44 patients carried fl-GHR isoform. At baseline, all patients were affected by active acromegaly: 46 patients were treated with Pegvisomant, in combination with first-generation SSAs, and 26 were treated with Pasireotide Lar. At the last follow-up, 58 patients achieved biochemical control of acromegaly. 18 patients carried prevalent VF (P-VFs), while 14 patients experienced the occurrence of I-VFs.

Results

From the group treated with Pegvisomant in combination with first-generation SSAs, 32 patients carried fl-GHR polymorphism and 14 carried d3-GHR polymorphism. From the group treated with Pasireotide Lar, 12 patients carried fl-GHR isoform and 14 patients carried d3-GHR isoform. I-VF occurred more frequently in patients carrying the fl-GHR isoform compared to d3-GHR ($P=0.04$); otherwise, I-VF occurred more frequently in patients carrying the d3-GHR isoform than fl-GHR ($P=0.01$) and in patients with P-VF as compared to patients without P-VF ($P=0.05$).

Conclusions

The GHR polymorphisms could improve the therapeutic approach in acromegaly, tailored to the individual patient, in the context of personalized medicine.

DOI: 10.1530/endoabs.93.OC27

OC28

Hepatic Steatosis Index as a non-invasive marker for liver steatosis in patients with endogenous Cushing Syndrome, ERCUSYN Krakow database

Mari Minasyan[1], Aleksandra Gamrat[2], Alicja Hubalewska-Dydejczyk[2], Elena Valassi[3] & Aleksandra Gilis-Januszewska[2]

[1]Endocrinology, Oncological Endocrinology, and Nuclear Medicine Department, University Hospital, Krakow, Poland, Endocrinology Department, Cracow, Poland; [2]Chair and Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland; [3]Endocrinology and Nutrition Department, Germans Trias I Pujol Hospital and Research Institute, Badalona, Spain.

Introduction

Liver Steatosis (LS) can be one of the metabolic complications of Cushing Syndrome (CS). The data on the impact of cortisol on liver function are very limited, according to one study the prevalence of LS in CS is 20%. However, the frequency seems to be much higher. Hepatic Steatosis Index (HSI) predicts LS based on ALT, AST, BMI, sex and co-existence of diabetes mellitus/impaired glucose intolerance. It can identify candidates for further liver examinations.

Objectives

To evaluate the prevalence of LS in patients with CS at the time of diagnosis by using HSI.

Methods

We analyzed retrospectively adult patients from the ERCUSYN, Krakow database with complete HSI data available. The HSI score was calculated using the following formula: $8\times(\text{ALT/AST})+\text{BMI}+2(\text{if type 2 diabetes})+2(\text{if female})$. Collected data were from the baseline CS diagnosis. Patients with score 36 or above were classified as highly likely to have LS. We compared the results with abdominal ultrasonography (USG), serum biomarkers and demographic factors.

Results

82 out of 135 patients, aged 27–87 years, predominantly women ($n=64$), were eligible for the study. The etiology of CS was mostly pituitary (47), followed by adrenal (20) and ectopic cause (15). 81.7% patients, showed high HSI (82.8% of females, 77.8% of males). HSI was elevated in 85, 80 and 73 percent of patients with pituitary, adrenal and ectopic CS. 41% of patients with elevated HSI were obese. HSI was elevated among: 100% patients with confirmed liver steatosis on USG, 72% patients with normal USG and 78% patients who hadn't have USG performed.

Conclusions

The prevalence of liver steatosis in active CS may be much higher than previously reported. Further investigations may show if patients with high risk of liver steatosis based on HSI and normal liver image on USG, may benefit from liver MRI in order to verify the diagnosis.

DOI: 10.1530/endoabs.93.OC28

OC29

Folliculo-stellate cells in nonfunctioning pituitary neuroendocrine tumors

Valeria Nicoleta Nastase[1], Iulia Florentina Burcea[2], Amalia Raluca Ceausu[3], Catalina Poiana[4] & Marius Raica[3]

[1]'victor Babes' University of Medicine and Pharmacy; Angiogenesis Research Center; 'pius Brinzeu' County Emergency Clinical Hospital, Department of Endocrinology, Timisoara, Romania; [2]'Carol Davila' University of Medicine and Pharmacy; 'C.I. Parhon' Institute of Endocrinology, Bucharest, Romania; [3]'victor Babes' University of Medicine and Pharmacy; Angiogenesis Research Center, Timisoara, Romania; [4]'Carol Davila' University of Medicine and Pharmacy, 'C.I. Parhon' Institute of Endocrinology, Bucharest, Romania.

Introduction

Folliculo-stellate cells (FSCs), non-endocrine star-like shaped population of cells located in the anterior pituitary, have very heterogenous function and phenotype. Located between the secretory cells, their first atributed role was connected to a supporting network. In literature, they were mentioned to be involved in the pathogenesis and evolution of pituitary neuroendocrine tumors (PitNETs).

Objectives

Analyse FSCs characteristics and distribution in a series of nonfunctioning PitNETs.

Materials and methods

Twenty-six nonfunctioning PitNETs obtained using transsphenoidal surgery were included. The diagnosis of 'nonfunctioning tumor' was based on the preoperative biochemistry. The histopathological diagnosis was performed using hematoxylin eosin morphological staining. Immunohistochemical (IHC) evaluation for anterior pituitary hormones was assesed for a proper classification of the tumors. FSCs were evaluated using glial fibrillary acidic protein (GFAP).

Results

Histopathologicaly, most PitNETs presented a papillary/ alveolar growth pattern, with acidophilic tinctoriality. Immunohistochemical hormonal profile revealed two silent somatotropinomas, three silent corticotropinomas, 14 silent gonadotropinomas (with IHC positivity for FSH/ LH/ both). Two cases were considered PitNETs with unusual immunohistochemical combinations, expressing both GH and ACTH. Five cases were negative for all anterior pituitary hormones.

FSCs were described using GFAP. They presented stellate shape, with cytoplasmic prolongations among the tumoral cells. Also, these cells formed networks inside the tumors, with a tendency to locate near blood vessels. Nine out of twenty-six tumors showed IHC reaction for FSCs. Eight were silent gonadotropinomas and the ninth was considered silent corticotropinoma.

Conclusion

Although there are many studies regarding FSCs, their entire function remains poorly understood, both in normal and pathological pituitary gland. In this study, 57% of silent gonadotroph PitNETs contained FSCs among the tumoral cells. The PitNETs with negative expression for all anterior pituitary hormones didn't express IHC positivity for FCSs. Further studies are needed in order to establish the link between these cells and PitNETs.

DOI: 10.1530/endoabs.93.OC29

Reproductive Endocrinology

OC30

Quantification of 27 sex hormones, precursors and metabolites thereof in human plasma by a mass spectrometry-based method combining direct detection and specific hydrolysis of glucuronide conjugates

Miriam Raps[1], Carolin Kleider[2], Daniela Pemp[2] & Leane Lehmann[2]
[1]University of Würzburg, Chair of Food Chemistry, Chair of Food Chemistry, Würzburg, Germany; [2]University of Würzburg, Chair of Food Chemistry, Würzburg, Germany.

Background
Steroid hormones such as the estrogen 17β-estradiol and the androgen testosterone play an important role in the etiology of hormone dependent diseases. To investigate factors influencing endogenous steroid hormone synthesis also biologically less active glucuronides and sulfates should be considered since they can serve as circulating reservoir for bioactive hormones. As the sensitivity of the available mass spectrometry (MS)-based method is lower for glucuronides than for unconjugated steroids and sulfates, the specific hydrolysis of glucuronides can extend the accessible metabolic profile. However, there is no published method available which allows the simultaneous analysis of unconjugated steroids, hydrolyzed glucuronides and intact sulfates from the same sample.
Objectives
Thus, the aim of the present study was to extend the accessible steroid hormone profile in human plasma by inclusion of detection of steroid glucuronides after hydrolysis in addition to the detection of conjugated and unconjugated steroids.
Methods
After extraction of unconjugated steroids and quantitation thereof by gas chromatography–MS/MS, the remaining aqueous phase was divided for a) the direct quantification of steroid conjugates by liquid chromatography–MS/MS and b) the indirect quantification of steroid glucuronides after hydrolysis with *Escherichia coli*-β-glucuronidase. Putative formation of artifacts during sample cleanup was investigated by spiking plasma with (isotope-labelled) reference compounds.
Results
The enzymatic hydrolysis of steroid glucuronides was successfully implemented and no changes in the steroid profile due to putative artifact formation by oxidation, reduction or unintended hydrolysis during sample cleanup were observed. Out of 42 steroids included in the method, 27 were quantifiable in most plasma samples derived from 10 pre- and 10 postmenopausal women as well as 5 men.
Conclusions
The extended method will contribute to a comprehensive insight in the steroid hormone profile in human plasma.

DOI: 10.1530/endoabs.93.OC30

OC31

Luteinizing hormone/choriogonadotropin receptor (LHCGR)/G protein-coupled estrogen receptor (GPER) heteromers impact on reproductive signals

Clara Lazzaretti[1], Elia Paradiso[2], Samantha Sperduti[3], Niamh Sayers[4], Ginevra Pelagatti[5], Sara D'Alessandro[6], Carmela Perri[7], Lara Baschieri[8], Manuela Simoni[9], Aylin Carla Hanyaloglu[4] & Livio Casarini[10]
[1]University of Modena and Reggio Emilia, Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia. Baggiovara Hospital, Via P. Giardini 1355, 41126 Modena, Italy., Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, Modena, Italy; [2]University of Modena and Reggio Emilia, University of Modena and Reggio Emilia, Dept. of Biomedical Sciences, Metabolic and Neuroscience, Modena, Italy; [3]Unit of Endocrinology, University of Modena and Reggio Emilia, Center for Genomic Research, University of Modena and Reggio Emilia. Via G. Campi 287, 41125 Modena, Italy., Department of Biomedical, Metabolic and Neural Sciences, Modena, Italy; [4]Imperial College London, Institute of Reproductive and Developmental Biology, Department of Metabolism, Digestion and Reproduction, London, UK; [5]University of Modena and Reggio Emilia, Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, Modena, Italy; [6]Unit of Endocrinology, University of Modena and Reggio Emilia., International Ph.D. School in Clinical and Experimental Medicine (Cem), University of Modena and Reggio Emilia., Department of Biomedical, Metabolic and Neural Sciences., Modena, Italy; [7]Unit of Endocrinology, University of Modena and Reggio Emilia., Department of Biomedical, Metabolic and Neural Sciences, Modena, Italy; [8]Unit of Endocrinology, University of Modena and Reggio Emilia, International Ph.D. School in Clinical and Experimental Medicine (Cem), University of Modena and Reggio Emilia, Department of Biomedical, Metabolic and Neural Sciences, Modena, Italy; [9]Department of Medicine, Endocrinology Metabolism and Geriatrics, University of Modena and Reggio Emilia, Modena, Italy; [10]Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Center for Genomic Research, University of Modena and Reggio Emilia, Modena, Italy.

Background
Follicle-stimulating hormone receptor (FSHR) and G protein-coupled estrogen receptor (GPER) are expressed on the surface of granulosa cells, where they form heteromeric complexes, shifting FSH-induced signals to survival pathways and determining the follicular fate.
Objectives
We evaluated whether GPER can interact with the luteinizing hormone (LH)/choriogonadotropin (hCG) receptor (LHCGR) and modulate the LH/hCG/dependent signalling pathways.
Methods
LHCGR-GPER heteromers were evaluated in transiently transfected HEK293 cells by bioluminescence resonance energy transfer (BRET) and photo-activated localization microscopy using photoactivatable dyes (PD-PALM). The LH/hCG-dependent signalling analyses were performed by evaluating LHCGR-coupling to G proteins, intracellular Ca^{2+}, cAMP and inositol monophosphate (IP1) increase by BRET and homogeneous time-resolved fluorescence (HTRF). Activation of LH/hCG-dependent gene transcription was evaluated using a reporter system. Data were analysed by non-linear regression or Kruskal–Wallis test and Dunn's *post-hoc* test ($P<0.05$; $n=4$ to 6), as appropriate.
Results
Super-resolution microscopy and BRET data revealed that LHCGR and GPER form heteromers and interact on the cell surface, causing a displacement of Gαq to LHCGR. Consistently, under GPER/LHCGR co-expression, hCG-induced Ca^{2+} response is inhibited as well as all other Gαq-dependent events, i.e. IP1 production and *NFAT* promoter activation, whereas LH and hCG activate the Gαq-dependent signalling in LHCGR-expressing cells. Conversely, GPER-LHCGR complexes have no impact on LH/hCG-induced cAMP/protein kinase A (PKA) pathway activation, suggesting that GPER specifically inhibits Gαq-, but not Gαs-mediated signals. Control experiments were performed using a mutant GPER (GPERmut) unable to interact with LHCGR, as confirmed by PD-PALM and BRET methods, demonstrating that LH/hCG induce IP1 accumulation and gene transcription in GPERmut/LHCGR-expressing cells.
Conclusion
GPER and LHCGR can form heteromers at the cell surface, biasing LH/hCG-induced signals via specific inhibition of Gαq-dependent cascades and suggesting their potential role in the regulation of reproductive functions in the ovary.

DOI: 10.1530/endoabs.93.OC31

OC32

Follicle stimulating hormone in male idiopathic infertility: How to predict its efficacy?

Marilina Romeo[1], Giorgia Spaggiari[2], Leonardo Dalla Valentina[3], Federico Nuzzo[4], Laura Roli[5], Maria Cristina De Santis[5], Tommaso Trenti[5], Antonio R. M. Granata[2], Manuela Simoni[3] & Daniele Santi[6]
[1]University of Modena and Reggio Emilia, Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, Modena, Italy, Department of Biomedical, Metabolic and Neural Sciences, Modena, Italy; [2]Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, Modena, Italy, Unit of Andrology and Sexual Medicine of the Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, Modena, Italy, Italy; [3]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy., Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, Modena, Italy, Italy; [4]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy, Italy; [5]Department of Laboratory Medicine and Pathology, Azienda Usl of Modena, Modena, Italy, Italy; [6]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy, Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, Modena, Italy, Italy.

Background
Testis stimulation with follicle stimulating hormone (FSH) is one of the empirical treatments proposed for male idiopathic infertility, although early reliable markers to predict its efficacy are still lacking.

Objective
To identify the improvement of semen parameters required to predict *a priori* FSH efficacy in terms of pregnancy achievement.
Methods
A real-world study was conducted, enrolling idiopathic infertile men treated with FSH 150IU 3 times weekly. According to the Italian rules, patients were treated until pregnancy achievement, or for a maximum of 2 years. For each patient, 2 visits were considered: V0 (baseline) and V1 (end of FSH treatment). Semen parameters were collected at both visits and their percentage changes after FSH therapy were calculated. Primary endpoints were the V1-V0 percentage of sperm concentration, total sperm count and total motile sperm number. Pregnancies were recorded, dividing the dataset in study (pregnancy gained) and control groups (no pregnancy).
Results
48 pregnancies were recorded (27.7%) among 173 men (age 37.9 ± 6.2 years, FSH duration 8.0 ± 4.5 months). All 3 endpoints increased after FSH administration, although the V1-V0 percentage did not differ between study and control groups. Logistic regression analysis showed that only V1-V0 percentage of sperm concentration significantly predicted pregnancy (Wald 7.392, $P = 0.007$). The second order polynomial function described the sperm concentration V1-V0 percentage (Y) needed to obtain a pregnancy according to its baseline values (x): $Y = 9.8x^2 - 203.7x + 958.3$.
Conclusion
Our study demonstrated that only the percentage increase of sperm concentration after FSH administration could predict the treatment efficacy in terms of pregnancy. The application of mathematical analyses on data distribution identified for the first time a function able to predict the sperm concentration increase needed to obtain a pregnancy in relation to the baseline sperm number.
DOI: 10.1530/endoabs.93.OC32

OC33

Variants in the neurodevelopmental gene bone morphogenic protein/-retinoic acid inducible neural-specific 2 (BRINP2) are associated with severe delayed puberty
Yasmin Al-Sayed
Queen Mary University of London, Department of Endocrinology, London, UK.

Gonadotropin-releasing hormone (GnRH) is the master hormone regulating the reproductive axis and its pulsatile secretion is crucial for puberty onset and fertility. Disruption in GnRH neuron development or hypothalamic function can lead to absent or delayed puberty (DP), with a phenotypic spectrum from severe DP to partial or complete Hypogonadotropic Hypogonadism (HH). We aimed to identify novel genetic etiology of severe DP by screening and identifying variants in associated genes in our cohort of patients; and ascertain the functional effects of identified variants of interest. Whole exome sequencing (WES) was performed on DNA samples from 180 probands with DP from our patient cohorts to identify potentially pathogenic novel, or rare coding variants in relevant gene pathways. Integrative analysis was performed on genomic data from human patients combined with transcriptomics analysis of rodent immortalized and primary GnRH neurons to determine novel regulators of GnRH neuronal development and function. BRINP2 was identified as a candidate gene of interest as it was found to be significantly upregulated during GnRH neuronal development in these single cell transcriptomics analyses. BRINP2 is localized to the olfactory bulb, a key site during GnRH neuron migration, and has been associated with neurodevelopmental disorders (NDD). WES analysis identified three rare predicted pathogenic variants in BRINP2 in four unrelated probands with severe DP or partial HH, in combination with NDDs. We have investigated the role of BRINP2 in GnRH biology via wildtype and mutant protein expression and sub-cellular localization, as well as tissue expression in mouse hypothalamic tissue across development.
DOI: 10.1530/endoabs.93.OC33

OC34

Testosterone serum levels in idiopathic male infertility: An epidemiological insight with pathophysiological and clinical consequences
Francesco Costantino[1], Giorgia Spaggiari[2], Leonardo Dalla Valentina[3], Marilina Romeo[3], Laura Roli[4], Maria Cristina De Santis[4], Tommaso Trenti[4], Antonio Granata[2], Manuela Simoni[3] & Daniele Santi[3]
[1]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Italy; Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, Italy; [2]Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, Italy, Unit of Andrology and Sexual Medicine of the Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, Italy; [3]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Italy, Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, Italy; [4]Department of Laboratory Medicine and Pathology, Azienda Usl of Modena, Italy.

