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Abstracts

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Abstracts

(in alphabetischer Reihenfolge der Presenting Authors)

001

The Association of Metabolic Parameters with BMI and Insulin Resistance in Young Children Beyond Maternal Hyperglycemia During Pregnancy

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Early experience of elevated insulin concentration during critical periods of perinatal development might contribute to a lasting malprogramming of endocrine systems regulating body weight and metabolism. The aim was to assess associations in BMI-SDS (Standard Deviation Score) and IR (insulin resistance) with regulating hormones in young children of mothers affected by different types of diabetes during pregnancy.

In a prospective study, 76 children aged 4–9 years were included for clinical examinations comprising anthropometric assessments and a fasting venous blood sample for metabolic measurements including determination of leptin, ghrelin, and GDF-15. Three groups were formed according to the diabetic status of the respective mothers during pregnancy, ie, pre-existing diabetes, gestational diabetes, and normal glucose tolerance (NGT).

We found significant correlations between BMI-SDS and leptin ($r = 0.61$; $p < 0.001$), ghrelin ($r = –0.32$; $p = 0.005$), usCRP ($r = 0.48$; $p < 0.001$), and HOMA ($r = 0.36$; $p = 0.002$) in the total population. Further, levels of IR as determined by HOMA were associated with leptin ($r = 0.37$; $p = 0.001$), ghrelin ($r = –0.30$; $p = 0.01$), GDF-15 ($r = –0.38$; $p = 0.001$), as well as BMI-SDS ($r = 0.36$; $p = 0.002$) in univariate analysis. The association of GDF-15, BMI-SDS, and leptin with IR was shown to be independent using a multiple linear regression explaining 38 % of the variance. Group-based analysis revealed that observed correlations depended on the maternal type of diabetes; with the exception of leptin to BMI, no other association occurred in NGT children.

Our results showed an inverse correlation of GDF-15 to IR in young children exposed to diabetes *in utero*. This association was independent of BMI-SDS and leptin. Further studies are needed to clarify the role of GDF-15 in the development of IR.

002

Das polyzystische Ovarialsyndrom (PCOS) und Labordiagnostik des Testosterons im Speichel

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Hintergrund Das polyzystische Ovarialsyndrom (PCOS) ist eine komplexe Erkrankung mit sehr heterogenen Symptomen, die über die Zeit variieren können. Das erschwert häufig, eine richtige Diagnose zu stellen. Betroffen sind mindestens 10 % aller Frauen in Österreich. Wichtig für die Diagnostik des PCOS ist die Bestimmung von Androgenen, die auch im Speichel als ungebundene Hormone nachweisbar sind.

Ziel Aus den laufenden Untersuchungen sollen sowohl neue diagnostische und leicht durchführbare Saliva-Tests für PCOS-Frauen in verschiedenen Generationen und Altersgruppen als auch Tests für Männer und Kinder aus PCOS-Familien entwickelt und validiert werden.

Methodik Saliva wird nach einem einheitlichen Protokoll zu gleichbleibenden Tageszeiten von den Probanden gewonnen und teils archiviert, teils den Saliva-Assays wie Testosteron, Androstendion, DHEA, Cortisol u. a. zugeführt.

Ergebnisse Im Rahmen des Projekts FEMBart wurden Frauen, Männer und Kinder einzeln und in Clusterfamilien untersucht. Dabei wurden bisher insgesamt 1265 Saliva-Proben von 235 Familien gewonnen, eine Saliva-Datenbank aufgebaut und mit der Routine-Labordiagnostik und Phänotypisierung verglichen.

Schlussfolgerungen Die nicht-invasive Diagnostik mittels versendbarer Speichelproben ist wissenschaftlich und in der Routinediagnostik wegen des Nachweises freier Hormone im Speichel besonders innovativ und kann einen Paradigmenwechsel in der PCOS-Diagnostik auslösen.

003

Die Rolle der Hypophyse beim polyzystischen Ovarialsyndrom

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Einleitung Beim polyzystischen Ovarialsyndrom (PCOS) handelt es sich um die häufigste endokrine Erkrankung von Frauen im gebärfähigen Alter. Sie weist in Mitteleuropa eine Prävalenz von 6–15 % auf. Klinisch finden sich ein erhöhter Androgenspiegel, erhöhte LH-Werte bzw. eine erhöhte LH-FSH-Ratio, polyzystische Ovarien und Oligo- bzw. Anovulation. Häufig leiden diese Patientinnen unter Insulinresistenz, Adipositas, Akne, Hirsutismus sowie einem unerfüllten Kinderwunsch. Die Kombination aus Hyperandrogenämie und Insulinresistenz hat ein erhöhtes kardiovaskuläres Risiko zur Folge.

Ziel dieser Studie ist es, den Zusammenhang zwischen den Hypophysenhormonen LH und FSH und metabolischen und endokrinen Aspekten des PCOS zu untersuchen.

Methoden Die Studie umfasst eine Gruppe von derzeit > 650 postmenarchischen prämenopausalen Frauen mit PCOS, bei denen andere endokrinologische Erkrankungen, die ein ähnliches klinisches Bild aufweisen können, ausgeschlossen wurden. Untersucht wurden die Blutkonzentrationen von LH und FSH (basal und nach GnRH-Stimulationstest), von 17-OH-Progesteron und von Testosteron, DHEAS und Androstendion. Außerdem wurde ein oraler Glukosetoleranztest durchgeführt sowie anthropometrische Parameter (Größe, Gewicht, Bauch- und Hüftumfang) erhoben.

Ergebnisse Über 80 % der Frauen weisen eine Zyklusunregelmäßigkeit auf, > 27 % haben eine pathologisch erhöhte LH-FSH-Ratio ≥ 2. Unter den getesteten Androgenen zeigen Gesamttestosteron ($r = 0{,}288$; $p < 0{,}01$) und Androstendion ($r = 0{,}234$; $p < 0{,}01$) die höchste Korrelation zur LH-FSH-Ratio.

Conclusio Diese retrospektive Kohortenstudie soll das Verständnis endokriner Einflüsse auf das PCOS verbessern. Erste Ergebnisse legen eine Assoziation einer hohen LH-FSH-Ratio mit der Hyperandrogenämie nahe.

004

Epigenetic Mechanisms and Their Role in the Regulation of the Calcium-Sensing Receptor Expression in Colorectal Cancer

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Epidemiological studies suggest a cancer-preventive role of calcium in colorectal cancer (CRC). The calcium-sensing receptor (CaSR) probably mediates the antiproliferative features of calcium in the colon. There is an inverse relationship between CaSR expression and tumor progression in human CRC. We hypothesized that epigenetic mechanisms such as DNA hypermethylation and histone deacetylation might be responsible for the reduction or loss of CaSR expression in colorectal tumors.

We analyzed CaSR mRNA expression in CRC patients (n = 100) and cell lines by real-time RT-PCR. In CRC patients we saw a down-regulation of CaSR expression in the tumor tissue when compared with the adjacent mucosa from the same patient. Immunofluorescence staining showed a down-regulation of the CaSR protein as well. Bisulfite sequencing of 2 promoter regions of the CaSR in CRC cell lines showed dense methylation of the second promoter. However, in patients, methylation ranged from 2–70 % but there was no difference in methylation patterns between the tumor and the respective adjacent mucosa. We treated colon tumor cell lines with 5-aza-2-deoxycytidine (5-aza-dC), a DNA methyltransferase inhibitor, and/or trichostatin A (TSA), a histone deacetylase inhibitor. Treatment with 5-aza-dC and TSA caused only modest increase of the CaSR expression despite the presence of densely methylated CpG islands in the promoter of the CaSR.

We conclude that the loss of CaSR expression in colon cancer is independent of DNA hypermethylation and histone deacetylation. In the future, we plan to assess the role of transcription factors responsible for regulating the CaSR expression.

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005

Tumor Markers of Primary Osteosarcoma in Human and Veterinary Medicine

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Osteosarcoma (OSA) is one of the most malignant bone tumors with a high potential for metastasis spreading. Human OSA occurs in young patients between 8 and 25 years. During tumor growth the metastatic rate rises to 50 %, particularly in pulmonary tissue. A similar behavior of the tumor, with regard to tumor location, metastasis spread, and malignancy has been observed in canine OSA. Hence, in contrast to other animal models, canine OSA appears to be a valuable model for human OSA. This joint study of the Medical University of Graz and the University of Veterinary Medicine in Vienna aims at the identification of novel biomarkers of canine and human OSA and at the evaluation of protein metabolic processes during this disease.

The project focuses on proteomic approaches and immunohistochemistry as tools to integrate data obtained from the analyses of osteosarcoma tissues, bone matrix, and cell cultures. Biomarker detection and function assays, particularly for matrix metalloproteinases (MMP-2, MMP-9), are currently conducted by means of gelatin-zymography techniques. Proteome analyses and mass spectrometry using MALDI TOF/TOF will be major tools for the identification of proteins in different species.

The main goal of this study will be the evaluation of canine osteosarcoma as a model for possible biomarker discovery in human medicine.

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006

Cost-Effective Screening for Gestational Diabetes Mellitus

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Introduction So far, it is not clear how to construct a time- and cost-effective screening strategy for gestational diabetes (GDM). Thus, we elaborated a simple screening algorithm combining (1) fasting plasma glucose (FPG) measurement and (2) a risk prediction model focused on subjects with normal FPG levels to decide if a further oral glucose tolerance test (OGTT) is indicated.

Methods 1336 women were prospectively screened for several risk factors for GDM within a multicenter study conducted in Austria. Out of 714 (53.4 %) women who developed GDM according to the most recent IADPSG diagnostic guidelines, 461 were sufficiently screened with FPG. A risk prediction score was finally developed on the remaining 253 GDMs and 622 healthy females. The screening algorithm was validated on an additional 258 pregnant women.

Results A risk estimation model including history of GDM, glucosuria, family history of diabetes, age, preconceptional hyperlipidemia, and race in addition to FPG was accurate for detecting GDM in subjects with normal FPG. Including an FPG pre-test, the area under the receiver-operating-characteristic curve was 0.90 (CI: 0.88–0.91). A cut-off value of 0.25 was able to decide between low and intermediate risk for GDM with a high sensitivity. The validation cohort revealed comparable results. Moreover, we demonstrated a strong and independent association between values derived from the risk estimation and macrosomic offspring.

Conclusion This study demonstrated a new concept for accurate but cheap GDM screening. This approach should be further evaluated in different populations to ensure an optimized diagnostic algorithm.

007

BNP Modulates Pituitary-Adrenal Axis and Adrenergic Activity: A Randomised Placebo-Controlled Cross-Over Study in Healthy Men

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Introduction B-type natriuretic peptide (BNP) released from the heart in response to volume overload is widely used in clinical practice as a diagnostic and prognostic biomarker for heart failure. BNP induces vasodilatation and increases natriuresis and diuresis, thereby releasing the preload. We recently described that BNP exerts ano-

rexigenic effects in men via reducing circulating concentrations of the gut hormone ghrelin.

Methodology The present study evaluates the acute effects of BNP on other hormones: pituitary-adrenal axis, plasma catecholamines, and thyroid hormones. Ten healthy male volunteers were recruited in a randomised placebo-controlled cross-over study, receiving once placebo and once an intravenous infusion of 3.0 pmol/kg/min human BNP (1–32) during 4 hours. Circulating levels of hormones were measured hourly.

Results BNP administration prevented the decrease in cortisol over time leading to elevated cortisol concentrations ($p = 0.022$), had no significant influence on basal ACTH levels, and increased circulating adrenaline and noradrenaline concentrations ($p = 0.018$ and $p = 0.036$, respectively). The thyroid and parathyroid hormone axes were not affected by BNP administration.

Discussion In summary, here we show that BNP increases circulating cortisol and catecholamine levels. These novel cross-talks within the human endocrine system highlight hitherto unknown mechanisms underlying the pathophysiology of subclinical inflammation and increased adrenergic activity accompanying heart failure and could provide the basis for new therapeutical strategies.

008

Copeptin: Der neue Biomarker ersetzt Vasopressin!?

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Einleitung Die diagnostische Messung des Hormons Vasopressin (ADH [Antidiuretisches Hormon, Adiuretin, Arginin-Vasopressin]) ist in der klinischen Routine oft eingeschränkt, durch die hohe präanalytische Instabilität müssen die Proben unmittelbar nach der Abnahme eingefroren und dürfen nur einmalig aufgetaut werden. Routinemäßig wird Vasopressin mittels Radio-Immuno-Assay aus dem Plasma bestimmt. Um die Präanalytik zu erleichtern, gäbe es die Möglichkeit, Vasopressin durch die Messung vom Copeptin (CT-pro-AVP) zu ersetzen. Copeptin ist ein chemischer Verwandter des körpereigenen Vasopressins und wird in gleichem Verhältnis vom gemeinsamen Prohormon abgespalten. Es stellt somit einen möglichen Surrogatmarker für Vasopressin dar.

Ziel Untersuchung einer Korrelation zwischen Vasopressin und Copeptin und deren klinische Validierung.

Methodik Von Patienten mit unterschiedlichen Hypophysenerkrankungen und gesunden Kontrollen werden Parallelanalysen von Vasopressin mittels kommerziellem RIA und Copeptin mittels LIA (Fa. Brahms) in Doppelbestimmungen durchgeführt.

Ergebnisse Die Etablierung und Validierung der Copeptin-Analytik wurde nach Herstellerangaben durchgeführt und im laufenden Betrieb validiert.

Schlussfolgerungen Copeptin als Surrogatmarker für Vasopressin ist präanalytisch stabiler und kann nach Adaptierung im Labor gemessen werden. Der Sandwich-Immuno-Assay für die Bestimmung von Copeptin ermöglicht die Messung aus Serum- oder auch aus Plasmaproben und es können bis zu 3 Gefrier-Auftau-Zyklen durchgeführt werden. Die Proben können 24 Stunden bei Raumtemperatur gelagert oder versendet werden.

009

Possible Causes and Consequences of the Overexpression of the Vitamin-D-Catabolizing Enzyme CYP24A1 in Colorectal Cancer

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Background Colorectal cancer is the third most common cancer in the world. Low vitamin D status is associated with an increased risk of colorectal cancer. The most active vitamin D metabolite, calcitriol, is catabolized by CYP24A1 (1,25-dihydroxyvitamin D_3-24-hydroxylase). This enzyme is overexpressed in colorectal cancer and likely reduces the anti-tumorigenic functions of calcitriol.