Background
Despite male idiopathic infertility is characterized by semen analysis alteration with gonadotropins within reference ranges, it is still considered a functional hypogonadotropic hypogonadism (FHH). This simple definition is fundamental to guide the empirical therapeutic approach of these men. However, the number of studies describing total testosterone serum levels (TT) in male idiopathic infertility is still limited.
Objective
To evaluate TT distribution in a cohort of men with idiopathic infertility.
Methods
A real-world study was conducted, enrolling all men evaluated for couple infertility. Each patient was evaluated by conventional semen analysis and hormones (i.e. follicle stimulating hormone [FSH], luteinising hormone [LH] and TT). When semen analysis alteration was detected and all known causes of male infertility excluded, the diagnosis of idiopathic infertility was reached. TT distribution was evaluated and the number of subjects with TT below than reference thresholds suggested by scientific societies (i.e. 3.5 ng/ml) was calculated.
Results
254 men were enrolled (mean age 38.2 ± 6.1 years), with an average infertility duration of 2.5 ± 3.1 years. According to inclusion criteria, the average semen analysis parameters were below than decisional limits and gonadotropins within reference ranges (LH: 4.1 ± 1.9 IU/l, FSH: 5.8 ± 4.7 IU/l). TT was not normally distributed ($P < 0.001$), with a positive asymmetric distribution (Curtosi 3.1, standard error 0.3), with mean 5.0 ± 2.1 ng/ml (min 2.2, max 10.5 ng/ml), 5th centile 2.6 ng/ml and 95th centile 9.4 ng/ml. In the 19.4% of the cohort (58 patients) TT was lower than 3.5 ng/ml. Semen parameters and gonadotropins did not differ between patients with TT below or above 5th centile of distribution.
Conclusions
About the 20% of men with idiopathic infertility showed reduced TT, confirming the suggestion of FHH. However, this result confirmed the heterogeneity of this condition, excluding the FHH in the remnant 80% of cases.
DOI: 10.1530/endoabs.93.OC34

OC35

Alteration of adrenal and sex steroid profiles in pregnant women with preeclampsia
Olivia Trummer[1], Christina Stern[2], Sharmaine Reintar[3], Veronika Tandl[3], Karoline Mayer-Pickel[2], Mila Cervar-Zivkovic[2], Martin Fassnacht[4], Max Kurlbaum[5], Berthold Huppertz[6], Herbert Fluhr[7] & Barbara Obermayer-Pietsch[8]
[1]Medical University of Graz, Medical University Graz; DIV. Endocrinology and Metabolism; Endocrinology Lab Platform, Graz, Austria, Department of Internal Medicine, Division of Endocrinology and Diabetology, Medical University of Graz, Graz, Austria; [2]Klinik für Frauenheilkunde und Geburtshilfe, Medizinische Universität Graz; Department of Obstetrics and Gynaecology, Division of Obstetrics, Medical University of Graz; [3]Medical University Graz; DIV. Endocrinology and Metabolism; Endocrinology Lab Platform, Graz, Austria; [4]University Hospital Würzburg, Medizinische Klinik I, Division of Endocrinology and Diabetes, Würzburg, Germany; [5]Core Unit Clinical Mass Spectrometry, Department of Internal Medicine I, Division of Endocrinology and Diabetology, University Hospital Würzburg, Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital Würzburg, Germany, Endokrinologie, Würzburg, Germany; [6]Division of Cell Biology, Histology and Embryology, Gottfried Schatz Research Center, Medical University of Graz; [7]Klinik für Frauenheilkunde und Geburtshilfe, Medizinische Universität Graz, Department of Obstetrics and Gynaecology, Division of Obstetrics, Medical University of Graz; [8]Medical University Graz, DIV. Endocrinology and Metabolism, Endocrinology Lab Platform, Graz, Austria.

Background
Preeclampsia (PE) is a serious and complex pregnancy-related condition, characterized by hypertension and endothelial dysfunction, which can potentially damage liver, brain and kidneys, resulting to an increased perinatal morbidity and

mortality. We investigated pregnancy-related steroid hormones such as progestogens, estrogens, androgens, and glucocorticoids to assess maternal and fetal development. We aim to compare steroid hormone profiles throughout pregnancy, with and without PE.
Methods
Fourteen pregnant women with PE and 36 normotensive pregnant women were included. Samples were collected at different time points throughout pregnancy (12, 20, 24, 28, 32, 36 weeks of gestational age, WGA), at delivery and 24h postpartum. Steroids were measured in serum by isotope-dilution liquid chromatography tandem mass spectrometry. Steroid-metabolizing enzymes was measured by TaqMan Gene Expression Assays at 24 and 28 WGA.
Results
Pregnant women with PE, showed higher mean values of dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone, and androstenedione ($P<0.05$), while lower mean values of cortisol/cortisone ratio, 11-deoxycortisol, dihydrotestosterone and estradiol ($P<0.05$) were observed compared to controls. A comparison of substrate-product ratios between pregnant women with and without PE was used to derive candidate genes for steroid-metabolizing enzymes. CYP11B1, CYP17A1 and HSD11B1 showed decreased substrate-product ratios, whereas an increased ratio in SRD5A1, and HSD3B1 were observed ($P<0.05$). While our qPCR data for CYP11B1, CYP17A1 and HSD11B1 showed higher steroid-related gene expressions in PE compared to controls, the difference was not statistically significant ($P>0.05$).
Conclusion
In women with PE, we found significantly altered serum steroid levels and substrate-product ratios compared to normotensive pregnant women. Steroid-metabolizing enzymes with decreased product-substrate ratios tended to exhibit higher steroid enzyme expressions in women with PE, but were not statistically significant. Further studies will address the expression profiles of steroid-metabolising enzymes in PE and its expression in placenta tissue to clarify its role as potential biomarker for the prediction of preeclampsia.

DOI: 10.1530/endoabs.93.OC35

OC36

Evolution of cardiovascular risk markers in polycystic ovary syndrome: Results from a long-term monocentric cohort study

Carolina Cecchetti[1], Srdjan Pandurevic[2], Paola Dionese[2], Elisabetta Belardinelli[2], Laura Rotolo[2], Flaminia Fanelli[3], Luca Bergamaschi[4], Carmine Pizzi[4], Uberto Pagotto[5] & Alessandra Gambineri[6]
[1]Division of Endocrinology and Diabetes Prevention and Care, Irccs Azienda Ospedaliero-Universitaria DI Bologna, Italy, Department of Medical and Surgical Sciences (Dimec), Alma Mater Studiorum, University of Bologna, Italy, Umbertide, Italy; [2]Division of Endocrinology and Diabetes Prevention and Care, Irccs Azienda Ospedaliero-Universitaria DI Bologna, Italy., Department of Medical and Surgical Sciences (Dimec), Alma Mater Studiorum, University of Bologna, Italy; [3]Center for Applied Biomedical Research, Dept. Of Medical and Surgical Sciences, Alma Mater Studiorum – Bologna University, Bologna, Italy, Department of Medical and Surgical Sciences (Dimec), Alma Mater Studiorum, University of Bologna, Italy; [4]Unit of Cardiology, Department of Specialist, Diagnostic and Experimental Medicine, Alma Mater Studiorum, University of Bologna, Italy, Department of Medical and Surgical Sciences (Dimec), Alma Mater Studiorum, University of Bologna, Italy; [5]St. Orsola General Hospital, Internal Medicin/Endocr Unit, Bologna, Italy; [6]Division of Endocrinology and Diabetes Prevention and Care, Irccs Azienda Ospedaliero-Universitaria DI Bologna, Italy., Department of Medical and Surgical Sciences (Dimec), Alma Mater Studiorum, University of Bologna, Italy, Italy.

Background
Many questions concerning polycystic ovary syndrome (PCOS) remain unsolved, such as the long-term evolution of cardiovascular (CV) risk markers and the risk for CV events.
Methods
A total of 119 PCOS patients diagnosed in 2009 by NIH criteria at our Unit were evaluated at baseline for cardiovascular risk markers (hypertension, diabetes mellitus-DM, dyslipidaemia, obesity, carotid intima media thickness-cIMT, and epicardial fat thickness-EFT) and cardiovascular events. All subjects were subsequently reevaluated between 2020 and 2021.
Results
Participants mean age was 39.9 ± 7.6 years at baseline and 51.9 ± 7.6 years at the end of the study, with a prevalence of menopausal state of 6.1% and 39.3%, respectively. At baseline, no major or minor CV events were detected, but 2 cases of angina pectoris (1.7%), 1 case of transient ischaemic attack (0.8%), 3 cases of arterial revascularization (2.5%), and 1 case of cardiac insufficiency (0.8%) were documented at the end of the study. Prevalence of hypertension, type 2 DM, dyslipidaemia, and obesity were initially 27.2%, 12.2%, 59.0% and 32.1%, and 44.4%, 18.6%, 87.2% and 47.2% at final reevaluation ($P<0.001$, $P=0.065$, $P<0.001$, $P<0.05$ vs. baseline, respectively). cIMT was significantly increased at final examination (0.58 ± 0.16 mm vs. 0.81 ± 0.27 mm, $P<0.001$), and the % of patients with cIMT$\geq$ 1 mm or with carotid plaques passed from 1% to 26.4% ($P<0.001$). In contrast, a significant decrease in EFT was detected from baseline to the end of the study (0.86 ± 0.35 cm and 0.41 ± 0.23 cm, $P<0.001$).
Conclusions
This cohort study shows that PCOS is indeed characterized by a high prevalence of cardiovascular risk markers, with a tendency to increase over time; nonetheless, not all cardiovascular risk markers worsen steadily, with some interesting beneficial variations occuring in the late reproductive or early post-menopausal years.

DOI: 10.1530/endoabs.93.OC36

OC37

Regulation of the postnatal activity of the HPG axis in male Callithrix jacchus – A project description

Amadeusz Odroniec & Alexander Busch
University of Münster, University Hospital Münster, Department of General Pediatrics, Münster, Germany.

Background
The control of the Hypothalamic–Pituitary–Gonadal (HPG) axis is a highly complex process, with the hypothalamic arcuate-median eminence complex (Arc-ME) as the master regulating region. The transient activation of the HPG axis is essential for the development and function of the reproductive system. This project's focus is the transient phase of HPG axis activation within the first weeks and months postpartum (minipuberty). The mechanisms guiding the HPG axis control in mammals are only partially understood, with kisspeptin, neurokinin B, dynorphin, and MKRN3 as crucial factors. Studies in humans are greatly limited due to the scarcity of biological material. The value of rodent animal models is limited as the existence and functional relevance of minipuberty in rodents is unclear.
Objectives
To create a temporally resolved transcriptomic atlas of the Arc-Me brain region in marmoset monkeys (*Callithrix jacchus*). We aim to elucidate the control mechanism of the HPG axis using *Callithrix jacchus* as an animal model due to its close similarity to humans with regard to the HPG axis control in early postnatal life.
Methods
We will perform the single nucleus Multiome ATAC + Expression sequencing using the marmoset Arc-Me brain region. We chose three developmental groups based on liquid chromatography–tandem mass spectrometry (LC–MS/MS) measurement of the serum androgen metabolome: 0–1 day, 3 weeks, and 12 weeks old, corresponding to the stages prior, during, and post-minipuberty, respectively.
Perspectives
We are currently in the process of generating transcriptomic data. We hope our marmoset brain transcriptomic atlas will unveil the processes controlling the HPG axis during minipuberty and lead to the discovery of new target genes and mechanisms for further downstream analysis. Considering the hypothetical similarities between the regulation of minipuberty and puberty, we believe our study will bring insights into the puberty process itself.

DOI: 10.1530/endoabs.93.OC37

OC38

Body composition in association with serum anti-Müllerian hormone (AMH) levels in adult males implies hemodilution effects

Veronika Tandl[1], Christoph Haudum[2], Katharina Eberhard[2], Barbara Hutz[2], Ines Foessl[2], Ewald Kolesnik[2], Andreas Zirlik[2], Dirk von Lewinski[2], Daniel Scherr[2], Nicolas Verheyen[2], Thomas Pieber[2] & Barbara Obermayer-Pietsch[2]
[1]Medical University of Graz, Division of Endocrinology and Diabetology, Department of Internal Medicine, Graz, Austria; [2]Medical University of Graz.

Background
A negative relationship between body mass index (BMI) and serum Anti-Müllerian hormone (AMH) levels has been previously reported. Whether this is

because of an adverse effect of adiposity on AMH production or the hormone's dilution in a higher blood volume that accompanies larger body size ('hemodilution') is not yet clear. Blood volume can be estimated by body weight, body surface area (BSA) or lean mass (LM). Of note, adipose tissue is poorly perfused and adds relatively little to the overall blood volume.
Objectives
To investigate a possible hemodilution effect, we analyzed the relationships between serum AMH levels and different body size and composition parameters in adult males.
Methods
We used data of 382 adult, male participants of the ongoing, prospective BioPersMed study cohort. Body parameters used include height, weight, waist circumference, BMI, waist-to-hip ratio, body surface area (BSA) and estimated lean mass (eLM). Of 278 participants, dual energy X-ray absorptiometry (DXA)-derived body composition data, including fat mass (FM) and LM, were available. We performed univariate and multivariate regression models with potential confounders (age, follicle-stimulating hormone, and estradiol) included as additional predictors.
Results
In the fully adjusted models, weight ($R2 = 0.201$; $\beta = -0.002$; $P = 0.0022$), BSA ($R2 = 0.206$; $\beta = -0.231$; $P = 0.0006$) eLM ($R2 = 0.206$; $\beta = -0.006$; $P = 0.0006$) and LM ($R2 = 0.197$; $\beta = -0.006$; $P = 0.003$) significantly predicted AMH. In an age adjusted model that challenged FM and LM against each other by including them both as predictors, only LM remained significant ($R2 = 0.061$; $\beta = -0.007$; $P = 0.0035$).
Conclusions
In adult males, weight, BSA, eLM and LM (proxies of blood volume) better predicted serum AMH levels than measures of adiposity – suggesting hemodilution is at least partly responsible for the observed inverse relationship between AMH concentrations and BMI. Thus, hemodilution should be considered for normalization in future studies.

DOI: 10.1530/endoabs.93.OC38

Thyroid Diseases and Tumors

OC39

Loss of thyroid receptor beta (THRB) results in circadian rewiring of the transcriptome and lipidome in livers of adult male mice

Leonardo Vinícius Monteiro de Assis[1], Lisbeth Harder[1,2], Jens Mittag[3] & Henrik Oster[4]
[1]Cbbm, Institute of Neurobiology, Lübeck, Germany; [2]Karolinska Institutet, Sweden; [3]Universität Lübeck, Cbbm / Medi, Cbbm, Molecular Endocrinology, Universität zu Lübeck, Lübeck, Germany, Lübeck, Germany; [4]Medizinische Klinik I, Universität zu Lübeck, Institute of Neurobiology, University of Luebeck, Lübeck, Germany.

Background
Thyroid hormones (THs) stimulate hepatic de-novo lipid biosynthesis but also lipolysis and beta-oxidation. Similarly, they simultaneously enhance cholesterol uptake, biosynthesis, and degradation. Thyroid hormone receptor beta (THRβ) is the main hepatic thyroid hormone receptor. Mammals have developed a circadian timekeeping system that controls physiological processes to adapt to time-of-day.
Hypothesis
We hypothesized that TH effects are subject to circadian regulation via an interaction of THRβ with hepatocyte clocks.
Methods
Adult male THRβ knockout and congenic wild-type mice were kept in a standard light/dark cycle, and livers were collected every 4 h during 24 h. Samples underwent transcriptome and lipidome analyzes.
Results
Approximately 9000 rhythmic mRNAs were identified in THRβWT and THRβKO livers. Differential rhythm analysis identified 1446, 314, and 369 genes with changes in mesor (baseline expression), amplitude (rhythm strength), and acrophase (time of peak expression), respectively. Gene set enrichment analysis followed by predictive exploration suggested elevated levels of triglycerides and cholesterol in THRBKO livers. A total of 148 rhythmic lipids were identified and 33 lipids showed rhythm parameter differences. Phosphatidylcholines (42:2, 18:0_22:5, 20:0_20:4, 22:0_20:4, 31:1) and phosphatidylinositols (18:0_22:6, 20:0_20:4) had reduced mesor while cholesterol esters (18:1), ceramides (42:3;2O and 18:1;2O/23:0), triglycerides (58:8, 55:5, 53:4, 52:5, 51:4), diacylglycerides (18:1_22:6, 18:2_20:2, 18:2_20:4, 18:1_18:2, 18:0_18:2, 16:0_18:2), phosphatidylglycerol (18:1_18:1, 18:1_18:2, 18:1_22:6, 18:2_22:6) and free fatty acids (18:2) showed increased mesor. Interestingly, the diacylglycerides 18:2_20:4 and 18:0_18:2 showed a phase advance of 3 and 6 h, respectively. An integrative pipeline was implemented to match the identified rhythmic transcriptome changes with lipidome alterations, thus providing a resource for further experimentation.
Conclusions
Our findings show that loss of THRβ contributes to metabolic changes resembling early-stage hepatic steatosis.