Aim We examined whether genomic rearrangements and promoter hypomethylation are causes behind the overexpression of CYP24A1 in colorectal cancer.

Methods We determined the CYP24A1 genomic copy number ($n = 127$) and mRNA expression of vitamin D pathway genes ($n = 82$) and proliferation markers ($n = 15$) in colorectal tumors and respective adjacent mucosa by quantitative real-time PCR. The methylation status of the promoter was assessed by bisulfite sequencing (region +494 to –609; $n = 20$).

Results We detected gene amplification of CYP24A1 in 60 % of colorectal cancer patients. A gain of CYP24A1 copy number correlated with increased mRNA expression (Spearman Correlation Coefficient [SCC] 0.334; $p < 0.005$). This correlation increased in the subgroup of patients with > 6 CYP24A1 copies (SCC 0.53; $p < 0.03$). Further, we found a strong correlation between CYP24A1 expression and proliferation markers MCM5 (SCC 0.952; $p < 0.001$), MCM2 (0.721; $p < 0.002$), and CDC6 (0.850; $p < 0.001$). We detected no differences in the CYP24A1 promoter methylation status between tumors and their respective adjacent mucosa.

Conclusion Gene amplification but not promoter hypomethylation is a mechanism behind the overexpression of CYP24A1 in colorectal cancer. The high expression of the calcitriol catabolizing enzyme CYP24A1 likely limits tissue exposure to the anti-proliferative effects of calcitriol and provides a growth advantage for the tumor.

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010

Differences in Systemic Inflammatory and Metabolic Markers in Pediatric Compared to Adult Obesity – TOBI Kids

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Obesity is associated with chronic low-grade inflammation, resulting in impaired glucose tolerance and type-2 diabetes mellitus. The aim of our study was to evaluate differences regarding metabolic and inflammatory alterations between obese children and adults.

71 non-diabetic obese (BMI > 97th percentile for age and sex) pediatric subjects, aged 10–18 years, were compared to 55 non-diabetic obese (BMI ≥ 40 kg/m²) adult patients aged 20–65 years. Anthropometric parameters, insulin resistance (HOMA-IR), as well as metabolic and inflammatory markers were evaluated.

Body weight was 100.1 (± 26.6) (mean ± SD) and 134.2 (± 24.3) kg ($p \leq 0.001$) in pediatric and adult patients, respectively. Plasma concentrations of glucose were 82.4 (± 9.7) and 93.5 (± 9.9) mg/dl ($p \leq 0.001$), and of hs-CRP 0.52 (± 0.6) and 1.0 (± 0.9; $p \leq 0.001$) mg/dl. Lower levels in pediatric vs adult patients were noted for the insulin-sensitizing adipokines adiponectin 6.9 (± 3.1) vs 8.6 (± 3.2) µg/ml and leptin 50.3 (± 26.9) vs 67.8 (± 22) ng/ml. The inflammatory adipokine IL-6 5.4 (± 9.9) vs 5.8 (± 3.2; $p \leq 0.001$) pg/ml was also significantly different and MCP-1 was increased: 306.3 (± 125.6) vs 185.5 (± 49.2; $p \leq 0.001$) pg/ml. A significant correlation was found for MCP-1 plasma concentrations with HOMA-IR specifically (Rho 0.340; $p = 0.013$) within pediatric patients.

Pediatric obesity is associated with alarming signs of low-grade inflammation and insulin resistance. In pediatric obesity, MCP-1 may be an early and sensitive marker for insulin resistance.

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011

Vitamin D und Testosteron im Zellkulturmodell

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Einleitung Vitamin D dürfte eine wichtige Rolle in der Regulation von Spermatogenese und Fertilität bei Männern spielen. Vitamin-D-Rezeptoren und Enzyme des Vitamin-D-Metabolismus in männlichen Gonaden und Spermien sind wichtige Hinweise dafür, ebenso eine parallele saisonale Rhythmik von Vitamin D und Testosteron und ansteigende Testosteronspiegel bei Vitamin-D-Supplementierung.

Ziel Neben der Untersuchung von primären Leydig- und Sertoli-Zellen bei Tieren soll eine humane Zelllinie etabliert werden, um wichtige Enzyme des Vitamin-D-Metabolismus nachzuweisen und die Auswirkungen von Vitamin D auf die Testosteronproduktion in vitro zu untersuchen.

Methoden Basierend auf einem Tiermodell werden Zellen aus Hodengewebe mechanisch und enzymatisch isoliert. Die heterogenen Primärzellkulturen werden mittels genetischer Methoden immortalisiert (hTERT, SV40 large TAg) und anschließend gesortet (FACS). Die morphologische, immunzytochemische und genetische Charakterisierung ermöglicht die Identifizierung von Leydig- und Sertoli-Zellen.

Ergebnisse Anhand ihrer Morphologie können Leydig- von Sertoli-Zellen bereits gut unterschieden werden. Nach Immortalisierung entsteht in den nächsten Schritten eine Reinkultur. Untersuchungen zu Immunzytochemie und Genetik sind im Laufen.

Schlussfolgerung Da eine gut charakterisierte infinite Zelllinie aus menschlichem Hodengewebe bisher noch nicht etabliert wurde, könnte dies ein Modell für In-vitro-Experimente für den Vitamin-D- und Testosteronstoffwechsel darstellen und weitere Untersuchungen des Steroid- und Mineralstoffwechsels und der Fertilität bei Männern ermöglichen.

012

High Dietary Vitamin D Can Reduce the Load of Chemically Induced Aberrant Crypt Foci in Mice

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Background Colorectal cancer (CRC) is one of the leading causes of cancer morbidity and mortality in the Western world. The most active metabolite of vitamin D_3, 1,25-dihydroxyvitamin D_3 (1,25-D_3), has anti-tumorigenic effects and is considered protective against CRC. High tissue levels of 1,25-D_3 in organs prone to sporadic cancer are assumed to counteract the development of incipient neoplasms.

Aim of this study is to investigate the effect of a high vitamin D diet on tumor development in vivo.

Methods We fed C57BL/6J mice with vitamin D concentrations ranging from 100–5000 IU/kg to determine the sufficient concentration preventing the development of chemically induced Aberrant Crypt Foci (ACF), a precursor of CRC. To induce ACF we injected mice once with 10 mg/kg azoxymethane intraperitoneally, followed by 3 cycles of Dextran Sodium Sulfate Salt (DSS) in the drinking water.

Results The colon of mice fed with a low vitamin D diet showed more and further progressed dysplasia compared with mice fed with a diet containing higher vitamin D concentrations (Spearman Correlation Coefficient [SCC] –0.558; p = 0,002). Expression of the vitamin D activating enzyme 25-hydroxyvitamin D_3 1α-hydroxylase (CYP27B1) in the kidney decreased with rising vitamin D concentration in the diet (SCC –0.452; p = 0.016), whereas the vitamin D degrading enzyme 1,25-dihydroxyvitamin D_3 24-hydroxylase (CYP24A1) increased (SCC 0.518; p = 0.005). The expression of vitamin D receptor (VDR) did not change (SCC 0.041; p = 0.016).

Conclusion Our data show that high vitamin D concentrations in the diet are able to reduce the development of chemically induced ACF.

013

Treatment with N-3 Polyunsaturated Fatty Acid for 8 Weeks Does Not Influence Vitamin D Status in Severely Obese Subjects

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Obese individuals are at risk for vitamin D deficiency. Recently, it was shown that the amount of ingested polyunsaturated fatty acids (PUFA) correlated negatively with the vitamin D status of patients receiving vitamin D_3 supplements. Due to this potential interaction and since both vitamin D and n-3 PUFA seem to prevent obesity-associated complications, we investigated whether treatment with long-chain n-3 PUFA impacts vitamin D status in obese patients.

55 severely obese (BMI > 40 kg/m^2) non-diabetic patients were treated with either 3.3 g/d n-3 PUFA (EPA/DHA) or the same amount of butter fat as control for 8 weeks in a randomized controlled trial. Plasma fatty acid profiles, circulating inflammatory marker, and serum 25-hydroxyvitamin D concentrations were determined at baseline and at treatment end. Statistical analysis was performed using RM-ANOVA and Spearman correlation.

At baseline, 53/55 patients were vitamin D-deficient. Serum 25-hydroxyvitamin D concentration correlated positively with plasma EPA content (rho = 0.30; p = 0.03) and negatively with both IL-6 and hsCRP serum concentration (rho = –0.31; p = 0.02 and rho = –0.29; p = 0.03, respectively). Treatment with n-3 PUFA did not affect vitamin D status ($p_{interaction}$ = 0.37 in RM-ANOVA), but significantly decreased median serum triglyceride and IL-6 concentrations by 15.9 % and 24.8 %, respectively. None of the baseline correlations could be replicated in the n-3 PUFA group after the treatment.

Vitamin D status was unaffected by n-3 PUFA treatment over 2 months in vitamin D-deficient, severely obese patients. Cumulative beneficial effects of n-3 PUFA and vitamin D on obesity-associated comorbidities remain to be evaluated.

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014

Effekt einer Insulintherapie auf Herzmorphologie und kardialen Lipidmetabolismus bei Patienten mit Diabetes mellitus Typ 2 (DM2): Eine Magnetresonanztomographie- (MRT-) und -Spektroskopie- (MRS-) Studie

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Einleitung Diabetes mellitus ist mit einer spezifischen Herzerkrankung, der „diabetischen Kardiomyopathie", assoziiert, deren Pathophysiologie nicht vollständig aufgeklärt ist. Rezente Studien legen nahe, dass die kardiale Lipidakkumulation und Hypertrophie

eine wichtige Schlüsselrolle hierbei spielen könnten. Insulin könnte als anaboles Hormon sowohl die Lipidspeicherung als auch die myokardiale Hypertrophie beeinflussen. Daher war das Ziel unserer Studie, zu untersuchen, ob die Einleitung einer konventionellen Insulintherapie (IT) die Herzlipidkonzentration und/oder -morphologie bei Personen mit DM2 beeinflusst.

Methoden Neun Personen mit DM2 (5 Männer, 4 Frauen; Alter: 58 ± 3 Jahre; HbA_{1c}: 11,2 ± 0,5 %) erhielten aufgrund unzureichender Blutzuckerkontrolle unter oraler Medikation eine standardisierte konventionelle IT. MRT/MRS-Untersuchungen wurden vor sowie 10 Tage nach Therapiebeginn durchgeführt. Follow-up-Untersuchungen fanden nach 181 ± 49 Tagen statt. Der myokardiale Lipidgehalt sowie die Geometrie des Herzens wurden mittels Elektrokardiographie- (EKG-) getriggerter lokalisierter ^{1}H-Single-Voxel-MRS und MRT gemessen. Der intrahepatale Fettgehalt wurde ebenfalls mittels MRS erhoben.

Ergebnisse Am 10. Tag der IT war die kardiale Lipidkonzentration bereits um das 1,6-Fache des Ausgangswertes angestiegen, wobei es nach mehrmonatiger Behandlungsdauer zu einer Normalisierung der Werte kam (Tag 0: 0,43 ± 0,46 vs. Tag 10: 0,69 ± 0,37 vs. Follow-up: 0,36 ± 0,17 % des Wassersignals; p = 0,038). Langfristig nahm die intrahepatale Lipidkonzentration signifikant ab (Tag 0: 8,67 ± 6,52 vs. Tag 10: 7,78 ± 6,28 vs. Follow-up: 4,18 ± 3,92 % des Wassersignals; p < 0,001). Zusätzlich war IT mit einem Anstieg der myokardialen Masse (+15 %; p = 0,003) und mit kardialem Remodeling (+34,8 %; p = 0,038) assoziiert.

Schlussfolgerungen Die Einleitung einer IT führt zu einem transienten Anstieg der Herzlipidkonzentration sowie einer persistierenden Hypertrophie des Myokards. Wir vermuten daher, dass unter bestimmten Bedingungen IT die Entstehung der diabetischen Kardiomyopathie begünstigen könnte.

015

Prevalence of Endocrine Disorders in Morbidly Obese Patients and the Effects of Bariatric Surgery on Endocrine and Metabolic Parameters

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Background Several endocrine abnormalities including hypothyroidism and Cushing's syndrome (CS) are considered as causative factors of obesity. The aim of this study was to evaluate the prevalence of endocrine disorders and obesity-associated comorbidities as well as the impact of substantial weight loss.

Methods Screening was performed in 433 consecutive, morbidly obese patients (age 41 ± 12 years; BMI 47 ± 6.9 kg/m^2; women: 76 %). A 1-mg dexamethasone suppression test (1 mg DST) was conducted to exclude CS and thyrotropin (TSH) was measured to exclude hypothyroidism. Insulin sensitivity was estimated from oral glucose tolerance tests employing the Clamp-Like Index (CLIX). Examinations were carried out at baseline, as well as at 6 and 12 months postoperatively.

Results The prevalence of CS was < 0.6 %. Before surgery, TSH was elevated compared to an age- and sex-matched normal-weight control group (2.4 ± 1.2 vs 1.5 ± 0.7 µU/ml; p < 0.001). 39.5 % fulfilled the NCEP criteria of metabolic syndrome (MetS). Impaired glucose tolerance and diabetes mellitus were observed in 23.5 % and 22.6 %, respectively. 72 % were insulin-resistant. During follow-up, weight (BMI 47 ± 6.9 vs 36 ± 6.4 vs 32 ± 6.6 kg/m^2; p < 0.001) and TSH decreased significantly (2.4 ± 1.2 vs 1.8 ± 1.0 vs 1.8 ± 1.0 µU/ml; p < 0.001). Serum cortisol was higher in the MetS$^+$ group compared to the MetS$^-$ group (15.0 ± 6.3 vs 13.5 ± 6.3 µg/dl; p = 0.003).

Conclusions CS appears to be a rare cause of morbid obesity. Normalization of slightly elevated thyrotropin after weight loss suggests that obesity causes TSH elevation rather than the reverse.

016

Associations of Aldosterone-to-Renin Ratio with 24-Hour Ambulatory Blood Pressure Measurements: The Styrian Vitamin D Study

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Introduction The aldosterone-to-renin ratio (ARR) may be associated with higher blood pressure but only limited data exists on the association of ARR with 24-hour ambulatory blood pressure (ABP) measurements.

Aims We evaluated whether the ARR is associated with 24-hour ABP in hypertensive patients.