DOI: 10.1530/endoabs.93.OC39

OC40

Thyroid hormone (TH) action in acute and chronic ischemic heart disease

Stefanie Dörr[1], Susanne Grund[2], G. Sebastian Hönes[3], Dagmar Führer[4], Lars Christian Möller[5] & Kristina Lorenz[6]
[1]Leibniz-Institut für Analytische Wissenschaften-Isas-e.V., Dortmund, Germany, Cardiovascular Pharmacology, Dortmund, Germany; [2]University Hospital Essen, Uniklinikum Essen, Department of Endocrinology, Essen, Germany; [3]University Hospital Essen, University of Duisburg Essen, Department of Endocrinology, Diabetes and Metabolism, Essen, Germany; [4]Universitätsklinikum Essen, University Hospital Essen, Klinik für Endokrinologie und Stoffwechselerkrankungen, Essen, Germany; [5]University Hospital Essen, University Hospital Essen, Department of Endocrinology, Diabetes and Metabolism, Essen, Germany; [6]Leibniz-Institut für Analytische Wissenschaften-Isas-e.V., Leibniz-Institut für Analytische Wissenschaften-Isas-e.V., Dortmund, Germany, Dortmund, Germany.

Ischemic heart disease (IHD) is one of the leading causes of death worldwide. TH have impact on cardiac function and even appear to improve outcome after acute ischemia/reperfusion and in chronic heart failure. This project aims to investigate the influence of TH receptor alpha (TRα) on IHD using specific mouse models to assess the contribution of canonical vs. non-canonical TH signaling. Mice underwent permanent ligation of the left descending coronary artery and were treated with 500 ng/ml T3 for 8 weeks. To evaluate the impact of the different TH signaling pathways, we used wild type (WT), TRα knockout (TRαKO) and knock-in mice with a mutation that abrogates canonical TRα signaling (TRαGS). Cardiac function was assessed by echocardiography, remodeling assessed by histological staining (HE/SR). Serum TH levels were analyzed by ELISA. Contractile parameters and cardiomyocyte (CM) hypertrophy were analyzed using isolated adult CM from WT, TRαKO and GS mice or neonatal mouse CM (NMCM). Cardiac vascularization was detected by anti-CD31 immunohistochemistry. Heart weight and CM size were increased in T3 treated WT mice. Echocardiography and histological analyses revealed reduced fibrosis in the remote area and reduced infarct size in response to T3. Total cardiac vessel number increased with T3 and proportional to heart weight, indicating T3-induced neoangiogenesis. Comparison of untreated WT, TRαKO and GS hearts suggests that this effect originates from noncanonical TRα signaling as GS mice had the highest total cardiac vessel length among the genotypes. *In vitro* analyses using CM suggest significant differences in contractility with reduced maximal sarcomere shortening of TRαKO and GS compared to WT. As observed *in vivo*, hypertrophic growth of NMCM was induced by T3. We show that T3 is indeed cardioprotective with improved infarct size. Current experiments will further reveal how canonical and noncanonical TRα signaling is involved in these T3 mediated cardioprotection.

DOI: 10.1530/endoabs.93.OC40

OC41

Clinical features of synchronous medullary and papillary thyroid carcinomas presenting as collision tumor

Ozge Bas Aksu[1], Özgür Demir[2] & ASENA Gokcay Canpolat[3]
[1]Ankara University School of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey; [2]Ankara University School of Medicine, Department of Endocrinology and Metabolic Diseases; Faculty of Medicine, Ankara, Turkey, Ankara University, Department of Endocrinology and Metabolism, Ankara, Turkey; [3]Ankara University, School of Medicine, Ankara University, Department of Endocrinology and Metabolism, Turkey.

Background and Objective
Thyroid collision tumors are extremely rare, accounting for just around 1% of all thyroid carcinomas. The objective of this study is to enhance our understanding of the clinical characteristics of these infrequently reported occurrences. In our study, we evaluated the clinical features of medullary thyroid carcinoma (MTC) that existed synchronously with papillary thyroid carcinoma (PTC).
Methods
We performed a retrospective analysis of 21 patients who were diagnosed between 2010 and 2022 at the Department of Endocrinology, Ankara University.

The demographics and clinical characteristics of the patients are the variables examined in this study.
Results
Mean age at diagnosis was 56.6 ± 12.4 years, %85.7 were women, and the follow-up duration was 34.4 mo (range 6–96). 85.7% of patients had a single focal MTC, the median MTC focus was 8 mm (range 0.6–56), 47.6% was localized on the left lobe, and 9.5% was multifocal in both lobes. 57.1% of patients had a single focal PTC, the median PTC focus was 5.5 mm (range 0.1–17), right and left lobe localization was equal (23.8% vs 23.8%) but 38.1% was multifocal in both lobes, common PTC subtypes: classical variant and mPTC (28.6% and 23.8%). The RET mutation status of twelve was unknown; six were negative, two had the S891A mutation, and one had the C618A mutation. Preoperative calcitonin levels were correlated with preoperative CEA (carcinoembryonic antigen) and post-operative calcitonin levels were statistically significant but not related to postoperative CEA levels ($r = 0.827$, 0.666, and 0.545 respectively). MTC foci diameter correlated with preoperative CEA and calcitonin levels and also postoperative CEA ve calcitonin levels ($r = 0.905$, 0.871, 0.588, and 0.626 respectively). PTC foci count negatively correlated with preoperative CEA levels ($r = 0.620$).
Conclusion
This study provides significant value in terms of improving awareness and advancing our knowledge and treatment of these uncommon carcinomas.
DOI: 10.1530/endoabs.93.OC41

OC42

Hyperthyroidism in 2 forms: The Marine-Lenhart syndrome
Maria Mathiopoulou[1] & Ivette Engel-Bicik[2]
[1]University Hospital of Zurich, Endocrinology, Zürich, Switzerland
[2]University Hospital of Zurich, Nuclear Medicine, Switzerland.

Background
The combination of a toxic adenoma and Graves' disease compose the Marine-Lenhart syndrome. It is estimated to occur in 0.8–2.7% of Graves' disease and only few are reported.
Case presentation
A 29-year old female was referred to our clinic due to subclinical hyperthyroidism and a newly discovered thyroid nodule on the right thyroid lobe. She had no thyreotoxic symptoms and the clinical examination was unremarkable. The blood tests showed: TSH 0.01 mU/l (reference 0.16–4.25 mU/l), fT3 8.3 pmol/l, (reference 3.6–6.4 pmol/l), fT4 15.6 pmol/l (reference 12.3–20.2 pmol/l) and TSH-Receptor-Ab titers < 0.30 U/l (reference < 1.75 U/l). The thyroid ultrasound and scintigraphy revealed a toxic adenoma in a right sided goiter. Following a radioiodine ablation with 200 MBq 131-I was performed. Follow-up ultrasound after six months revealed a 70%-volume reduction of the formerly toxic adenoma of (2.6 ml, pre-therapy 8.7 ml). Two months later at the regular after-therapy follow-up, a manifest hyperthyroidism was revealed [TSH 0.004 mU/l, fT3 28.1 pmol/l and fT4 21.4 pmol/l] and the TSH-Receptor-Ab titers were elevated [1.85 U/l], while the patient was asymptomatic. A new thyroid scintigraphy showed a symmetrical, elevated uptake, leading to the diagnosis of Graves' disease. A thyrostatic therapy with carbimazole was initiated for 8 months, until the thyroid function markers were normalised.
Conclusions
The co-existence of both a toxic adenoma and a Graves' disease is termed Marine-Lenhart syndrome. It may be observed simultaneously or in different stages, according to the bibliography. In cases where radioiodine treatment of a toxic adenoma is indicated, attention is required, because it may trigger the Graves' disease, as shown in this case. Every new presentation of hyperthyroidism should be investigated as a new pathology, as it may reveal a new underlying condition indicating the need for different therapeutical pathways.
DOI: 10.1530/endoabs.93.OC42

Diabetes, Obesity and Metabolism

OC43

Statin use and perimenopausal BMI determine the risk of incident diabetes mellitus in the postmenopause: Results of Palladia study
George Mavraganis[1], Nektaria Papanikola[2], Anastasia Angelopoulou[2], Aikaterini Stefanaki[2], Eleni Armeni[2], Stavroula Paschou[3], Valentina Anelli[4], Areti Augoulea[2], Kimon Stamatelopoulos[1] & Irene Lambrinoudaki[2]
[1]University of Athens, Department of Therapeutics, Alexandra Hospital, Greece; [2]University of Athens, 2nd Department of Obstetrics and Gynaecology, Aretaieio Hospital, Athens, Greece; [3]School of Medicine, National and Kapodistrian University of Athens, Department of Clinical Therapeutics, Alexandra Hospital, Athens, Greece; [4]University of Brescia, Department of Clinical and Experimental Sciences, Brescia, Italy.

Background
The menopausal transition has been associated with a heightened risk of cardiometabolic complications, including new onset diabetes mellitus (NODM). Statin-use increases the NODM-risk in the general population, however, their impact on NODM-risk specifically in postmenopausal populations has not been adequately studied.
Objectives
To estimate the effect of statin-use at baseline on the risk of NODM in postmenopausal women.
Methods
The PALLADIA study, a large prospective cohort, consists of middle-aged women assessed in the Menopause Clinic of Aretaieio Hospital, Athens Greece. All women were reviewed for symptoms related to menopause and followed-up (FU) annually based on their risk factors. We included 473 postmenopausal women (median duration of FU, 10 years).
Results
The prevalence of cardiovascular risk factors at baseline and FU were as follows: smoking 26% vs 19.4%, diabetes mellitus 3% vs 9.9%, hypertension (HTN) 22.4% vs 29.6%, dyslipidemia 30.9% vs 46.9%, statin-use 16.7% vs 34.2%. NODM was identified in 38 women, while NODM ± impaired fasting glycaemia was found in 44 women. The use of statin at baseline increased the risk for NODM in the univariable analysis (OR = 3.58, 95%CI: 1.74–7.37); multivariable analysis showed that NODM-risk was associated with statin use at baseline (OR = 4.5, 95%CI, 1.67–12.11) adjusted for age, BMI, HTN, smoking. The combination of statin-use/BMI was associated with a higher risk for NODM ± hyperglycemia (OR = 4.63, 95% CI, 1.80–11.90).
Conclusions
Our results indicate that the NODM-risk attibuted to the use of statins in the Greek cohort of PALLADIA is higher compared to the risk reported in previous studies. Amidst traditional cardiovascular risk factors, baseline BMI appears to be the factor mostly related with the future risk for dysglycemia. Further research is required to explore the pathogenetic mechanisms underlying these observations.
DOI: 10.1530/endoabs.93.OC43

OC44

Insulin secretion defect in children and adolescents with obesity: Clinical and molecular genetic characterisation
Helena Enders-Seidlitz[1], Klemens Raile[2], Angela Galler[1] & Susanna Wiegand[1]
[1]Charité Universitätsmedizin Berlin, Pediatric Endocrinology, Berlin, Germany; [2]Vivantes Neukölln, Pediatric Department, Germany.

Background
Childhood obesity is increasing worldwide and presents as a global health issue due to multiple metabolic comorbidities. About 1% of adolescents with obesity develop type 2 diabetes (T2D), however little is known about the genetic background in young age. The objective of this study was to assess the prevalence of impaired glucose regulation (IGR) in a large cohort of children and adolescents with obesity and to characterize insulin sensitivity and insulin secretion. We also wanted to investigate adolescents with insulin secretion disorder more closely and analysed possible candidate genes of diabetes in a subcohort.
Methods
We included children and adolescents with obesity who completed an oral glucose tolerance test (OGTT, glucose + insulin) in outpatient clinic. We calculated Matsuda-Index, the area under the curve (AUC (Ins/Glu)) and an oral Disposition Index (ISSI-2) to estimate insulin resistance and beta-cell function. We identified patients with IGR and low beta cell function (maximum insulin during OGTT <200 mU/l) and tested a subgroup using Next Generation Sequencing to identify possible mutations in 103 candidate genes.
Results
The total group consisted of 903 children and adolescents with obesity. 4.5% showed impaired fasting glucose, 9.4% impaired glucose tolerance, and 1.2% T2D. Matsuda Index and Total AUC (Ins/Glu) showed a hyperbolic relationship. Out of 39 patients with low insulin secretion, we performed genetic testing in 12 patients. We found 5 monogenetic defects (ABCC8 ($n = 3$), GCK ($n = 1$), GLI2/PTF1A ($n = 1$)).
Conclusion
Using surrogate parameters of beta-cell function and insulin resistance can help to identify patients with insulin secretion disorder. The prevalence of 40% mutations of known diabetes genes in the subgroup with low beta-cell function suggests a

minimum of about 1.7% monogenic T2D in a cohort of adolescents with obesity. A successful molecular genetic diagnosis can help to improve the individual therapy.

DOI: 10.1530/endoabs.93.OC44

OC45

Influence of diabesity in the visceral adipose tissue miRNA expression profile

Carmen Lambert[1], Elsa Villa-Fernandez[2], Ana Victoria García Gómez[3], Miguel García-Villarino[4], Sandra Sanz[5], Raquel R. Uria[5], Maria Moreno[5] & Elias Delgado[6]
[1]Ispa, Endo, Oviedo, Spain [2]Health Research Institute of the Principality of Asturias (Ispa), Endocrinology, Nutrition, Diabetes and Obesity Group (Endo), Oviedo, Asturias, Spain; [3]Health Research Institute of the Principality of Asturias (Ispa), Oviedo, Asturias, Spain, Instituto de Investigación Sanitaria del Principado de Asturias (Ispa), Endocrinology, Nutrition, Diabetes, Obesity Investigation Group, Oviedo,Asturias, Spain; [4]Health Research Institute of the Principality of Asturias (Ispa), Oviedo, Asturias, Spain; [5]Health Research Institute of the Principality of Asturias (Ispa), Oviedo, Asturias, Spain, Asturias Central University Hospital. Oviedo, Asturias, Spain; [6]Health Research Institute of the Principality of Asturias (Ispa), Oviedo, Asturias, Spain, Asturias Central University Hospital, Oviedo, Asturias, Spain, Endocrinology in Hospital Universitario Central de Asturias (Huca), Oviedo, Spain.

Influence of Diabesity in the visceral adipose tissue miRNA expression profile.
Background
The term diabesity arose in 2001 to refer to the coexistence of obesity (OB) and type 2 diabetes (T2D). It is estimated that 89% of adults diagnosed with T2D have a BMI greater than 25 kg/m^2, and of them, 45% are obese. However, the mechanisms because why some obese patients develop T2D and other do not, are still unclear.
Objectives
The principal objective of this work is to analysis the differential microRNA expression profile in the visceral adipose tissue (VAT) of obese patients regarding on the presence of T2D.
Methods
The miRNA expression profile of TAV from 48 patients (10 nonOb controls, 19 Ob_noT2D, and 19 Ob_T2D) was analyzed by NGS, identifying 288 different miRNAs. Among them, 12 miRNAs were selected for their validation by RT-PCR and their expression analyzed based on the presence of obesity and/or T2D.
Results
We observed that the miRNAs miR-200b-3p and miR-144-5p presented a differential profile between the 3 group of patients (Kruskal–Wallis test: $P=0.002$ and $P=0.011$ respectively). Additionally, miR-200b-3p, miR-144-5p, miR-335-3p and miR-224-5p were increased in the group of Ob_noT2D patients compared to those Ob_T2D, although only the first two showed a significant change (Dunn Post- Hoc test: $P=0.001$, $P=0.011$, $P=0.068$ and $P=0.078$ respectively).
Conclusions
Our study shows the influence of diabesity in the miRNA expression profile of VAT. A better understanding of the differences between the VAT of obese patients with and without diabetes can help to better understand the metabolism of diabesity, helping us to understand what causes an obese patient to develop DM2 or not.

DOI: 10.1530/endoabs.93.OC45

OC46

Glycaemic and inflammatory profile changes in patients with hybrid closed loop systems

Ana Victoria García Gómez[1], Pedro Pujante Alarcon[2], Elsa Villa-Fernandez[3], Carmen Lambert Goitia[4], Miguel García Villarino[5], Alicia Cobo Irusta[6] & Elías Delgado Álvarez[6]
[1]Health Research Institute of the Principality of Asturias (Ispa), Oviedo, Asturias, Spain., Instituto de Investigación Sanitaria del Principado de Asturias (Ispa), Endocrinology, Nutrition, Diabetes, Obesity Investigation Group, Oviedo,Asturias, Spain; [2]Endocrinology, Nutrition, Diabetes and Obesity Group (Endo), Health Research Institute of the Principality of Asturias (Ispa), Endocrinology and Nutrition Department, Asturias Central University Hospital, Oviedo, Asturias, Spain, Endocrinology and Nutrition, Spain; [3]Health Research Institute of the Principality of Asturias (Ispa), Endocrinology, Nutrition, Diabetes and Obesity Group (Endo), Oviedo, Asturias, Spain; [4]Endocrinology, Nutrition, Diabetes and Obesity Group (Endo), Health Research Institute of the Principality of Asturias (Ispa), Health Research Institute of the Principality of Asturias (Ispa), Endocrinology, Nutrition, Diabetes, Obesity Group (Endo), Oviedo,Asturias, Spain; [5]Endocrinology, Nutrition, Diabetes and Obesity Group (Endo), Health Research Institute of the Principality of Asturias (Ispa), Instituto de Investigación Sanitaria del Principado de Asturias (Ispa), Endocrinology, Nutrition, Diabetes, Obesity Investigation Group, Oviedo,Asturias, Spain; [6]Endocrinology, Nutrition, Diabetes and Obesity Group (Endo), Health Research Institute of the Principality of Asturias (Ispa), Spain.

Background
the treatment of individuals with type 1 diabetes (T1D) has significantly evolved in recent years. Therefore, with the aim of achieving glycaemic targets to prevent or slow down the progression of the disease and its complications, hybrid closed-loop systems (AID) have been developed. These systems integrate three components: a continuous real-time glucose monitor, a control algorithm and an insulin pump. The objective of this study is to analyse the glycaemic and inflammatory profile changes in patients after one year of using these systems.
Materials and methods
19 patients who initiated treatment with a hybrid closed-loop system (Medtronic 780G 26%, Tandem-ControlIQ 26%, and Roche-Diabeloop 48%) since November 2019 were included in this study, where 74% had previously used insulin pumps. Blood samples were taken previous (T0) and after (at 3, 6, and 12 months) pump implantation for inflammatory and biochemical analysis.
Results
a significant increase in time in range (TIR) was observed from the first month, with significant differences at all time points compared to T0 ($P<0.001$). The coefficient of variation (CV) decreased significantly from T0 to 3 months, and this reduction was maintained until the one-year mark ($P<0.001$). Regarding to HbA1c, a decreasing trend was observed ($P=0.025$), as well as a decrease in blood glucose levels ($P<0.001$). Additionally, the same parameters were studied based on whether patients had had previous insulin pump experience or not, and significant differences in TIR were found between T0 vs 6 months and T0 vs 1 year. Regarding the inflammatory profile, measured by protein expression of IL-6 and CPR, no significant changes were observed.
Conclusion
Hybrid closed-loop systems are a valuable tool for optimizing management of T1D, improving glycaemic control and variability. However, further studies with larger patient cohorts are necessary to analyse the effect of those systems on patients' inflammatory profile.

DOI: 10.1530/endoabs.93.OC46

OC47

Amino acids and biogenic amines circadian fluctuation in health and in hypercortisolism states

Greta Galante[1], Lorenzo Tucci[2], Ilaria Improta[3], Valentina Bissi[4], Alessandro Perrone[4], Kimberly Coscia[4], Giacomo Colombin[4], Ilaria Di Cintio[4], Valentina Vicennati[3], Uberto Pagotto[5], Guido Di Dalmazi[6] & Flaminia Fanelli[7]
[1]Endocrinology and Prevention and Care of Diabetes Unit, Center for Applied Biomedical Research, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, Irccs Azienda Ospedaliero-Universitaria DI Bologna, Bologna, Italy., Department of Medical and Surgical Sciences, Bologna, Italy; [2]Alma Mater Studiorum University of Bologna, Irccs Sant'orsola Polyclinic Endocrinology Unit, Medical and Surgical Sciences, Bologna, Italy; [3]Alma Mater Studiorum University of Bologna, Irccs Sant'orsola Polyclinic Endocrinology Unit, Italy; [4]Endocrinology and Prevention and Care of Diabetes Unit, Center for Applied Biomedical Research, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, Irccs Azienda Ospedaliero-Universitaria DI Bologna, Bologna, Italy; [5]St. Orsola General Hospital, Internal Medicin/Endocr Unit, Bologna, Italy; [6]Division of Endocrinology, Dept. of Medical and Surgical Sciences, Division of Endocrinology, Department of Medical and Surgical Sciences, Alma Mater University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy, Bologna, Italy; [7]Center for Applied Biomedical Research, Dept. Of Medical and Surgical Sciences, Alma Mater Studiorum – Bologna University, Bologna, Italy, Department of Medical and Surgical Sciences (Dimec), Alma Mater Studiorum, University of Bologna, Italy.

Background
Chronic hypercortisolism exhibits irregular circadian rhythm and deranged protein metabolism. Altered amino acid(AA) and biogenic amine(BA) circulating levels were found in patients with hypercortisolism. However, there is limited information about the physiologic circadian fluctuation of AA and BA levels, and it is not known whether this is affected by states of hypercortisolism.
Aim
To characterize levels and daily fluctuations of AA and BA in convenient dried blood spots (DBS) from finger-prick in healthy subjects(HS) and in patients affected by autonomous cortisol secretion(ACS) or Cushing syndrome(CS).
Methods
HS ($n=9$), ACS ($n=6$) and CS ($n=5$) patients underwent a 7-days standardized isocaloric Mediterranean diet. On the 7th day, subjects collected DBS 30 min before and 2 h after breakfast, lunch and dinner and at bedtime. 21 AA and 21 BA were measured in DBS by LC–MS/MS.
Inizio modulo
Results
Compared to HS, ACS patients had lower His($P=0.026$), while CS patients had lower Asn($P=0.030$) and higher spermidine($P=0.003$). CS also had higher spermine($P=0.028$) and t4-OH-proline($P=0.032$) when compared to ACS patients. A daily rhythm was detected for 11 AA in HS (e.g.: Met, Leu, Ile and Arg; P:0.001–0.006), mostly with levels higher at awakening and bedtime, and lower in the morning. Of these, some maintained their rhythm also in ACS(e.g.: Ile and Leu; both P:0.001) and CS patients(Leu; P:0.006). Fluctuation of other compounds were found in ACS (e.g.: Gly and Ser; P: <0.001) and in CS (ADMA, creatinine, spermine; P:0.003–0.018).
Conclusions
In health condition, a panel of AA displayed a diurnal fluctuation consistent with physiologic night protein catabolic processes. Daily fluctuations were revealed in ACS for a different panel of AA, and were almost all lost in CS. In addition, fluctuations in some BA were specifically detected in ACS and CS. Our data highlighted deranged histidine metabolism in ACS, and increased production of spermidine and spermine in CS.

DOI: 10.1530/endoabs.93.OC47

OC48

Abstract withdrawn

OC49

Effects of chronic pancreatitis in beta-cell function and incretin secretion

Gea Ciccarelli[1], Gianfranco Di Giuseppe[2], Laura Soldovieri[2], Michela Brunetti[2], Umberto Capece[2], Simona Moffa[2], Francesca Cinti[2], Andrea Giaccari[2] & Teresa Mezza[2]
[1]Fondazione Policlinico Universitario A. Gemelli, Endocrinologia e Diabetologia, Rome, Italy; [2]Fondazione Policlinico Universitario A. Gemelli, Rome, Italy.

Background
Chronic pancreatitis (CP) is the most frequent cause of diabetes of the exocrine pancreas (DEP). Although the specific alterations of DEP are not completely understood, individuals with DEP are considered affected by pancreatic endocrine insufficiency and treated with insulin. To investigate the functional alterations of DEP, we evaluated differences in glucose metabolism in patients with and without CP, classified according to their glucose tolerance (NGT, IGT, DM).
Methods
We recruited 50 patients with CP and 96 individuals without CP (NCP). All participants underwent OGTT, hyperglycemic clamp (HC), hyperinsulinemic euglycemic clamp and mixed meal test (MMT) with measurement of GLP-1 and glucagon. Basal insulin secretion rate (ISR), total ISR, rate secretion and β-cell glucose sensitivity (RS and GS) were estimated by mathematical models from OGTT, MMT and HC.
Results
Comparing individuals classified into NGT, IGT or DM based on OGTT-derived glucose tolerance, we found no differences in beta-cell function derived by OGTT and MMT. GLP-1 and glucagon secretion during MMT was not significantly different in the two groups. Of note, we found that insulin secretion after arginine stimulus in HC, an indirect measure of beta-cell mass, is reduced only in diabetic patients with CP compared to diabetic patients without CP ($P=0.023$). No difference was found in insulin sensitivity evaluated as glucose uptake at hyperinsulinemic euglycemic clamp.
Conclusion
At equivalent levels of glucose tolerance, patients with CP had similar beta-cell function and GLP-1 and glucagon secretion to individuals without CP. People with DEP have a lower beta-cell response to a maximus stimulus than patients with DM without CP, but analogous residual beta-cell function, so they could benefit from other therapies apart from insulin. Future studies are warranted to investigate differences in beta-cell function decline between type 2 diabetes mellitus and DEP.

DOI: 10.1530/endoabs.93.OC49

Interdisciplinary Endocrinology and Environment, Society and Governance

OC50

Bisphenols in adrenocortical cell culture

Lydia Kürzinger[1], Benedikt Pötzl[2], Sabine Kendl[3], Martin Fassnacht[4], Max Kurlbaum[5] & Ulrich Dischinger[6]
[1]Uniklinikum Würzburg, Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital Würzburg, Germany, Endokrinologie und Diabetologie, Würzburg, Germany; [2]Uniklinikum Würzburg, Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital Würzburg, Germany, Medizinische Klinik und Poliklinik I – Endokrinologie, Würzburg, Germany; [3]Department of Medicine I, University Hospital Würzburg, University Hospital of Wuerzburg, Würzburg, Germany; [4]University Hospital Würzburg, Medizinische Klinik I, Division of Endocrinology and Diabetes, Würzburg, Germany; [5]Core Unit Clinical Mass Spectrometry, Department of Internal Medicine I, Division of Endocrinology and Diabetology, University Hospital Würzburg, Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital Würzburg, Germany, Endokrinologie, Würzburg, Germany; [6]University Hospital Würzburg; Medizinische Klinik I; Division of Endocrinology and Diabetes, Würzburg, Germany, 1department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital Würzburg, Germany, Endocrinology, Würzburg, Germany.

Background
Bisphenol A (BPA) acts as an endocrine disruptor in different endocrine systmes. However, its impact on the adrenal cortex and steroidogenesis is largely unknown. This also applies to its substitute substances bisphenol F (BPF) and S (BPS). Therefore, experiments addressing this subject are urgently needed.
Methods
The human adrenocortical cell lines NCI-H295R and MUC-1 were treated with increasing concentrations (1 nM–1 mM) of bisphenol A, F, and S. Concentrations of fifteen adrenal steroids in cell supernatants were measured via liquid-chromatography–tandem-mass spectrometry (LC–MS/MS) after different periods of exposure (24 h, 72 h). Cell viability was monitored to assess cytotoxicity.
Results
All tested bisphenols are able to interfere with steroid production compared to untreated cells in a dose- and time-dependent manner in both cell lines: in the NCI-H295R hormone levels of 11-deoxycortisol, testosterone, androstenedione, dihydrotestosterone, cortisol and cortison were significantly decreased after 72 hours of exposure (at >100 μM BPA, BPF and BPS respectively, $P<0.05$). For instance, 100μM BPA treatment resulted in a 0.29-fold decrease of testosterone, and a 0.43-fold decrease of cortison. Interestingly, tested bisphenols showed ambiguous effects on some parameters, e.g. a 0.39-fold decrease of progesterone was detected in 100 μM BPA, while BPF led to a 26-fold increase. Furthermore, we found an increased level of estradiol, 21-deoxycortisol and 17-hydroxyprogesterone in BPF-treated cells ($P<0.05$). At large, reported effects were confirmed in MUC-1 cells, which seem to be more resilient against tested bisphenols. In this sense, calculated median lethal doses (LD_{50}) were: BPA 110.1 μM, BPS 229.4 μM, BPF 344.5 μM for NCI-H295R and BPA 279.4 μM BPF 356.8 μM and BPS 1.31mM for MUC-1.
Conclusions
Our results provide further evidence that bisphenol A, F, and S act as disruptors of steroidogenesis and steroid secretion. Underlying mechanisms and pathways are yet to investigate. This reinforces the need for further research efforts focusing on EDCs' effects on the adrenal gland.

DOI: 10.1530/endoabs.93.OC50

OC51

Identifying and characterizing novel HSP90 inhibitors with senolytic activity in a hormone-induced breast cancer-senescence model

Luca Cis[1], Sandra Atlante[2], Sara De Martino[3], Chiara Cencioni[3], Aurora Aiello[3], Davide Pirolli[4], Marco Malavolta[5], Simona Nanni[6], Maria Cristina De Rosa[4], Carlo Gaetano[2] & Antonella Farsetti[3]
[1]Università Cattolica del Sacro Cuore, Medicina e Chirurgia Traslazionale, Roma, Italy; [2]Istituti Clinici Scientifici Maugeri-Irccs, Pavia, Italy; [3]National Research Council Cnr-Iasi, Roma, Italy; [4]National Research Council Cnr-Scitec, Roma, Italy; [5]Irccs Inrca – Istituto Nazionale Riposo e Cura Anziani, Ancona, Italy; [6]Università Cattolica del Sacro Cuore, Roma, Italy.

Background
Cell senescence is characterized by halted cell proliferation and the acquisition of a pro-inflammatory profile. Cancer cells can enter into senescent state following treatments that inflict DNA damage. Intriguingly, these cells can evade the senescent state, gaining enhanced proliferative capabilities and resistance to further treatment, thereby prompting tumor recurrence. Senolytics offer the potential to eradicate selectively senescent cells, preventing tumor recurrence and catalyzing tumor regression. Several senolytics with varying targets have been recognized. Nevertheless, these drugs, pose safety and specificity challenges.
Objectives
Our research, therefore, strives to identify and characterize innovative HSP90 inhibitors with senolytic features for application in hormone-driven cancers.
Methods and results
We utilized *in silico* strategy to pinpoint several new, optimized HSP90-inhibiting compounds with minimal cytotoxicity, exploiting a structure- and ligand-based virtual screening approach. Among them, two HSP90α inhibitors, K4 and K5, exhibited senolytic activity *in vitro* without any observable cytotoxicity in non-senescent cells (patent pending). We selected the MCF7 cell line as our *in vitro* model. Senescence was induced via treatment with 4-Hydroxytamoxifen (Tam, 10uM 96h). Growth curve and beta-galactosidase (β-gal) assays confirmed that Tam effectively blocked MCF7 cell proliferation and triggered senescence up to 35–40% of cells compared to control. To assess the potential senolytic activity of K4 and K5, we treated senescence-induced cells with both drugs (10 μM, 96 h). β-gal staining was notably reduced, with only 10% of senescent cells remaining with K4 or K5 compared to DMSO. Interestingly, compared to control, the mortality rate rose significantly with K5 but not with K4. Western blot confirmed that p21 and γH2AX were stabilized by Tam, corroborating the induction of DNA damage.
Conclusions
Our findings suggest that the two newly identified HSP90 inhibitors, particularly K5, display senolytic properties and may be leveraged with tamoxifen to inhibit proliferation and stimulate cell death in breast cancer cells.

DOI: 10.1530/endoabs.93.OC51

OC52

Factors determining number of top performances in short, middle, and long-distance running in women – impact of doping, antidoping and testosterone limitations

Jelena Jaksic[1], Lukas Libric[2] & Ozana Jaksic[2]
[1]University of Zagreb, School of Medicine, Zagreb, Croatia; [2]University of Zagreb School of Medicine, Zagreb, Croatia.

Background
Sport results might be influenced by advances in sport science leading to better training, but also by new knowledge of human physiology and endocrinology. Doping and its detection as well as impact of regulations like testosterone limitations for women category eligibility might be reflected in top sport performances.
Objectives
We aimed to retrospectively analyse factors influencing top performances in short, middle, and long-distance running in women.
Methods
We have analysed the number of top performances per year in the world (www.alltime-athletics.com) in women from 1980 to 2022 among 250 all-time outdoor top performances. Disciplines with different physiologic requirements (100 m, 800 m and 5000 m running) were included. We have performed multivariate analysis evaluating impact of time progression, years with Olympic games, implementation of athlete's biological passport, out-of-competition testing, years without erythropoietin detection, years with tetrahydrogestrinone availability, years with testosterone limitations, year 2020 (onset of COVID-19 pandemic), and COVID era (2021 and 2022).
Results
In multivariate analysis model was significant for 100 m (R^2 0.79, $P<0.05$) with positive influence of tetrahydrogestrinone availability and COVID-19 era, while negative influence of the year 2020. For 800 m model was significant (R^2 0.41, $P<0.05$), with positive influence of Olympic year, and negative influence of testosterone limitations and out-of-competition testing. For 5000 m model was also significant (R^2 0.77, $0<0.05$) with positive influence of time progression, but negative influence of testosterone limitations and year 2020.
Conclusions
Our results show that testosterone limitations negatively impacted the number of top performances in both middle and long-distance categories. Out-of-competition tests crucial for anabolic detection also negatively influenced results in middle-distance category. The tetrahydrogestrinone, a strong anabolic that escaped detection for several years is important in short distance category. The particular impact of COVID-19 years with irregular antidoping testing suggests that many other factors could directly or indirectly influence top sport performances.