Methods We performed 24-hour ABP measurements in hypertensive patients derived from a tertiary care centre. Plasma levels of aldosterone and active renin concetration were determined by Radio-Immunoassay.

Results AAR and 24-hour ABP measurements were available in 56 patients (aged 58.8 ± 11.7 years; 44.6 % females; 24-hour systolic and diastolic ABP were 129 ± 59 and 78 ± 10 mmHg, respectively). Pearson correlation analyses showed a significant association of ARR with diastolic (r = 0.345; p = 0.009) but not with systolic 24-hour ABP (r = 0.123; p = 0.365). ARR was significantly correlated with daytime diastolic ABP (r = 0.329; p = 0.013) but not with daytime systolic ABP (r = 0.241; p = 0.074) whereas at nighttime, ARR was significantly correlated with both diastolic (r = 0.385; p = 0.004) and systolic ABP (r = 0.314; p = 0.020). In multiple linear regression analyses including age, sex, Body Mass Index, and number of antihypertensive drugs as independent variables, ARR was only significantly correlated with diastolic 24-hour ABP (β = 0.289; p = 0.023), daytime diastolic ABP (β = 0.267; p = 0.034), nighttime diastolic ABP (β = 0.363; p = 0.006), and nighttime systolic ABP (β = 0.339; p = 0.016). Aldosterone was not significantly positively correlated with any 24-hour ABP parameter.

Conclusions ARR but not aldosterone itself is significantly associated with 24-hour ABP values, in particular with nighttime diastolic ABP.

017

Androgenstoffwechsel und reproduktives Outcome

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Einleitung Das polyzystische Ovarialsyndrom (PCOS) ist die häufigste endokrine Störung von Frauen im gebärfähigen Alter. Die Definition „PCOS" erfolgt nach den Rotterdam-Kriterien; 2 der 3 Kriterien müssen erfüllt sein: (1) Oligo- oder Anovulation, (2) klinische und/oder biochemische Zeichen des Hyperandrogenismus und (3) polyzystische Ovarien. Durch Veränderungen der endokrinen Regelkreise werden verschiedene Aspekte beeinflusst. Infolge von Infertilitätsbehandlungen kann es zum Auftreten von Mehrlingsschwangerschaften und eines Hyperstimulationssyndroms kommen. Während der Schwangerschaft sind das Risiko für eine Frühgeburt, das Auftreten eines Gestationsdiabetes, einer schwangerschaftsinduzierten Hypertonie, einer Präeklampsie und die Sectiorate erhöht. Neugeborene von PCOS-Müttern müssen häufiger intensivmedizinisch betreut werden. Ätiologisch lassen Untersuchungen von PCOS-Familien einen genetischen Hintergrund vermuten. Als weiterer wichtiger Einflussfaktor gilt das hyperandrogene Milieu *in utero*, dem ein weiblicher Fetus einer Frau mit PCOS ausgesetzt sein kann.

Ziele Ziel dieser klinischen Studie ist es, den Androgenstatus kurz vor, während und nach der Schwangerschaft zu bestimmen und den Einfluss von Störungen des Androgenmetabolismus auf Schwangere und deren Nachwuchs zu erforschen.

Methoden Die Studie gliedert sich in 2 Arme: In einer prospektiven Querschnittsstudie soll bei Gebärenden der Androgenspiegel aus dem Nabelschnurblut bestimmt und mit dem der Mutter am Tag der Geburt und 6 Wochen postpartal verglichen werden. Weiters werden endokrine Veränderungen und Schwangerschaftskomplikationen in einer prospektiven Beobachtungsstudie evaluiert.

Schlussfolgerungen Es ist wahrscheinlich, dass Veränderungen des mütterlichen Androgenstoffwechsels Einfluss auf Mutter und Kind haben, was vermehrte Komplikationen vor, während und nach der Schwangerschaft sowie in der Perinatalperiode zur Folge haben kann. Möglichweise beeinflusst der mütterliche Hyperandrogenismus während der Schwangerschaft auch die Androgenkonzentrationen im Nabelschnurblut der Neugeborenen.

018

Higher Myocardial Lipid Content in Female Diabetics Compared to Males with Similar Diabetes Duration Correlates with GDF-15 Serum Concentrations

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Background Type-2 diabetes is associated with a diastolic dysfunction of the heart, the reason possibly being the increased myocardial lipid content due to cardiac glucolipotoxicity common in diabetic and obese subjects. GDF-15 is an inflammatory and apoptotic protein up-regulated in the injury of the heart. Female diabetics have a 4–6-fold increased risk for cardiovascular events possibly due to a lack of the protective estrogen effect compared to non-diabetic subjects.

Methods 60 patients, 30 male and 30 female, treated at our diabetes metabolic unit of the Medical University of Vienna, underwent magnetic resonance spectroscopy performed with 3 Tesla Siemens MRT. GDF-15 was measured in the serum of the patients by means of Quantikine ELISA assays.

Results Mean age was 55.9 ± 7.2 years, weight 88.3 ± 17 kg, BMI 31.6 ± 5.1 kg/m^2, and duration of diabetes 6 ± 2 years. Female patients had significantly higher myocardial lipid content than male diabetics (1.9 ± 0.5 vs 0.9 ± 0.3; p = 0.003). Ejection fraction was decreased similarly in both sexes (51.4 ± 2.3 vs 49.2 ± 0.9; ns). GDF-15 levels were increased in both sexes and did not differ significantly (2358 ± 180 pg/ml). However, GDF-15 serum concentrations strongly correlated with cardiac lipid content (r_S = 0.33; p = 0.015, r_S = 0.35; p = 0.009) especially in female patients (r_S = 0.35; p = 0.009) pointing toward the fact that female diabetics suffer from severe cardiac injury after even 6 years of diabetes duration compared to male patients.

Conclusion We conclude that type-2 diabetes *per se* is a risk factor for cardiovascular events, especially in women, perhaps due to increased myocardial fat resulting in diastolic dysfunction, strongly correlating with increased GDF-15 levels. GDF-15 can be seen as a possible early marker for cardiac injury in type-2 diabetic patients, with a special focus on women being at higher risk.

019

Insulin Metabolism and Relation of a Genetic Variant of MEP1A in Women with Polycystic Ovary Syndrome

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Background There is accumulating evidence suggesting that insulin resistance and compensatory hyperinsulinemia affect 65–70 % of women with polycystic ovary syndrome (PCOS). The development of insulin resistance has been associated with vitamin D deficiency. Our genome-wide association study (GWAS) revealed MEP1A loci as a potential candidate gene in PCOS.

Aim The aim of this study was the detection of a new genetic pathway for potential diagnostic and therapeutic targets in PCOS.

Methods MEP1A variants were replicated in 586 PCOS women and 105 controls. Metabolic, hormonal, functional, and anthropometric parameters were determined. Human hepatocellular carcinoma (HepG2) cells were treated with insulin, vitamin D, and parathyroid hormone (PTH).

Results The replicated SNPs showed a significant association with insulin metabolism in overweight/obese PCOS. MEP1A GG carriers showed a significantly increased HOMA index (p = 0.005), elevated fasting insulin (p = 0.006), and stimulated insulin after 30 min (p = 0.003), 1 h (p = 0.003), and 2 h (p = 0.009). HepG2 cell experiments showed a relation of MEP1A to the expression of bone genes and vitamin D while MEP1A expression in cell lines was different using vitamin D/PTH stimulation.