DOI: 10.1530/endoabs.93.OC52

OC53

Metabolic and growth outcome of two-years growth hormone treatment in children born small for gestational age (SGA): A retrospective study

Rosario Ferrigno, Maria Cristina Savanelli, Daniela Cioffi, Valeria Pellino & Antonella Klain
UOSD di Endocrinologia ed Auxologia, AORN Santobono-Pausilipon, Napoli, Italy.

Children born small for gestational age (SGA) not showing catch-up growth in early life may show decreased growth rate and adult height and worse metabolic profile compared to general population. In these patients, growth hormone (GH) treatment showed positive effects on growth rate and metabolic profile, with good tolerability. The aim of the study was to evaluate auxological and metabolic effects and safety of GH treatment in SGA children. Study included 34 SGA children (15 F, 19 M; mean age: 8.72±2.48 years) treated with GH (starting dosage: 32.24±2.88 μg/kg per die) for 24 months. Growth and metabolic parameters, including glycemic and lipid profile, transaminases, and urycemia, were collected every six months. Compared to baseline, SGA children showed significant improvements in height, weight, and growth rate after 24 months of treatment ($P<0.001$), already evident after six months ($P<0.001$). Noteworthy, patients showed constant, significant improvement in height throughout the treatment ($P<0.001$ T12 vs T0, $P=0.03$ T24 vs T12). Conversely, although significantly higher than baseline at each visit ($P<0.001$), after month six growth rate significantly decreased until month 18 ($P<0.001$ T6 vs T12; $P=0.015$ T12 vs T18), remaining thereby stable. Considering metabolic parameters, recurring increases in glycemia ($P\leq0.042$ vs T12 and T18) and urycemia ($P \leq 0.01$ vs T12, T18, and T24) and decrease in AST ($P \leq 0.021$ vs T12, T18, and T24) and an occasional decrease in LDL cholesterol ($P=0.03$ vs T24) were observed. Considering safety profile, treatment was well tolerated, as the most frequently reported adverse event was poor compliance (11.8%). In conclusion, GH treatment in SGA children is an effective, safe treatment for short stature, although the metabolic profile of treated patients should be carefully monitored during time.

DOI: 10.1530/endoabs.93.OC53

Calcium and Bone

OC54

Bone metabolism in mice requires canonical TRA action

Ann-Kathrin Schoerding[1], Daniela Geist[2], G Sebastian Hönes[3], Lars Christian Möller[4], Graham Richard Williams[5] & John Howard Duncan Bassett[6]
[1]Universitätsklinikum Essen, Klinik für Endokrinologie, Diabetologie und Stoffwechsel, Essen, Germany; [2]Department of Endocrinology, Diabetes and Metabolism, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [3]University Hospital Essen, University of Duisburg Essen, Department of Endocrinology, Diabetes and Metabolism, Essen, Germany; [4]University Hospital Essen, University Hospital Essen, Department of Endocrinology, Diabetes and Metabolism, Essen, Germany; [5]Imperial College London, Department of Medicine, Room 10n5, Commonwealth Building, London W12 Onn, UK; [6]Molecular Endocrinology Laboratory, Room 10n6 Commonwealth Building, Hammersmith Campus,, London, UK.

Background
Thyroid hormone (TH) action is mediated by TH receptors (TRs) α&β. Both regulate gene expression by binding TREs on the DNA (canonical signaling) or activate cellular signaling pathways (noncanonical signaling). Bone is a major TH target and noncanonical TR α & β effects on bone metabolism were suggested. We studied mouse model bones to distinguish between signaling types.
Methods
Growth of WT mice and mice with either knockout (TRαKO, TRβKO) or selective loss of canonical action (TRαGS, TRβGS) was recorded until P112. Femurs and caudal vertebrae were analysed with Faxitron-X-ray-microradiography (BMC, bone length) and high resolution μ-CT (cortical/trabecular thickness, BMD). 3-point-bend testing to destruction with a 100 N load cell revealed yield, maximal and fracture load.
Results
Longitudinal growth of TRαKO and TRαGS mice was equally delayed and normalized after postnatal week 8. Caudal vertebrae height did not differ between genotypes at P112. Trabecular bone stretched farther in TRαKO and TRαGS femurs than in WT (39% & 41% vs. 33%). Trabecular number and connectivity density were increased in both mutants, while spacing was reduced. Trabecular thickness was similar in all groups, as were cortical parameters and BMD. TRα mutant bones contained a dense and more extensive network of normally shaped trabecular bone. No difference was found in yield or fracture load. After T3 treatment, structural differences between TRα mutants and WT were similar. Growth of TRβKO and TRβGS did not differ from WT. T4 serum concentration was elevated in both models due to abolished negative feedback in the HPT axis. BMC was equally reduced in mutant femurs with thinner cortical bone. There were no differences in trabecular parameters.
Conclusion
Adult mice without canonical but preserved noncanonical TRα action showed the TRα knockout phenotype. Thus, these results demonstrate that TH effects in bone are predominantly mediated by canonical TRα action.

DOI: 10.1530/endoabs.93.OC54

OC55

Pregnancy-related osteoporosis – difficulties regarding diagnosis and treatment

Andreea Barbulescu
National Institute of Endocrinology C.I.Parhon, Endocrinology, Bucharest, Romania.

Introduction
Pregnancy-related osteoporosis represents a very rare pathology, which manifests through fractures that appear during pregnancy or early postpartum in patients who didn't have related risk factors prior to the pregnancy. Due to the low number of cases reported, this pathology raises problems regarding diagnosis, etiology and the optimal treatment scheme, as we are going to illustrate through the following case. The etiology of this pathology is unknown – the vascular and neurogenic hypotheses have been suggested so far.
Methods
We are presenting the case of a 34 year old patient, who started to complain of cervical-thoracic-lumbar spine pain 2 days postpartum, which grew in intensity and determined her to ablactate after 2 months. The infectious and hematologic etiologies were excluded and the MRI and histopathologic exams revealed severe osteoporotic lesions in her hips and spine. The diagnosis was confirmed by osteodensitometry. The patient started treatment with denosumab 60 mg every 6 months, calcium and vitamin D, which she followed for four years, with significant increase in bone density (BMD increase in L1–L4 from 0.592 g/cm^2 to 0.863 g/cm^2), then she stopped.
Results
The last evaluation revealed a small increase in bone density compared to the previous year, with no further fragility fractures. The patient expressed her desire to have another pregnancy. We considered there weren't any contraindications, but she was informed about the risk of new fractures.
Conclusions
Raising the suspicion of this rare diagnosis in a patient who complains of intense bone pain during pregnancy or early postpartum could prevent osteoporotic fractures.

DOI: 10.1530/endoabs.93.OC55

OC56

Parameters of calcium and phosphate homeostasis in patients with predialysis CKD in response to 150 000 IU cholecalciferol treatment

Artem Zhukov[1], Axenia Bondarenko[2], Alexandra Povaliaeva[2], Zamira Zuraeva[2], Natalia Trubitsyna[2], Larisa Nikankina[2], Minara Shamkhalova[2], Ekaterina Pigarova[2], Liudmila Rozhinskaya[2] & Natalia Mokrysheva[2]
[1]Endocrinology Research Centre, Department of Neuroendocrinology and Bone Diseases, Moscow, Russian Federation; [2]Endocrinology Research Centre.

Objectives
To study the response of calcium and phosphate homeostasis parameters to the cholecalciferol loading dose in patients with predialysis chronic kidney disease (CKD).
Methods
We examined 17 patients with stage 3 CKD (CKD3) and 9 patients with stages 4–5 CKD (CKD4-5) without previously known disorders of mineral metabolism and intake of interfering drugs during last 3 months. The assessments included serum 25-hydroxyvitamin D (25(OH)D), free 25(OH)D, vitamin D-binding protein (DBP), parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23) and biochemical parameters before and 7 days after oral administration of 150 000 IU cholecalciferol.
Results
The groups did not differ significantly in age, sex, BMI, duration of CKD and baseline laboratory parameters: 25(OH)D 10.3[9.8;24.3] vs. 16.0[8.8;20.7] ng/ml (RI 30–60), albumin-adjusted calcium 2.30[2.29;2.36] vs. 2.27[2.24;2.31] mmol/l (RI 2.15–2.55), phosphorus 1.31[1.09;1.50] vs. 1.49[1.22;1.51] mmol/l (RI 0.74–1.52), PTH 71.9[50.4;115.2] vs. 92.4[78.5;117.3] pg/ml (RI 15–65), magnesium 0.89[0.82;0.97] vs. 0.81[0.79;0.86] mmol/l (RI 0.7–1.05), FGF23 1.20[0.86;2.14] vs. 2.24[1.61;3.30] pmol/l (RI NA), DBP 243[201;256] vs. 256[206;266] mg/l (RI 176–623), free 25(OH)D 4.23[3.84;5.25] vs. 4.91[3.63;5.66] pg/ml (RI 2.4–35) in CKD3 and CKD4-5, respectively ($P > 0.05$). By day 7 we observed an increase in 25(OH)D (32.4[23.5; 42.5] ng/ml, $P < 0.001$) and free 25(OH)D (6.52[5.96; 7.87] pg/ml, $P < 0.001$) and a decrease in PTH (63.4[48.6;79.3] pg/ml, $P = 0.03$) in CKD3 and increase in 25(OH)D (28.6[17.8;29.8] ng/ml, $P = 0.008$), free 25(OH)D (6.77[5.75;7.41] pg/ml, $P = 0.004$), FGF23 (4.86[3.00;5.74] pmol/l, $P = 0.008$) in CKD4-5; the changes in the rest of the parameters were not statistically significant. The levels of PTH and FGF23 by day 7 were higher in CKD4-5 than in CKD3 ($P = 0.045$ and $P = 0.009$, respectively).
Conclusions
A bolus 150 000 IU cholecalciferol treatment results in a decrease in PTH in CKD3 and an increase in FGF23 in CKD4-5, despite an equivalent increase in total and free 25(OH)D. This work was supported by the Russian Science Foundation (grant number 19-15-00243-P).

DOI: 10.1530/endoabs.93.OC56

OC57

Challenging diagnosis and management of tumor induced osteomalacia – A story of alternating bad news and good news

Jelena Jaksic[1], Lukas Libric[2] & Jelena Andric[3]
[1]University of Zagreb, School of Medicine, Zagreb, Croatia; [2]University of Zagreb School of Medicine, Zagreb, Croatia; [3]Dubrava University Hospital, Zagreb, Croatia.

Background
Moderate hypophosphatemia is not an uncommon finding. As usually requiring no specific intervention, it might be neglected and serum phosphate measurements are sometimes skipped. Only 1% of phosphorus is in extracellular fluid so it is not a reliable marker of body phosphorus reserve and refractory chronic hypophosphatemia might be a sign of severe phosphorus depletion.
Case presentation
A fifty-two-year-old male patient presented with a 12-month history of lumbar, thoracal, and inguinal pain with weight loss, progressive severe muscle weakness, impaired gait and he became wheel-chair dependent. After thorough oncological, hematological, and neurological investigation imaging revealed rib fractures, compressive lumbar vertebral fractures, and bilateral femoral neck insufficiency fractures with no confirmation of metastatic tumor disease. He was finally sent for metabolic bone disease consultation and it was immediately noticed that not a single serum phosphate measurement was performed. Moderate hypophosphatemia, low ratio of tubular maximum phosphate reabsorption to glomerular filtration rate, elevated alkaline phosphatase, and elevated fibroblast growth factor-23 (FGF-23) were found. Considering the late age of onset and no family

history, the abnormal secretion of FGF-23 impairing proximal tubule phosphate reabsorption was recognized. The rare diagnosis of tumor induced osteomalacia was presumed. No evident tumor on ^{68}Ga-DOTATE-PET/CT scan was revealed. High phosphorus diet and calcitriol were prescribed. Joulie's solution as the only available phosphate supplement was administered. Patient's clinical condition progressively improved during several months. His mobility recovered and bone pain almost disappeared, but secondary hyperparathyroidism as a limiting factor of conservative therapy developed.

Conclusions

^{68}Ga-DOTATE-PET/CT is planned to be repeated after a year of follow-up. If unsuccessful again, selective FGF23 venous sampling might be tried to localize the responsible tumor. Newly developed treatments aimed to block FGF-23 might also be only temporary measures and every effort should be made toward tumor detection and final cure.

DOI: 10.1530/endoabs.93.OC57

Poster Presentations

Guided Poster Tour 1: Adrenal and Neuroendocrine tumors

P1

Proposition of an histopathological classification of bilateral macronodular adrenal disease (BMAD) and its correlation with ARMC5 and KDM1A mutations

Florian Violon[1], Lucas Bouys[2], Annabel Berthon[3], Ragazzon Bruno[4], Maxime Barrat[5], Benoit Terris[5], Jerome Bertherat[6] & Mathilde Sibony[3]
[1]Cochin Institute, Genomic and Signaling of Neuroendocrine Tumors Team, Inserm U1016, Cnrs Umr8104, Paris, France; [2]Institut Cochin, Faculté de Médecine, 24 Rue du Faubourg Saint Jacques, Paris, France; [3]Institut Cochin, Genomic and Signaling Pathway of Neuroendocrine Tumors, Paris, France; [4]Inserm U1016, Institut Cochin, Cnrs Umr8104, Endocrinology Metabolism Diabetes Department, Paris, France; [5]Institut Cochin, Paris, France; [6]Hospital Cochin, Endocrinology, Cochin Institute, Inserm U1016, Paris, France.

Introduction
Bilateral macronodular adrenal disease (BMAD, former PBMAH) is a rare cause of Cushing's syndrome. The few morphologic descriptions of BMAD mention multinodular hyperplastic adrenal glands composed of clear spongiocytic cells and fewer compact eosinophilic cells without any morphologic variation. The discovery of *ARMC5* and *KDM1A* mutations argues for genetic heterogeneity. The aim of this work was to describe the morphological and immunohistochemical characteristics of a series of BMAD in order to search for heterogeneity and to correlate the results with the genetic profile.
Methods
35 PBMAH patients operated at the Cochin Hospital between 1998 and 2021 whose genetic status was known were reviewed. Immunohistochemistry was performed on DAB2, HSD3B1, HSD3B2, Cyp11B1, Cyp11B2, Cyp17A1, inhibin and KDM1A.
Results
Four morphological subtypes are identified: two with round fibrous septa within macronodules: subtype 1 has a majority of spongiocytic cells and 10–30% of compact eosinophilic cells and subtype 2 has more compact eosinophilic cells (> 30%) Two subtypes have sparse fibrous trabeculae within macronodules: subtype 3 has a majority of clear spongiocytic cells and less than 10% compact eosinophilic cells and subtype 4 has many oncocytic cells (>40%). Their immunohistochemical profile is different. Subtype 1 correlated with *ARMC5* mutations and subtype 2 with *KDM1A* mutations ($P<0.0001$). Diffuse HSD3B2 expression on clear spongiocytic cells correlated with *ARMC5* mutations ($P<0.0001$).
Conclusion
The study of this series suggests four morphological groups. Two of these subtypes are correlated with the presence of germline mutations. This model highlights the heterogeneity of the pathological characteristics of BMAD as well as their link with the genetic characteristics.

DOI: 10.1530/endoabs.93.P1

P2

Assessment of the hypothalamus–pituitary–adrenal axis in patients following adrenalectomy

Sabrina Taylor[1], Hao Gao[2], Kalyan Shekhda[3], Efthimia Karra[3] & Eleni Armeni[4]
[1]University College London, Medical School, London, UK; [2]University College London Medical School, Medical School, London, UK; [3]Royal Free Hospital NHS Foundation Trust, London, UK; [4]Royal Free Hospital NHS Foundation Trust, Endocrinology and Diabetes, London, UK.

Background
Resection of the adrenal gland is a challenging intervention that requires close endocrinological supervision for the correct assessment of hormones to minimise complications peri-operatively (peri-op) and post-operatively (post-op).
Objectives
This study assessed the function of the hypothalamus–pituitary–adrenal axis and the related management according to underlying adrenal disorders.
Methods
We reviewed 163 patients who underwent unilateral adrenalectomy between April 2016 and October 2022. Patients were divided into cohort A (Cushing's disease (CD), adrenocortical carcinoma and adrenal metastasis) and cohort B (Conn's disease, incidentaloma, and phaeochromocytoma (PCC)). We audited the pre-operative (pre-op) and post-op assessments, including the peri-op steroid plan.
Results
Cohort A vs B was more frequently investigated with pre-op urine cortisol (20.8% vs 12.1%) and overnight dexamethasone suppression test (ODST) (25.0% vs 6.9%). Cohort A vs B had more frequently documented peri-op steroid plans (41.7% vs 29.3%) and more frequently required post-op steroid treatment (62.5% vs 17.2%). Post-op ODST and Short Synacthen Test (SST) was done more frequently for cohort A vs B (ODST 29.2% vs 13.8%, SST 4.2% vs 0.0%). Within cohort A, CD patients vs endocrine cancers had more frequenlty documented peri-op steroid plans (55.6% vs 33.3%) and more frequently required post-op steroid treatment (88.9% vs 46.7%). Post-op OSDT was only done in CD patients (ODST 77.8%, SST 11.1%). Within cohort B, peri-op steroid plans were implemented more frequently for Conn's patients, followed by incidentaloma patients and PCC patients. Post-op ODST was performed only in incidentaloma (17.2%) and PCC cases (13.6%).
Conclusion
A uniform protocol is recommended for the hormonal assessment of patients who are planned for unilateral adrenalectomy in order to minimise the risk of post-op cortisol deficiency and/or life-threatening adrenal crisis.