Conclusion MEP1A is a possible target for disease modification in PCOS and new therapy options. It might contribute to the involvement of vitamin D deficiency in abnormalities of glucose metabolism and insulin sensitivity. Whether MEP1A is such a universal risk factor for PCOS and how it affects gene function and expression will be further investigated.

020

Role of Tumor Stem Cells in Pituitary Adenomas

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Over the last decades, a new model of cancer development based on the identification of tumor-initiating "cancer stem cells" (CSC) has evolved. The small population of CSC shares common features with adult stem cells and is thought to be the driving force in tumor initiation, maintenance, growth, and relapse. Recent data suggest that the CSC model could not only be of relevance for the pathogenesis of malignant cancer but also of benign tumors.

Therefore, the present study was designed to evaluate a potential role of tumor stem cells in the pathogenesis of pituitary adenomas. We studied expression levels of the embryonic, neural, and glioma-associated stem cell markers SOX2, NANOG, NESTIN, CD133, and GLI1 in 24 human pituitary adenomas (hormone-expressing and non-functioning, respectively) by qRT-PCR and immunofluorescence staining. In addition, volumetric tumor measurements were performed using OsiriX imaging software.

SOX2, NANOG, NESTIN, and CD133 showed a significant co-expression in all investigated adenomas (p < 0.001), the type of adenoma having no influence. Of note, the expression of GLI1, which is a member of the Hedgehog signalling pathway, showed a correlation with other stem cell markers only in patients with relapsing adenomas (p < 0.001). The Hedgehog signalling pathway is active during embryogenesis and reactivated in various cancer types. It is important to note that the first Hedgehog signalling inhibitor, vismodegib, was only recently approved, in January 2012. Based on our data, vismodegib could be a promising treatment option for pituitary adenomas expressing GLI1.

021

Parathyroid Hormone Levels Are Associated with Insulin Resistance in Women with Polycystic Ovary Syndrome

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Introduction Accumulating evidence suggests an association of vitamin D with insulin resistance (IR) in women with polycystic ovary syndrome (PCOS). The role of PTH in insulin metabolism is less clear.

Aims We aim to study the association of PTH and 25-hydroxyvitamin D (25[OH]D) levels with metabolic and endocrine parameters in a cohort of PCOS women.

Methods We measured PTH and 25(OH)D levels in 544 PCOS and 139 healthy control women within the same age range. Metabolic, endocrine, and anthropometric measurements and oral glucose tolerance tests were performed.

Results PCOS women had higher PTH levels than controls in an age-adjusted analysis ($p = 0.018$). PCOS women with higher PTH levels were significantly older, had a higher BMI, waist-to-hip ratio (WHR), systolic and diastolic blood pressures, fasting and stimulated insulin levels, homeostatic model assessment-IR (HOMA-IR), CRP levels, and Ferriman Gallwey scores as well as significantly lower 25(OH)D, SHBG, quantitative insulin sensitivity check index (QUICKI), serum calcium, and phosphorus ($p < 0.05$ for all). In linear regression analysis, BMI ($p < 0.001$), age ($p < 0.001$), and PTH ($p = 0.016$) were independent predictors of AUCinsulin, whereas 25(OH)D was not. In linear regression analysis using the same covariates, BMI ($p < 0.001$) and PTH ($p = 0.006$) independently predicted HOMA-IR, whereas age and 25(OH)D did not. Likewise, in linear regression analysis, BMI ($p < 0.001$) and PTH ($p = 0.037$) independently predicted insulin sensitivity assessed by QUICKI, whereas age and 25(OH)D were not related to insulin sensitivity.

Discussion We present evidence that PTH levels are independently associated with IR and insulin sensitivity in a large cohort of PCOS women.

022

Combination of Low Free Testosterone and Low Vitamin D Predicts Mortality in Older Men Referred for Coronary Angiography

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Introduction Low levels of 25-hydroxyvitamin D (25[OH]D) and free testosterone (FT) are both associated with increased mortality. Experimental studies show a complex interplay of vitamin D and androgen metabolism suggesting that a deficiency of both hormones may be associated with a particularly adverse clinical outcome.

Objective To evaluate the impact of parallel FT and 25[OH]D deficiency in a large cohort of older men.

Methods We measured total testosterone (TT), SHBG, and 25(OH)D levels in 2069 men routinely referred for coronary angiography (1997–2000). Main outcome measures were Cox proportional hazard ratios (HRs; with 95-% confidence intervals) for mortality from all causes, cardiovascular, and non-cardiovascular causes according to combined deficiency of FT and 25(OH)D.

Results In multivariate adjusted analyses, we found a significantly increased risk for all-cause mortality, cardiovascular, and non-cardiovascular mortality for men in the lowest FT (HR 1.35 [1.11–1.63], 1.31 [1.02–1.68], and 1.40 [1.03–1.91], respectively) and 25(OH)D quartile (HR 1.90 [1.59–2.27] 1.78 [1.42–2.24], and 2.09 [1.58–2.76], respectively) compared to men in higher FT and 25(OH)D quartiles. There was no independent association of TT levels with mortality. Multivariate adjusted HRs progressively increased with the number of hormones (FT and 25[OH]D) in the lowest quartile (0 vs 2 hormone deficiencies: 2.37 [1.82–3.09] for all-cause, 2.14 [1.52–3.02] for cardiovascular, and 2.73 for non-cardiovascular mortality [1.80–4.16], respectively).

Conclusion A combined deficiency of FT and 25(OH)D is significantly associated with fatal events in a large cohort of men referred for coronary angiography.

023

Urinary Iodine Concentration in Pregnant Women as a Measure of Iodine Supply

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Background Iodine is essential for fetal development, especially of the brain. Although Austria is considered to be iodine-sufficient, the situation of pregnancy, when iodine requirements are higher, is unclear. Iodine supply can be determined by measuring urinary iodine concentration (UIC). According to the WHO, a UIC of 150–250 µg/l indicates an optimum iodine supply.

Objective Evaluation of whether iodine supply is sufficient during pregnancy and of whether a diabetic condition influences iodine supply.

Methods Pregnant women from the outpatient clinics of Diabetes and of Obstetrics and Fetomaternal Medicine were divided into a diabetic (n = 115) and a control group (n = 131). Standardized food histories and spot urine samples were obtained. The urine samples were digested in pressure vessels in a microwave oven after adding nitric acid and potassium chlorate, and iodine concentrations were measured by means of an inductively coupled plasma mass spectrometer.

Results 81 % of the women had a UIC <150 µg/l, indicating a (partly severe) iodine under-supply. There was no statistically significant difference between diabetic and non-diabetic women. The difference in UIC between women who substituted iodine (32.1 %, 100–150 µg/d) and those who did not was statistically significant, but only 30 % of the women who supplemented iodine had a UIC ≥ 150 µg/l.

Conclusions Most pregnant women in our study were under-supplied with iodine, almost a quarter of them severely. A diabetic condition does not seem to influence the iodine metabolism.

Substituting 100–150 µg of iodine daily slightly increases the UIC but is not enough for 70 % of the women.