DOI: 10.1530/endoabs.93.P2

P3

MEN 2 syndrome heterogeneity in a cohort of Romanian patients

Tiberiu Manole[1], Ionela Baciu[1], Simona Galoiu[1], Nicoleta Baculescu[1], Dan Niculescu[1], Serban Radian[1], Andrei Muresan[2], Elena Braha[3] & Catalina Poiana[1]
[1]C I Parhon National Institute of Endocrinology, Bucharest, Romania, Pituitary and Neuroendocrine Pathology, Bucharest, Romania; [2]C I Parhon National Institute of Endocrinology, Bucharest, Romania, Clinical Research Laboratory, Bucharest, Romania; [3]C I Parhon National Institute of Endocrinology, Bucharest, Romania, Medical Genetics Department, Bucharest, Romania.

Background
Multiple endocrine neoplasms (MEN) are a rare hereditary syndrome, caused by an autosomal dominant mutation due to germline mutation in the rearranged during transfection (RET) proto-oncogene. According to the new WHO guidelines, MEN type 2 (formerly known as MEN 2A) is characterised by medullary thyroid cancer (MTC), paragangliomas, primary hyperparathyroidism (PHP) and cutaneous lichen amyloidosis.
Objectives
To present the clinical and paraclinical heterogeneity, treatment options and post-surgical complications in a cohort of Romanian patients with MEN 2 syndrome.
Methods
A retrospective non-interventional clinical study analysing data from patients evaluated in a tertiary centre diagnosed with a RET gene mutation or who were already diagnosed and came to follow-ups in the 2017–2022 period.
Results
We analysed data from 23 patients (average age at diagnosis of 42.8 years), with one patient diagnosed at birth through active screening, while the oldest patient was 74 years. 4 patients had a de novo mutation, while 19 had a positive familial history (15 separate families) and were diagnosed through active screening. 21 patients were diagnosed with MTC, 10 had adrenal paragangliomas, out of which 8 had bilateral disease (3 at the time of diagnosis and 5 at follow-ups) and 1 patient had PHP. 19 had as a first diagnosis MTC, 3 had paragangliomas and 1 had all 3 diseases synchronously. 9 of the patients with CMT had a persistent disease with a calcitonin doubling time of 91.4 months and 2 had a recurrence of the disease after 5 years. Out of the thyroidectomised patients, 18 had metastatic disease, while 2 patients refused the surgery, even though they had the genetic diagnosis.
Conclusions
MEN 2 syndrome requires surveillance for the development of each disease and treatment when needed, as well as active screening of the patients' first grade relatives for the genetic mutation and prompt intervention.

DOI: 10.1530/endoabs.93.P3

P4

Decrease in anticortisolic drug osilodrostat plasma exposure in patients treated with mitotane for an adrenocortical carcinoma

Louis Thomeret[1], Alicja Puszkiel[2], David Balakirouchenane[2], Lucas Bouys[3], Jonathan Poirier[4], Annabel Berthon[1], Bruno Ragazzon[1], Anne Jouinot[1], Laurence Guignat[4], Laura Bessiene[4], Rossella Libe[4],

Leopoldine Bricaire[4], Lionel Groussin[3], Guillaume Assie[3], Benoit Blanchet[2], Fideline Bonnet-Serrano[5] & Jerome Bertherat[3]
[1]Institut Cochin, Team 'Genomic and Signaling of Endocrine Tumors', Inserm U1016-Cnrs Umr8104, Paris, France; [2]Department of Pharmacokinetics and Pharmacochemistry, Cochin Hospital, Ap-Hp, Paris, France; [3]Endocrinology Department, Reference Center for Rare Adrenal Disorders, Cochin Hospital, Ap-Hp, Institut Cochin, Team 'Genomic and Signaling of Endocrine Tumors', Inserm U1016-Cnrs Umr8104, Paris, France; [4]Endocrinology Department, Reference Center for Rare Adrenal Disorders, Cochin Hospital, Ap-Hp, Paris, France; [5]Hormonology Department, Cochin Hospital, Ap-Hp, Institut Cochin, Team 'Genomic and Signaling of Endocrine Tumors', Inserm U1016-Cnrs Umr8104, Paris, France.

Introduction
The steroidogenesis inhibitor osilodrostat (OSI), indicated for the medical treatment of endogenous Cushing's syndrome, exhibits significant interindividual variability regarding the response to treatment (Pivonello *et al*. 2020). Plasma exposure may contribute to this variability. Our objective was to investigate the effect of concomitant use of mitotane (MIT), a potent inducer of CYP450 (3A4), on circulating OSI concentrations in patients treated for an adrenocortical carcinoma (ACC).
Methods
Plasma OSI concentrations were determined every 4 hours over 24 hours (sampling at 8 h, 12 h, 16 h, 20 h, 24 h and 4 h) by LC–MS/MS (Balakirouchenane *et al*. 2023) in 27 patients (19 with Cushing's disease, 4 with ectopic adrenocorticotropic secretion, 3 with macronodular bilateral adrenal hyperplasia and 1 with ACC) treated with OSI as a monotherapy ('OSI' group, 33 cycles), and in 3 patients treated with OSI in association with MIT ('OSI-MIT' group, 8 cycles) for ACC. OSI was administered twice daily. Daily doses of OSI and plasma levels of MIT were expressed as median (min-max). The area under the OSI concentration curve (AUC-OSI) was used as pharmacokinetic endpoint.
Results
The AUC-OSI was well correlated with the daily dose of osilodrostat in both the 'OSI' group (Spearman $r=0.83462$; OSI 10 mg/day (2–40)) and the 'OSI-MIT' group with plasma MIT level $>$ 10 mg/l (Spearman $r=0.9487$; OSI 50 mg/day (20–60); plasma MIT level 19.1 mg/l (13.5–26.6)). Normalized to the daily dose, the AUC-OSI was statistically decreased in the 'OSI-MIT' group compared to the 'OSI' group (medians: 14.10 vs 27.10 ng/ml.h; $P<0.001$), as well as the residual concentration ($P=0.003$). In a single patient, higher plasma MIT level seemed associated with higher reduction in OSI plasma exposure.
Discussion
Mitotane significantly decreases plasma exposure to osilodrostat in patients treated for a cortisol-secreting ACC. Monitoring plasma levels of osilodrostat could thus be particularly useful for therapeutic adaptation in these patients.

DOI: 10.1530/endoabs.93.P4

P5

An overview of adrenal vein sampling for primary aldosteronism in Croatia (2016–2023)

Ivan Lekić[1], Karin Zibar Tomšić[2], Ana Marija Alduk[3] & Darko Kaštelan[4]
[1]Health Center Zagreb Centar, General Practice, Zagreb, Croatia; [2]University Hospital Centre Zagreb, Clinic for Internal Medicine, Department of Endocrinology, Zagreb, Croatia; [3]University Hospital Center Zagreb, Department of Radiology, Zagreb, Croatia; [4]University Hospital Center Zagreb, Clinic for Internal Medicine, Department of Endocrinology, Zagreb, Croatia.

Background
Although adrenal vein sampling (AVS) is a technically demanding procedure, it is still considered the gold standard for subtyping primary aldosteronism (PA). The aim of the study was to analyze the success rate of AVS in patients with PA.
Methods
In all patients AVS was performed sequentially during continuous stimulation with adrenocorticotrophic hormone by one interventional radiologist. Adrenal vein cannulation was considered successful if the selectivity ratio was $\geq$5:1.
Results
Over the 7-year period, 179 procedures were performed in 166 patients (101 men; age 44–60, median 52 years). In the first two years (2016–2017) 30 AVS procedures were performed (group 1) with the success rate of 60% (18/30) whereas in the period from 2018 to 2020 (group 2) and from 2021 to May 2023 (group 3), the success rate of AVS procedures was 79% (57/72 and 61/77), ($P=0.019$, $\chi2=21.294$). Out of 43 unsuccessful AVS, cannulation of the right and left adrenal veins failed in 31 and 7 cases, respectively, whereas in five patients catheterization failed on both sides. In 13 patients, AVS was repeated after an unsuccessful first procedure, and the success rate of the second AVS was 85% (group 1 50%; group 2 87%; group 3 100%).
Conclusion
The AVS success rate has increased over time from an initial 60% to 79% at the end of the observed period. In selected cases, repeated AVS might be justified after an unsuccessful first procedure.

DOI: 10.1530/endoabs.93.P5

P6

New possible pathogenic variants involved in pheochromocytomas and paragangliomas

Sofia Maria Lider Burciulescu[1], Monica Livia Gheorghiu[2], Attila Patocs[3], Elena Emanuela Braha[4] & Corin Badiu[5]
[1]National Institute of Endocrinology CI Parhon, Thyroid II, Bucharest, Romania; [2]Parhon National Inst Endocrinology, C Davila Univ Medicine and Pharmacy, C Davila Univ Medicine and Pharmacy, Bucharest, Romania; [3]Clinical Genetics and Endocrinology Laboratory, Semmelweis University National Institute of Oncology, 1122, Budapest, Hungary, Department of Laboratory Medicine and Department of Molecular Genetics, Hungary; [4]'Institutul National de Endocrinologie CI Parhon', National Institute of Endocrinology CI Parhon, Genetics, Bucuresti, Romania; [5]National Institute of Endocrinology, 'C.Davila' University of Medicine, Carol Davila University of Medicine, Bucharest, Romania.

New possible pathogenic variants involved in pheochromocytomas and paragangliomas
Introduction
Pheochromocytomas and paragangliomas (PPGLs) are rare tumors of the chromaffin tissues that store and release catecholamines in excess. Most pheochromocytomas are sporadic, usually resulting in unilateral adrenal tumor, but 25–45% harbour a germline mutation.
Aim
To describe new possible pathogenic variants (VUS) involved in PPGLs.
Material and methods
From a cohort of 125 patients with PPGLs we prospectively performed genetic test of 80 patients. More than a half of those tested patients 59.4% ($n=47$) had a mutation (*20 RET, 3 VHL, 1 SDHB, 1 NF1, 1 SDHD, 1 FANCA, 1 CASR, 19 VUS*). From those 19 patients with VUS, 4 had less than 40 years old at the time of diagnosis. One patient (*MSH 6 c.1474A>G*) associated PHEO with pulmonary adenocarcinoma. One patient (*BRIP 1 c.728T>C*) had malignant PHEO, with an aggressive pattern and family history of colonic cancer. One patient had clinical phenotype of neurofibromatosis. She had 35 years at diagnosis, and her son has clinical features of neurofibromatosis. In her case, we identified somatic mutation of NF1 (*c.7966del*), and germline VUS of *MSH2+ATM c.1134_1136delAGA+c.1444A>C*. One patient (*MEN1 c.526G>T*) associated PHEO and familial hypocalciuric hypercalcemia, and 2 other had PHEO and idiopathic hypercalcemia (*RB2 c.644C>T*) respectively primary hyperparathyroidism (*ATM c.5639C>T*). Another patient, with PHEO, papillary thyroid carcinoma and colonic polyps, had a VUS of *BARD1* (*c.1333G>A*).
Conclusion
In the presence of clear heritability and other syndromic tumors, we can suppose that a VUS is probably a pathogenic variant. Further clinical and molecular evaluation of VUS carriers should corroborate our results with others from the literature. When the clinical aspects and heritability are suggestive for a pathogenic variant, a functional assessment would help us to classify VUS as pathogenic variants related to PHEOs.

DOI: 10.1530/endoabs.93.P6

P7

Identification and characterization of biologically active small molecules against primary aldosteronism driver mutations

Sanas Mir-Bashiri[1], Martin Reincke[2] & Tracy Williams[1]
[1]Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Campus Innenstadt, München, Germany; [2]Ludwig-Maximilians-University, Medizinische Klinik IV, Endocrine Research Unit, München, Germany.

Primary aldosteronism (PA) is a form of endocrine hypertension characterized by autonomous aldosterone secretion. Aldosterone-producing adenomas (APAs) are a significant cause of unilateral PA, where aldosterone overproduction is driven by a somatic mutation in an ion pump or channel. Multiple studies have shown that mutations in the *KCNJ5* gene are the most prevalent in PA patients suffering

from the unilateral subtype, and unilateral laparoscopic total adrenalectomy is currently the preferred treatment strategy for these patients. Pharmacological intervention targeting mutated KCNJ5 channels could provide an alternative therapy for unilateral PA. Previous studies suggest that macrolides are potent inhibitors of mutated KCNJ5 channels. Nevertheless, for the treatment of PA patients, the potential induction of pathogen resistance through antibiotic treatment or increased gastrointestinal side effects through motilide activity would not be desirable (Scholl *et al*., 2017). We hypothesize that APAs carrying mutated KCNJ5 channels can be specifically targeted both via pharmacological channel inhibition as well as through pharmacological ablation of mutated cells. Therefore, we designed a study to identify small molecule compounds potentially applicable for the personalized treatment of a subset of PA patients. *In silico* screenings of over six million compounds detected small molecules structurally similar to the KCNJ5 channel pore, which were tested for their agonist and antagonist performance through different *in vitro* assays. The most promising antagonist candidates are currently being characterized to assess their effect on *CYP11B2* expression and aldosterone levels. In contrast, agonist candidates are being further investigated for potential toxicity effects. A successful therapeutic outcome using a targeted pharmacological strategy could potentially replace surgical intervention.

DOI: 10.1530/endoabs.93.P7

P8

Remission rate of primary aldosteronism after unilateral adrenalectomy

Mirjana Đukić[1], Karin Zibar Tomšić[2], Nikola Knežević[3] & Darko Kaštelan[4]
[1]General Hospital Sisak, Department of Endocrinology, Sisak, Croatia; [2]University Hospital Centre Zagreb, Department of Endocrinology, Zagreb, Croatia; [3]University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Department of Urology, Zagreb, Croatia; [4]University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Department of Endocrinology, Zagreb, Croatia.

Background
The existing consensus for patients with primary aldosteronism (PA) after unilateral adrenalectomy recommends annual follow-up to rule out persistence or recurrence of the disease.
Objectives
The aim of the study was to assess the remission rate in patients with PA ≥ 1 year after adrenalectomy.
Methods
Of the 41 patients who underwent adrenalectomy for PA between 2016 and 2021, 24 had available follow-up data and were included in the study. To diagnose unilateral disease we used lateralization index ≥ 4 or contralateral suppression index ≤ 0.37. Biochemical and clinical remission of PA was defined according to PASO criteria.
Results
The median age of participants was 50 years (IR 42–56), 50% were women. The median follow-up time after surgery was 5 years (IR 3–5). Aldosterone concentration before and after surgery was 998 pmol/l (IR 583–1284) and 240 pmol/l (IR 194–369), $P < 0.001$. Plasma renin activity before surgery was 0.15 μg/l per hour (IR 0.1–0.38) whereas after surgery it was 1.5 μg/l per hour (IR 0.9–5.7), $P < 0.001$. Finaly, median potassium level after surgery was significantly higher compared to the level before surgery (4.3 mmol/l *vs* 2.9 mmol/l; $P < 0.001$). At the time of data collection, 92% of patients were in complete biochemical remission, whereas 8% were in partial biochemical remission. Regarding clinical remission, the respective rates of patients who were in complete and partial remission were 54% and 38%. Only 8% of patients did not achieve clinical remission of the disease after unilateral adrenalectomy. Both patients who were in partial biochemical remission achieved complete clinical remission.
Conclusion
Our results showed that with a lateralization index ≥ 4 or contralateral suppression index ≤ 0.37, long-term, complete or partial, biochemical remission of PA was achieved in all patients after unilateral adrenalectomy. Furthermore, long-term, complete or partical, clinical remission, was achieved in 92% patients.

DOI: 10.1530/endoabs.93.P8

P9

A rare case of bilateral micronodular adrenal cortical disease

Ozge Ozer[1], Goknur Yorulmaz[2] & Medine Nur Kebapci[2]
[1]Eskisehir Osmangazi University, Endocrinology and Metabolism, Eskisehir, Turkey; [2]Eskisehir Osmangazi University, Department of Endocrinology and Metabolism, Turkey.