024

Identifikation von Androgen-Subtypen bei polyzystischem Ovarialsyndrom (PCOS)

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Einleitung Das polyzystische Ovarialsyndrom (PCOS) ist eine der häufigsten endokrinen Erkrankungen von Frauen. Zu den typischen klinischen und phänotypischen Merkmalen des Syndroms zählen

u. a. Zyklusstörungen, polyzystische Ovarien, Hirsutismus, Akne, Alopezie, Übergewicht, Insulinresistenz und ein Überschuss an verschiedensten Androgenen, welche bei Frauen sowohl in den Ovarien als auch in der Nebennierenrinde gebildet werden.

Ziele Massenspektrometrische Analyse verschiedener Steroidhormone zur Identifizierung von Androgen-Subytpen des PCOS in Ergänzung der bisherigen Laboruntersuchungen. Eine Zuordnung der verschiedenen phänotypischen Merkmale des PCOS zu den einzelnen Androgen-Subtypen und deren genetischer Hintergrund sollen hierdurch ermöglicht werden.

Methoden Serum, Saliva und Harn von > 950 PCOS-Patientinnen und > 300 Kontrollen werden mittels Massenspektrometrie mit einem SteroIDQ-Kit (Biocrates) einer quantitativen Analyse unterzogen, in der 16 Steroidhormone simultan analysiert werden können. Zellkulturversuche mit Granulosa- und Thekazellen ergänzen die androgenetische Charakterisierung.

Ergebnisse Die Steroidprofile bisheriger Laboranalysen wurden quantifiziert und anhand internationaler Kriterien gruppiert. Wichtige Subanalysen von genetischen Determinanten aus dem Steroidstoffwechsel wurden bereits etabliert und validiert, Zellkulturen sind im Laufen.

Schlussfolgerungen Da bis heute noch keine umfangreiche quantitative Analyse aller wichtigen Steroidhormone bei Patientinnen mit PCOS erfolgte, könnte diese Studie dazu beitragen, die pathophysiologischen und genetischen Unterschiede dieser Erkrankung besser zu verstehen und in weiterer Folge effektivere Behandlungsmöglichkeiten und neue Targets zu finden.

025

Two Cases of Osteoitis Fibrosa (OF) Due to Secondary Hyperparathyroidism in Children with Chronic Kidney Diseases After rhGH Treatment

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Chronic hyperparathyroidism is a key factor for the development of OF. We report on 2 boys (patient P1: 14 years, patient P2: 9 yrs) with end-stage renal disease. Because of height deficits they were treated with recombinant human growth hormone (rhGH). Serum examination after one-year treatment revealed an increase (up to 992 pg/ml) of PTH levels.

Transiliacal biopsies were taken before and after rhGH treatment with informed consent from the parents. Bone histomorphometric indices and bone mineralization density distribution (BMDD) (by quantitative backscattered electron imaging [qBEI]) were evaluated. The BMDD-derived indices were: weighted mean (Ca_{Mean}) and the most frequently measured (Ca_{Peak}) calcium concentrations, the heterogeneity of mineralization (Ca_{Width}), the portion of fully (Ca_{High}) and low (Ca_{Low}) mineralized bone areas.

After rhGH treatment, numerous areas of OF were found **(Figure 1).** Indices of bone formation and osteoclast activity were increased. In P1, dynamic indices were not available as the entire newly formed bone matrix did not mineralize and thus prevented labeling. BMDD was shifted towards lower matrix mineralization with increased heterogeneity in mineral content **(Table 1).**

The data demonstrate the importance of continuously monitoring PTH serum levels in children with CKD when treated with rhGH to prevent potential impairment of bone quality.

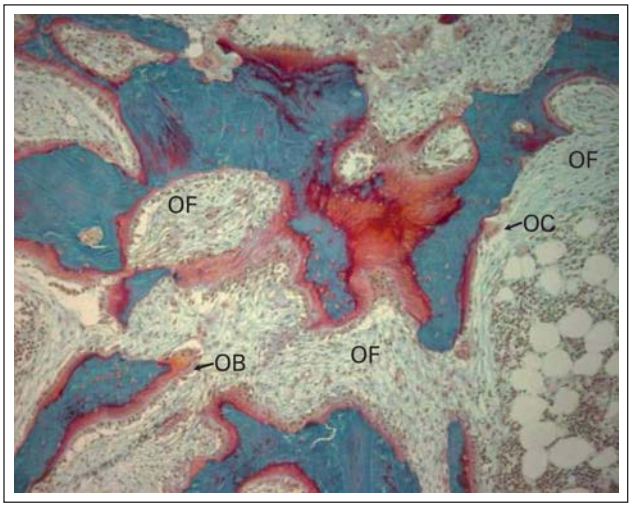

Figure 1. K. Nawrot-Wawrzyniak et al. Trichrome-Goldner stains bone section from P1. **OC:** osteoclast; **OB:** osteoblast; **OF:** osteitis fibrosa

026

Kortisolmessung im Haar von Hunden zur Diagnostik von Morbus Cushing

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Der Hyperadrenokortizismus (Morbus Cushing) wird ausgelöst durch eine lang andauernde exzessive Produktion von Glukokortikoiden. Er gehört zu den am häufigsten vorkommenden endokrinen Erkrankungen beim Hund und ist in den meisten Fällen durch einen Tumor in der Hypophyse bedingt. Um den Einfluss kurzfristiger spontaner Fluktuationen der Kortisolkonzentrationen im Blut auf Untersuchungsergebnisse auszuschließen, sind für die Labordiagnostik Stimulations- bzw. Suppressionstests erforderlich, was einen gewissen Zeitaufwand für den Tierbesitzer bedeutet. Es wäre daher wünschenswert, einen Langzeitparameter für die Kortisolproduktion zu haben.

Es ist aus der Literatur bekannt, dass Kortisol auch in Haaren gemessen werden kann. Wir untersuchten daher, ob die Messung der Kortisolkonzentration im Haar ein geeignetes Verfahren für die Diagnostik des Hyperadrenokortizismus beim Hund ist.

Dazu wurden Haarproben von 12 Hunden mit diagnostiziertem Cushing-Syndrom und von 10 Hunden mit physiologischer Kortisolkonzentration gesammelt. Die Proben wurden im Zuge der Entfernung des Fells für die Blutentnahme (oberhalb der V. cephalica) gewonnen. Die Konzentrationen von Kortisol, Kortison und Kortikosteron wurden nach Extraktion aus den Haaren mit Methanol mittels verschiedener Enzym-Immunoassays bestimmt. Die Validierung erfolgte mittels RP-HPLC.

Die Ergebnisse zeigen, dass bei Patienten mit Hyperadrenokortizismus die Kortisol-, Kortison- und Kortikosteronwerte in den Haaren signifikant höher waren als in der Kontrollgruppe. Wir schließen daraus, dass die Glukokortikoidmessung im Haar ein nützliches Werkzeug für die Messung langfristiger Glukokortikoid-Exposition und zur Diagnose „Hyperkortisolismus“ bei Hunden ist.

Table 1. K. Nawrot-Wawrzyniak et al. Histomorphometric and BMDD indices of P1 and P2 with OF after rhGH treatment. Values are given in %-deviation from published reference data.