Background
Bilateral micronodular adrenal cortical disease (miBACD) is a rare and difficult-to-manage disease. miBACD is one of the causes of Cushing's syndrome. miBACD is divided into primary pigmented nodular adrenocortical disease (PPNAD) and isolated micronodular adrenocortical disease. Its more common presentation is familial PPNAD, as part of Carney syndrome. We also presented a rare case of miBACD.
Case presentation
A 20-year-old female patient presents to the emergency department with left flank pain and 140/100 mmHg blood pressure. On physical examination, there were purple striae in the abdomen. In the computed tomography scan, an increase in the size of both surreal glands, and a few nodular appearances, in both surreal glands. Cortisol was 28.43 μg/dl, ACTH (adrenocorticotropic hormone) was <10 pg/mI, while other functional screening tests were normal. As a result of suppression tests and 24-hour urine cortisol tests, she was evaluated as having ACTH-independent hypercortisolism. Bone mineral densitometry (BMD) was osteoporotic. She had a left adrenalectomy operation, and the pathology presented as a pigmented nodular adrenocortical disease. Before the operation, the presence of Carney complex and especially cardiac myxomas, was ruled out. In the fifth month after the operation, ketoconazole treatment was started because of the suppression tests. Seven years after the first operation, she complained of severe abdominal pain again. The operation of the other surreal gland was performed and was also operated, and the pathology was the same. She was followed up with hydrocortisone and fludrocortisone replacements.
Conclusions
miBACD is a rare and challenging disease. Management of the disease is critical in multidisciplinary centers. Bilateral adrenalectomy is generally the treatment of choice in patients with overt CS and miBACD, but unilateral adrenalectomy may be considered in cases with asymmetric disease and mild hypercortisolism.

DOI: 10.1530/endoabs.93.P9

P10

The fibroblast growth factor-23/Klotho axis in patients with acromegaly

Jowita Halupczok-Żyła[1], Aleksandra Jawiarczyk-Przybyłowska[2], Agnieszka Zembska[2], Natalia Słoka[2] & Marek Bolanowski[3]
[1]Wroclaw Medical University, Department of Endocrinology, Diabetes and Isotope Therapy, Wrocław, Poland; [2]Department of Endocrinology, Diabetes and Isotope Therapy, Wroclaw Medical University, Poland; [3]Wroclaw Medical University, Department of Endocrinology, Diabetes and Isotope Therapy, Wroclaw, Poland.

Background
Acromegaly is a rare disease, mostly caused by a GH (growth hormone)-secreting pituitary adenoma. The pathomechanism of bone complications remains not fully explored. The fibroblast growth factor-23 (FGF-23)/Klotho axis regulates phosphate and vitamin D metabolism.
Objectives
The study aimed primarily at evaluating FGF-23 and Klotho concentrations with regard to acromegaly activity. The secondary goal was to identify associations between FGF-23/Klotho axis and GH, IGF-1, calcium and phosphate metabolism parameters, and bone mineral density (BMD) measurements.
Methods
The study group comprised 67 patients with acromegaly and 50 controls (CG). Based on clinical presentation and hormonal evaluation (GH and IGF-1 concentrations) acromegaly group was divided into three subgroups: active acromegaly (AA); controlled disease (CD), and cured acromegaly (CA). We measured concentrations of the hormones and biochemical parameters. The lumbar spine (LS) and femoral neck (FN) BMD were assessed using dual-energy X-ray absorptiometry.
Results
The highest Klotho levels were found in the AA group and the lowest in the CG group ($P=0.008$). There were no statistically significant differences in FGF-23 concentrations among the subgroups of patients, despite of used classification. Similarly, we did not observe significant differences in age, sex, BMI, calcium, inorganic phosphate, alkaline phosphatase, 25(OH)D, creatinine, and BMD measurements. The patients with controlled disease had significantly higher PTH levels than in the AA and the CG group ($P=0.011$; $P=0.001$, respectively). FGF-23 correlated positively with alkaline phosphatase in the AA group ($r=0.692$, $P=0.039$) and with inorganic phosphate and age in the CA group ($r=0.704$, $P<0.001$; $r=0.670$, $P<0.001$; respectively). There was also a positive correlation between Klotho and IGF-1 in the AA group ($r=0.733$, $P=0.025$). Negative correlations between Klotho and LS *T*-score, LS BMD were observed in the CA group ($r=-0.639$, $P=0.034$; $r=-0.745$, $P=0.009$; respectively).

Conclusions
The FGF-23/Klotho system seems not to play a crucial role in bone metabolism in acromegaly patients.

DOI: 10.1530/endoabs.93.P10

Guided Poster Tour 2: Miscellaneous

P11

Postpartum osteoporosis: A case report

Deniz Türküm Atikcan Şimşek[1] & Özlem Turhan Iyidir[2]
[1]Başkent University Division of Endocrinology and Metabolism, Endocrinology and Metabolism, Ankara, Turkey; [2]Başkent University Division of Endocrinology and Metabolism, Turkey.

Background
Pregnancy and lactation-related osteoporosis can be associated with fractures during the last trimester or early postpartum period. During lactation, a 3–10% bone loss in the lumbar vertebrae has been detected within 3–6 months. When lactation is reduced bone mineral density(BMD) values reach early postpartum levels within 6–18 months. Certain comorbidities, such as hypercalciuria, premature ovarian failure, low body mass index, oligoamenorrhea, severe vitamin D deficiency, low calcium intake, glucocorticoids can trigger fractures. Compression fractures are typically observed in the lower thoracic and lumbar vertebrae. It's generally self-limiting, but in some cases should be treated.
Case presentation
A 35-year-old woman experienced severe lower back pain in 2018 during the eighth month of her pregnancy. In February 2018, she underwent a C-section delivery and was diagnosed with osteoporosis while being examined for her persistent pain. The patient does not have any known additional medical conditions. The calcium level is 9.6 mg/dl, 25-hydroxyvitamin D is 6 ng/ml, parathyroid hormone is 48.5 pg/ml. In March 2018, BMD showed a *Z*-score of −2.6 for lumbar vertebrae and −2.5 for total femur. Due to multiple lumbar vertebral fractures, she underwent a kyphoplasty. Vitamin D3 is given 15.000 international unit per week. Lactation period was almost a year. The control BMD in 2022 showed a *Z*-score of −1.5 for lumbar vertebrae and −1.9 total femur. With the treatment and cessation of lactation, her bone mineral density improved.
Conclusion
Postpartum osteoporosis is a rare condition that affects otherwise healthy women during the postpartum period. The etiology remains poorly understood, but hormonal changes, particularly the abrupt decline in estrogen levels following childbirth, are believed to play a significant role. This case report highlights the importance of considering postpartum osteoporosis in the differential diagnosis of young women presenting with bone pain and fractures shortly after childbirth.

DOI: 10.1530/endoabs.93.P11

P12

Severe osteoporosis in a 21-year-old female with primary hyperparathyroidism and multiple additional risk factors

Maria Mathiopoulou[1] & Jan Krützfeldt[2]
[1]University Hospital of Zurich, Endocrinology, Zürich, Switzerland; [2]University Hospital of Zurich, Zurich, Switzerland.

Osteoporosis is a skeletal condition of low bone mass and increased risk of fractures and occurs most commonly in postmenopausal women. Severe osteoporosis is characterised by the presence of fragility fractures and high mortality and morbidity. We present the case of a 21-year-old female with primary hyperparathyroidism (pHP) who, despite her young age, surprisingly presented with severe osteoporosis. The 21-year-old female was hospitalised due to a recurrent flare of Still's disease initially diagnosed 2 years earlier and for which she had received continuous steroid treatment. During hospitalisation increased calcium levels up to 3.12 mmol/l were noted and a diagnosis of pHP was made: PTH was elevated (107 ng/l) and fractional calcium excretion rate 4.4%. As part of the pre-surgery work-up severe osteoporosis was diagnosed (*T*-Score of −4.5 in the lower spin and numerous atraumatic fractures Th7-12, L1-5). The patient was bedridden for several weeks due to severe pain due to inflamed joints and fractures. A parathyroid adenoma was successfully removed and calcium and PTH levels normalised, but 3 months later the patient suffered a new Th5 fracture and a therapy with denosumab was initiated. In search for additional risk factors for severe osteoporosis we could identify besides the glucocorticoid treatment, severe vitamin-D-deficiency and a history of secondary amenorrhea for 18 months with spontaneous normalisation and currently normal gonadotropin levels. There were no signs of juvenile osteoporosis and the patient had reached the expected height.
Severe osteoporosis is uncommon in premenopausal patients with primary hyperparathyroidism but can occur when multiple risk factors accumulate. Careful evaluation for risk factors of increased fracture risk should be undertaken even in young pHP patients. Little evidence is available for when to best start anabolic bone treatment post-surgery in such patients.

DOI: 10.1530/endoabs.93.P12

P13

Analysis of membrane fluidity in patients with vascular diabetic foot

Gaetano Emanuele Rizzo[1], Giada Bianchetti[2], Linda Tartaglione[3], Alessandro Rizzi[3], Giuseppe Maulucci[2] & Dario Pitocco[4]
[1]Diabetes Care Unit, Fondazione Policlinico Universitario A. Gemelli Ircss, Università Cattolica del Sacro Cuore, 00168, Rome, Italy, Endocrinologia e Diabetologia, Rome, Italy; [2]Department of Neuroscience, Biophysics Section, Università Cattolica del Sacro Cuore, 00168 Rome, Italy, Italy; [3]Diabetes Care Unit, Fondazione Policlinico Universitario A. Gemelli Ircss, Università Cattolica del Sacro Cuore, 00168, Rome, Italy, Italy; [4]Università Cattolica del Sacro Cuore, Diabetes Care Unit, Fondazione Policlinico Universitario A. Gemelli Ircss, Università Cattolica del Sacro Cuore, 00168, Rome, Italy, Diabetes Care Unit, Fondazione Policlinico Universitario A. Gemelli Ircss, Università Cattolica del Sacro Cuore, 00168, Rome, Italy, Roma, Italy.

Background
red blood cells (RBC) membrane fluidity in patients with type 2 diabetes mellitus (T2DM) can be influenced by various factors like oxidative stress, aging, glycosylation, lipid homeostasis and exposure to nutrients.
Objective
To analyze RBC membrane fluidity in patients with long-duration T2DM (more than 10 years), looking for any differences between patients without and with macroangiopathy (vascular diabetic foot).
Methods
27 patients with long-lasting T2DM, 15 affected by vascular diabetic foot (DF group) and 12 without complications (DM group), and 10 healthy subjects have been enrolled. We have used confocal microscopy to analyze images of RBC labeled by Laurdan, a fluorescent probe which varies its fluorescence emission based on membrane polarity (490 nm for the fluid-crystalline state and 440 nm for the gel-like). Membrane fluidity has been measured as GP index, 'generalized polarization', (GP = (I440 nm – I490 nm) / (I440 nm + I490 nm)), with values between −1 and +1, where GP values tending to −1 are indicative of higher membrane fluidity.
Results
DM and DF have been resulted comparable for age, body mass index, disease duration, glycated haemoglobin, total cholesterol, HDL, LDL and triglycerides. GP index has been significantly lower in DF (mean GP 0.501, s.d. 0.026) than in DM (mean GP 0.519, s.d. 0.007) (*P*-value 0.04), with a higher value in healthy subjects (mean GP 0.534, s.d. 0.018) compared both to DM (*P*-value 0.03) and to DF (*P*-value 0.008).
Conclusions
RBC membrane has been resulted more fluid in diabetic patients with macroangiopathy than in patients without complications, despite a similar duration of disease. Variations in membrane fluidity may underlie the development of macrovascular complications due to possible alterations in gas exchange and in the expression of membrane receptors; membrane fluidity analysis could be useful in to the future to identify patients at risk of developing chronic complications of diabetes.

DOI: 10.1530/endoabs.93.P13

P14

Assessment of knowledge and awareness of disease in patients with diabetes

Luka Vasiljevic[1] & Rada Sparavalo[2]
[1]General Hospital Nikšić, Montenegro, Internal Medicine, Nikšić, Montenegro; [2]Jzu Goverment Hospital, General Hospital, Nikšić, Montenegro, Endocrinology, Niksic, Montenegro.

Introduction and objective
The research was conducted with the aim of highlighting the awareness and understanding of the disease among diabetic patients.

Methods
The study included 85 patients with type 2 diabetes, aged 40+ years old, who had been monitoring their blood glucose levels and HbA1c levels in the previous 4 months. Patients were presented a questionnaire with 5 questions about diabetes. The patients' responses were classified and expressed in percentages.
Results
The questions and answers were as follows: 1) What is diabetes? 26% – lack of insulin / obesity, 74% – incorrect / no response; 2) What causes diabetes? 23% – pancreas, 15% – kidney, 7% – liver, 44% – don't know, 11% – other organs; 3) What is the optimal value of fasting and postprandial blood glucose? 47% – correct or acceptable answer, 53% – incorrect answer / don't know; 4) What happens if diabetes is not treated properly or effectively? 58% – eye or kidney disorder, 40% – insignificant response, 2% – don't know; 5) What is insulin? 62% – medicine / hormone, 37% – injection, 1% – don't know. The majority of patients have had diabetes for 5 years or longer and have comorbidities. 48% of patients are on oral medications, 7% on GLP-1 analogs in combination with OAD, 8% receive GLP-1 analogs, 16% are on insulin therapy, and 21% are on oral medications in addition to insulin therapy. HbA1c levels (%) are ≤ 7 in 32% of patients, 7 – 9 in 44%, and ≥ 9 in 24%. Despite mostly having high HbA1c levels, a small percentage are on insulin therapy.
Conclusion
Patient education aimed at developing a positive attitude towards the disease, understanding the disease, providing motivation, and encouragement to keep the disease under control is essential for the management of diabetic patients.
DOI: 10.1530/endoabs.93.P14

P15

Metformin effect on retinal epithelial cells under different concentrations of glucose
Elsa Villa-Fernandez[1], Ana Victoria García Gómez[2], Miguel García Villarino[3], Alejandra Fernández-Fernández[4], Carmen Lambert Goitia[5] & Elias Delgado[6]
[1]Health Research Institute of the Principality of Asturias (Ispa), Endocrinology, Nutrition, Diabetes and Obesity Group (Endo), Oviedo, Asturias, Spain; [2]Health Research Institute of the Principality of Asturias (Ispa), Oviedo, Asturias, Spain., Instituto de Investigación Sanitaria del Principado de Asturias (Ispa), Endocrinology, Nutrition, Diabetes, Obesity Investigation Group, Oviedo,Asturias, Spain; [3]Endocrinology, Nutrition, Diabetes and Obesity Group (Endo), Health Research Institute of the Principality of Asturias (Ispa), Instituto de Investigación Sanitaria del Principado de Asturias (Ispa), Endocrinology, Nutrition, Diabetes, Obesity Investigation Group, Oviedo,Asturias, Spain; [4]Hospital Universitario Central de Asturias (Huca), Biochemistry, Oviedo, Asturias, Spain; [5]Endocrinology, Nutrition, Diabetes and Obesity Group (Endo), Health Research Institute of the Principality of Asturias (Ispa), Health Research Institute of the Principality of Asturias (Ispa), Endocrinology, Nutrition, Diabetes, Obesity Group (Endo), Oviedo,Asturias, Spain; [6]Health Research Institute of the Principality of Asturias (Ispa), Oviedo, Asturias, Spain, Asturias Central University Hospital. Oviedo, Asturias, Spain, Endocrinology in Hospital Universitario Central de Asturias (Huca), Oviedo, Spain.

Background
Metformin is one of the first line drugs used to treat type 2 diabetes mellitus, even though there are still many gaps on how exactly metformin works. This is due to many years of research using various concentrations of metformin and also, not considering the conditional effect that glucose can have in its action.
Objectives
Study the effect of different concentrations of metformin and glucose in cell culture.
Methods
a commercial cell line (hTERT RPE-1) was cultured under two different conditions of glucose (high-4.5 g/l or low-1 g/l) and under different concentrations of metformin.
Results
the concentration of glucose affects directly to cell proliferation, being higher in the cells exposed to high glucose. Considering metformin concentration, it could be observed that under suprapharmacological conditions (1 M) cells showed a complete cell dead under both conditions of glucose at 12 h; however, when the suprapharmacological concentrations were lower (10 mM), the cell dead could only be seen at 48 h and under the low glucose condition. When pharmacological concentrations (50 μM) were used, even though there was a decrease in cell viability, cells didn't show major signs of dead after 15 days of growth. This same tendency was observed when analysing cell culture supernatant, where glucose levels of 10 mM treatment were almost none after 48 h in the low glucose condition, while for the 50 μM treatment, the levels were very close to control cell culture.
Conclusions
it is important to consider glucose concentration as well as metformin concentration when analysing the effect of this drug.
DOI: 10.1530/endoabs.93.P15

P16

If not soon, at least not late (two cases report of Lada)
Enalda Demaj[1], Marjeta Kermaj[2] & Ilirjan Komini[3]
[1]Hospital of Berat, Albania; [2]Mother Theresa Hospital of Tirana, Albania; [3]Clinic Center Dimal, Albania.

Latent autoimmune diabetes of adulthood (LADA) is the most common form of autoimmune Diabetes diagnosed in Adults. Approximately 5–12%of cases in Europeans with apparent type2Diabetes are in facts misdiagnosed LADA. This is a heterogeneous condition that presents with clinical and laboratory manifestations common to type1diabetes and type2 diabetes. Its main feature is the presence of diabetes-associated autoantibodies (mostly autoantibody against glutamicaciddecarboxylase), which leads to progressive destruction of the Langerhans'islets. The Immunology of Diabetes Society (IDS) has established three main criteria, including (1) adult age of onset (>30 years) (2) presence of at least one islet-cell autoantibody (3) absence of insulin requirement for at least six months after diagnosis, to Diagnose LADA.
Introduction
We report two cases of a57-Yo woman and a 40-YO man, initially diagnosed with D.M.T2.
Case 1
The woman was poorly controlled for2Years with oral antidiabetic therapy, and worsening in the third year. She had a negative family history of type 2 diabetes and no autoimmune disease. Her body mass index was 23 kg/m^2 and glycated hemoglobin was 15.8%. The laboratory tests were normal. Screening for diabetic retinopathy revealed Non Proliferative Diabetic Retinopathy Laboratory workup revealed positive glutamic acid decarboxylase (anti Gad) and anti Tyrosine Phosphatase (anti IA2) antibodies, and LADA diagnosis was confirmed. A therapeutic regimen with Insulin was Initiated, and at follow-up3 mo later HBA1c improved to 8.4%. HerC-peptide was not measured. The second case, had a negative family history of type 2 diabetes and autoimmune disease. Body mass index 22 kg/m2 and glycated hemoglobin 9.8%. His physical examination and general lab test were unremarcable. Only positive anti Gad was found. He was keept on Diet and physical activity. After a 8 mo His HBa1c 6.9%, C-peptide was normal.
Conclusions
These cases highlights
*The importance of being aware of Lada and implemention of screening diagnostictest
*An early diagnosis are crucial for better glycemic control, to delaying disease progression and complications.
*Immunologic markers hint to autoimmune involvement and is also a key factor for diagnosis.
*The titer and number of autoantibodies may indicate progression of LADA and Complications
*Identifying LADA patients early and initiating insulin therapy helps preserve beta cell function.
*Measure of C-peptide helps in LADA management
DOI: 10.1530/endoabs.93.P16

P17

Alcohol induced ketoacidosis with hyperglycaemia: A case report
Suleyman Sami Guzel[1] & Aikaterini Theodoraki[2]
[1]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Internal Medicine, Istanbul, Turkey; [2]Chelsea and Westminster Hospital, Beta Cell Diabetes Department, London, UK.

Background
Diabetes is the commonest cause of ketoacidosis, with alcoholic and starvation ketoacidosis encountered less frequently. We present a case of high anion gap metabolic acidosis whose features were not categorigal for usual causes.
Case presentation
A 42-year-old female patient was admitted with a 3 day history of nausea, vomiting and abdominal pain, that begun 1 day after binge alcohol intake, on the

background of alcohol excess. AKI, transaminitis and high anion gap metabolic acidosis were noted: lactate 7.6 mmol/l, pH 7.08, venous glucose 18.1 mmol/l, on urinalysis glucose 1+, ketones 4+, blood ketones 6.7 mmol/l. Amylase was mildly elevated and liver imaging showed hepatosteatosis. Due to the triad of a metabolic acidosis with hyperglycaemia and ketonaemia, a new diagnosis of insulinopenic diabetes was considered with a differential of alcoholic ketoacidosis and chronic pancreatitis, and the patient was treated with the DKA protocol followed by initiation of basal bolus insulin. AntiGAD and IA2 antibodies were negative, C-peptide 1971 pmol/l with paired venous glucose 8.7 mmol/l and HbA1c 27 mmol/mol. The patient self-discharged and didn't attend of outpatient reviews in the diabetes clinic. 10 months later she presented with a 3 day history of epigastric pain and vomiting, and reported having discontinued all insulin a week prior. On presentation a metabolic acidosis was noted with glucose 12 mmol/l and blood ketones 6.6 mmol/l. FRII was initiated during which she rapidly developed hypoglycaemia. Repeat HbA1c was 29 mmol/mol. A week after her discharge she reported repeated hypoglycaemia while on insulin glargine 6 units once daily.

Discussion

The differential diagnosis of alcoholic from diabetic ketoacidosis in the setting of hyperglycaemia is challenging in a patient without a history of diabetes who reports alcohol excess, and hyperglycaemia in alcoholic ketoacidosis is reported in 11% of cases. Underlying chronic pancreatitis is likely to exacerbate the hyperglycaemia.

DOI: 10.1530/endoabs.93.P17

P18

Adrenal gland metastasis of endometrial cancer: A case report

Deniz Türküm Atikcan Şimşek[1] & Özlem Turhan Iyidir[2]
[1]Başkent University Division of Endocrinology and Metabolism, Endocrinology and Metabolism, Ankara, Turkey; [2]Başkent University Division of Endocrinology and Metabolism, Turkey.

Background

Although most solid primary tumors can metastasize to the adrenal glands, lung cancer is the most common, followed by renal cell carcinoma, melanoma and colorectal cancer. However endometrial cancer metastasis to adrenal gland is very rare. There are only a few case in literature. Endometrial cancer is the most common gynecological malignancy. In this case, we present a case of adrenal gland metastasis of endometrial cancer.

Case presentation

83-year-old female, presented with a 3 months history of nausea. She doesn't have any comorbidities other than endometrial carcinoma. In 2022, she was diagnosed with endometrium carcinoma, stage IIB, endometrioid type. She hadn't received chemotherapy and radiotherapy. In computerized thomography (CT) of December 2021, there was no adrenal gland mass. In the past 3 months she had lost 4 kilograms. So a new abdomen CT has performed. On the left adrenal gland 68 mm mass has spotted. The patient was normotensive, she hadn't have a moon face, buffalo hump, thinning of skin. The preoperative laboratory findings are as follows: Dehydroepiandrosterone sulfate 13.6 μg/dl, total testosteron < 12.98 ng/dl, aldosteron/renin activity 0.4, 1 mg dexamethasone suppression test was normal. On May 2023 left adrenalectomy, distal pancreatectomy, splenectomy had performed. Pathology result is high grade endometrial adenocarcinoma metastasis. After operation, she has been discharged from the hospital.

Conclusion

Endometrial carcinoma metastasis to adrenal gland is a rare occurrence, and its diagnosis requires suspicion, especially in patients with new symptoms. Definitive diagnosis is achieved through imaging and biopsy. The management of adrenal gland metastasis in endometrial carcinoma depends on the extent of disease and the patients' overall condition. In isolated cases, surgical resection can be considered. This case highlights the importance of considering distant metastases, including adrenal gland involvement, in patients with a history of endometrial carcinoma.

DOI: 10.1530/endoabs.93.P18

P19

Two cases of anticoagulation-induced pituitary macroadenoma apoplexy

Maja Jelinić[1], Karin Zibar Tomšić[2], Tina Dusek[3] & Darko Kastelan[3]
[1]Specijalna Bolnica Za Medicinsku Rehabilitaciju Krapinske Toplice, Odjel Za Unutarnje Bolesti, Krapinske Toplice, Croatia; [2]Zavod Za Endokrinologiju, Klinika Za Unutarnje Bolesti, Klinički Bolnički Centar Zagreb, Zagreb, Croatia; [3]Zagreb University School of Medicine, Zavod Za Endokrinologiju, Klinika Za Unutarnje Bolesti; Klinički Bolnički Centar Zagreb, Zagreb, Croatia.

Background

Pituitary apoplexy is a rare complication of pituitary adenomas, especially nonfunctioning tumors. It is associated with severe headache, which may be accompanied by visual disturbances or ocular palsy. Here we present two patients who suffered from pituitary adenoma apoplexy while receiving anticoagulation therapy with non-vitamin K antagonists.

Case presentation

A 74-year old woman was diagnosed with a non-functioning pituitary macroadenoma measuring 20×30×30 mm. In addition to arterial hypertension and essential thrombocytemia, her medical history included atrial fibrillation, for which anticoagulant therapy (dabigatran) had been initiated. One month later the patient presented with severe headache and vertigo due to pituitary apoplexy associated with subarrachnoid hemorrhage. There were no signs of pituitary insufficiency. She was managed conservatively and a brain MRI performed three months later revealed shrinkage of the pituitary mass. The second patient was a 69-year old man with arterial hypertension, coronary artery disease and arterial fibrillation who was taking apixaban. Three years after initiation of anticoagulation treatment the patient presented to the emergency department with severe headache, vomiting and complete ocular palsy of his right eye. An MRI showed apoplexy of pituitary macroadenoma with compression of the right oculomotor nerve. The patient underwent urgent transsphenoidal surgery but, although pituitary mass was completely removed, no improvement of neurological symptoms was observed.

Conclusion

These cases show that anticoagulantion treatment sholud be used with caution in patients with pituitary macroadenoma. Therefore, further stuides are needed to determine the safest anticoagulation treatment option in these patients.

DOI: 10.1530/endoabs.93.P19

P20

Venous thromboembolism in Cushing syndrome – A call for standardized anticoagulation regimen in hypercortisolism

Mari Minasyan[1], Agata Bryk-Więzania[2], Aleksandra Gamrat[3], Alicja Hubalewska-Dydejczyk[2] & Aleksandra Gilis-Januszewska[4]
[1]Endocrinology, Oncological Endocrinology, and Nuclear Medicine Department, University Hospital, Krakow, Poland, Endocrinology Department, Cracow, Poland; [2]Chair and Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland, Endocrinology, Oncological Endocrinology, and Nuclear Medicine Department, University Hospital, Krakow, Poland, Endocrinology Department, Cracow, Poland; [3]Chair and Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland; [4]Endocrinology, Oncological Endocrinology, and Nuclear Medicine Department, University Hospital, Krakow, Poland, Endocrinology Department, Cracow, Poland, Chair and Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland.

Cushing Syndrome (CS) is associated with a 18-fold higher risk of venous thromboembolism (VTE) when compared to the general population with the similar demographic characteristics. Despite numerous studies on hypercoagulability in CS, the unequivocal recommendations regarding timing and dosing of thromboprophylaxis in hypercortisolism are still lacking. We present a case series of patients with CS and VTE, hospitalized in the Endocrinology Department of University Hospital in Krakow. Among 135 patients with CS, we found 7 cases of VTE (5.19%), aged 35–65 years, mostly females ($n=6$). The etiology of CS was pituitary ($n=3$), adrenal ($n=2$), ectopic($n=1$) and adrenal carcinoma ($n=1$). Pulmonary embolism (PE) was found in 3 patients, deep venous thrombosis (DVT) in 2 patients, while 2 patients suffered from concomitant DVT and PE. We found that 5 patients had VTE at the moment of active hypercortisolemia, while 2 patients within the 30 days after inducing the biochemical remission by either a transsphenoidal surgery in one, or metyrapone treatment in 2nd case. In 3 patients VTE was the first manifestation of CS. Among patients, 2 PE episodes were associated with other predisposing factors, such as postpartum period in a 36-year-old woman and combined oral contraceptive in a 35-year-old woman. Of note, at the time of VTE episode, 1 patient was treated with warfarin, another one took apixaban. One fatal PE occurred on the thromboprophylaxis with low molecular weight heparin, in the hypocortisolemia following metyrapone implementation.

To summarize

VTE may be the first, life threatening presentation of CS.VTE may occur after treatment of hypercortisolism. VTE may happen in patients on

thromboprophylaxis or anticoagulant treatment.VTE should be included in the differential diagnosis of a thrombotic event despite coexisting transient factor. Multicenter studies are essential to create the recommendations on thromboprophylaxis in CS.

DOI: 10.1530/endoabs.93.P20

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Association of the elevated level of prenatal testosterone, maternal stress and vitamin D3 deficiency during pregnancy with the development of ADHD like symptoms in toddlers

Tamar Kacharava[1], Ketevan Nemsadze[1] & Ketevan Inasaridze[2]
[1]David Tvildiani Medical University, General Pediatrics, Tbilisi, Georgia; [2]Ministry of Education and Science of Georgia, Association of Neuroscience, Neuroscience, Tbilisi, Georgia.

Background
There is preliminary evidence that prenatal maternal stress (PNMS) is a risk factor for attention deficit hyperactivity disorder (ADHD). Vitamin D deficiency during critical periods of development could lead to persistent brain alterations. Some studies support the hypothesis that prenatal Testosterone exposure contributes to the development of ADHD in children. This study aimed to investigate the hypothesis, that presence of prenatal maternal stress, increased level of prenatal testosterone and low level of D3 vitamin in pregnancy is associated with the development of the ADHD like symptoms in toddlers (< 2 years).
Materials and Methods
A population cohort of 53 pregnant women was recruited at their 35 to 37th week of pregnancy and investigated prospectively. The participants were selected through targeted selection. Maternal experience of stressful life events was assessed by stress standardized questionnaires, prenatal testosterone was determined in mothers' saliva by using radioimmunoassay and maternal plasma D vitamin was measured using ECLIA method, during pregnancy. When offsprings age was 6 month and then less than 2 years, mothers completed the child behavior and temperament checklist.
Results
the testosterone level was increased only in 26% and D3 Vitamin deficiency revealed in 44.4% of study groupparticipants.There was statistically significant difference between degrees of level of maternal stress, in study group pregnant women was more pronounced high and moderate stress levels compared to the control group. A small but statistically significant association was found between common symptom complex of ADHD and the level of testosterone and Vitamin D3, in the presence of prenatal maternal stress. Multiple regression analysis showed that maternal stressful events during pregnancy significantly predicted ADHD behaviors in offspring.
Conclusion
The study supported the hypothesis that prenatal maternal stress, increased level of prenatal testosterone and low level of D3 vitamin during pregnancy increases the risk of development of ADHD like symptoms in toddlers (<2 years).

DOI: 10.1530/endoabs.93.P21

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Post-covid precipitates cardiovascular risk in women – premenstrual syndrome worsening, weight gain, and mental health disturbances

Kristina Saravinovska[1], Ljiljana Marina[2], Neda Delic[3], Antoan Stefan Sojat[4], Dunja Simona Petkovic[5], Tijana Petkovic[5], Natalija Antic[5], Sladjana Mihajlovic[6], Milan Lackovic[7], Nevena Radonjic[8], Miomira Ivovic[9], Zorana Arizanovic[5] & Svetlana Vujovic[2]
[1]Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Centre of Serbia, National Centre for Infertility and Endocrinology of Gender, Belgrade, Serbia; [2]Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia, National Centre for Infertility and Endocrinology of Gender, Belgrade, Serbia, Belgrade, Serbia; [3]Faculty of Medicine, University of Belgrade, Belgrade, Serbia, Belgrade, Serbia; [4]Ukcs, Ukcs, Belgrade, Serbia; [5]Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Centre of Serbia, National Centre for Infertility and Endocrinology of Gender, Belgrade, Serbia, Belgrade, Serbia; [6]Clinical Hospital Centre 'Dragisa Misovic', Faculty of Medicine, University of Belgrade, Belgrade, Serbia, Department of Obstetrics and Gynecology, Belgrade, Serbia; [7]Kbc Dr. Dragisa Misovic Dedinje, Clinical Hospital Centre 'Dragisa Misovic', Department of Obstetrics and Gynecology, Belgrade, Serbia, Belgrade, Serbia; [8]Upstate Medical University, Syracuse, Ny, USA, Department of Psychiatry and Behavioral Sciences, Syracuse, United States, Syracuse, United States; [9]Clinic For Endocrinology, Diabetes and Metabolic Disease, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia, National Centre for Infertility and Endocrinology of Gender, Belgrade, Serbia, Belgrade, Serbia.

Background
Premenstrual syndrome (PMS) and mental health disturbances have been identified as cardiovascular risk factors.
Objectives
To determine the effects of Sars-CoV-2 infection on PMS and mental health.
Methods
An anonymous survey about reproductive and mental health was shared with women of reproductive age between May and December, 2022. All women used their menstrual cycle (MC) diary while filling out the survey. Surveys were stratified based on RT-PCR/Antigen test results: positive (CP) or negative (CN). All reported changes in CP referred to time after the Sars-CoV-2 infection and in CN to a pandemic period in general.
Results
704 women completed the survey. Based on inclusion, exclusion, and complete data availability 461 surveys were taken into the final analysis: 129/28% CN-mean age 28.8 ± 9.7, mean BMI 22.5 ± 4.1 kg/m^{2,} and 332/72% CP, mean age 28.3 ± 8.7, mean BMI 22.3 ± 3.7 kg/m^2, with no difference in age or BMI between the groups ($P > 0.05$). 94/20.3% of CP reported shortening of MC length ($P = 0.001$) and worsening of PMS (wPMS) ($P < 0.001$). 61/64.9% CP with wPMS reported worsening of their mental health ($P = 0.02$); 42/44.7% CP women with wPMS reported low mood ($P = 0.02$), 34/36.2% anxiety ($P < 0.001$), 37/39.4% poor sleep ($P < 0.001$), 33/35.1% diminished concentration ($P < 0.001$), and 26/27.7% reported repeated partner/family conflict ($P = 0.004$). 26/27.7% CP with wPMS reported increased appetite ($P = 0.001$), 42/44.6% decreased physical activity ($P < 0.001$), and 56/59.5% reported weight gain ($P = 0.017$); these changes weren't observed in CN. In 73/67% CP wPMS was still present ($P < 0.05$) with an average duration of 280 days. In CP, Sars-CoV-2 infection was the only wPMS predictor ($P = 0.001$, B = 1.046, OR 2.847; 95% CI = 1.544–5.250).
Conclusions
Sars-CoV-2 infection leads to PMS worsening associated with weight gain and mental health disturbances, further adding to the already established COVID-19 cardiovascular risk. Identification of these patients and timely treatment could prevent potential cardiovascular events.

DOI: 10.1530/endoabs.93.P22