	OV/BV	OS/BS	BV/TV	BFR/BS	Ca_{Peak}	Ca_{Mean}	Ca_{Width}	Ca_{High}	Ca_{Low}
P1	+717 %	+166 %	+40 %	na	–10 %	–15 %	+67 %	–81 %	+484 %
P2	+232 %	+124 %	+67 %	+108 %	–4.2 %	–5.8 %	+67 %	+79 %	+194 %

Offen bleibt jedoch die Frage, ob es sich bei den Glukokortikoiden im Haar um Hormone aus der Nebenniere handelt oder ob die Kortisolkonzentration in den Haaren ein Parameter für die Glukokortikoidproduktion in der Haut ist.

027

Correlates of Food Craving and Quality of Life in Polycystic Ovary Syndrome

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Introduction Increased appetite, weight gain, and obesity are known problems in patients with polycystic ovary syndrome (PCOS) and obesity is a main risk factor for metabolic diseases. Moreover, changes in outer appearance strongly affect quality of life.

Aims This study investigated the relationship between food craving (FC), quality of life, hormone levels, and metabolic parameters in PCOS patients.

Methods 164 patients completed a Food Craving Inventory and the Polycystic Ovary Syndrome Questionnaire (PCOSQ) on quality of life in PCOS. Body weight, height, glucose and insulin levels were obtained. Food Craving subscales were built and a sum score and food category-specific subscores were calculated. Pearson correlations evaluated statistical relationships between variables. Significant correlations ($p < 0.05$) are reported.

Results The most frequently craved single food item was chocolate followed by pasta. Across categories, craving was strongest for sweets and carbohydrates. General FC (particularly craving for fat and carbohydrates) was associated with increased weight, Body Mass Index; and waist-to-hip-ratio. General FC and craving for fat and carbohydrates was also associated with a decreased quality of life in PCOS. Furthermore, the higher the subjective stress because of being overweight, the higher the overall food craving score as well as the scores for fat, fast food, and carbohydrate craving. General FC was associated with increased insulin and glucose levels.

Conclusion Stronger FC in PCOS is associated with a decreased quality of life. FC, weight gain, and metabolic problems seem to be a coherent burden in PCOS.

Clinicians should be aware of FC and its possible consequences in PCOS.

028

Lebensqualität bei polyzystischem Ovarialsyndrom aus endokrinologisch-psychiatrischer Betrachtung

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Einleitung Das polyzystische Ovarialsyndrom (PCOS) ist die häufigste endokrine Erkrankung von Frauen und ist charakterisiert durch Hyperandrogenismus, Ovulationsstörungen und polyzystische Ovarien. Betroffene sind stark belastet durch die Veränderungen ihres Äußeren, der Hormone sowie durch Unsicherheiten hinsichtlich ihrer Reproduktionsfähigkeit.

Ziele Ziel dieser Studie ist die Evaluation von unterschiedlichen Einflussfaktoren auf die Lebensqualität von PCOS-Patientinnen.

Methode 160 PCOS-Patientinnen beantworteten den krankheitsspezifischen Lebensqualitätsfragebogen PCOSQ. In den Gesamtscore fließen 5 Belastungsdimensionen ein: Emotionen, Körperbehaarung, Gewicht, Infertilität und Menstruationsstörungen. Erhoben wurden weiters Alter, Gewicht, Lipometriedaten, Akne- und Hirsutismusausprägung, Zyklusregelmäßigkeit, Kinderwunsch sowie Hormonparameter der Patientinnen. Spearman-Korrelationen und Mann-Whitney-U-Tests wurden zur statistischen Datenanalyse verwendet.

Ergebnisse Höhere Body-Mass-Indizes sowie Waist-to-Hip-Ratios gehen mit einer geringeren Lebensqualität einher. Ebenfalls in einem negativen Zusammenhang mit der Lebensqualität stehen die gesamte Körperfettmasse, die viszerale und subkutane Fettmasse, ein hoher Hirsutismus-Score und das Vorhandensein von Akne. Ebenfalls korreliert die Höhe der Testosteronwerte und des freien Androgenindex negativ mit der Lebensqualität. SHBG- und Kortisol-Werte stehen dagegen in einem positiven Zusammenhang ($p < 0,05$ für alle).

Verglichen mit Frauen ohne Kinderwunsch haben Frauen mit Kinderwunsch eine geringere Lebensqualität, geprägt durch höhere emotionale Belastung, Infertilitätssorgen und Menstruationsprobleme. Verglichen mit Frauen mit regelmäßigem Menstruationszyklus haben Frauen mit unregelmäßigem Zyklus eine niedrigere Lebensqualität assoziiert mit höherer emotionaler Belastung und Menstruationsproblemen.

Schlussfolgerungen Sowohl sichtbare als auch unsichtbare Merkmale stehen in Zusammenhang mit herabgesetzter Lebensqualität bei PCOS. Die meisten Parameter hiervon können klinisch rasch als Indikatoren herangezogen werden. Eine interdisziplinäre Zusammenarbeit zur Diagnostik oder Prävention von psychischen Folgeerkrankungen in der Behandlung von PCOS-Patientinnen ist erstrebenswert.

029

Aldosterone-to-Active-Renin Ratio as Screening Test for Primary Aldosteronism: Reproducibility and Influence of Orthostasis and Salt Loading: the GECOH Study

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Introduction Measurement of the aldosterone-to-active-renin ratio (AARR) is the recommended screening test for primary aldosteronism (PA), but several sampling conditions impact on the AARR.

Aims We aimed to evaluate the reproducibility and the influence of orthostasis and salt loading on the AARR.

Methods The Graz Endocrine Causes Of Hypertension (GECOH) study is a diagnostic accuracy study among hypertensive patients at a tertiary care centre in Graz, Austria. With a median interval of 4 weeks we determined the AARR under standardized sampling conditions twice in the sitting position, after 1 hour in the supine position, and after a salt infusion test (SIT).

Results We identified 9 patients with PA and 151 patients with essential hypertension (EH). The Pearson correlation coefficient between both AARR measurements in the sitting position was 0.79 ($p < 0.001$). In EH, recumbency was associated with a significant decrease of aldosterone and, to a lesser extent, of renin, thus lowering the AARR as compared to the sitting position ($p < 0.001$ for all). In PA, recumbency had only minor effects, but it increased the rate of false-negative AARR. SIT suppressed the AARR and its components in EH, whereas in PA only renin was slightly decreased.

Conclusions AARR has a good intra-individual reproducibility and decreases during recumbency. These results suggest that a single AARR determination in the sitting position is a reliable screening tool for PA.

030

C6orf62 as a Potential Novel Player Interacting with Cytokine Signalling

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C6orf62 is a gene whose protein expression and function have not been characterized in detail to date; its primary structure shows no homology to any other previously described domains or signal sequences. We previously cloned C6orf62 and showed that C6orf62 is up-regulated in pituitary macroadenomas but down-regulated in functioning pituitary tumors including somatotrophinomas and prolactinomas.

Immunofluorescence and western blot experiments confirm that C6orf62 protein expression is ubiquitous and highest in heart, liver, and kidney, but also in endocrine tissues, including pancreas. Further functional experiments were conducted in kidney and liver cell lines. Cell fractionation experiments reveal that C6orf62 protein is highly expressed in the nucleus and membrane-bound organelles, and less within the cytoplasm, pointing towards a function in cell signaling or hormone secretion.

To gain first functional insights, C6orf62 mRNA expression was studied during stimulation of different intracellular signaling pathways. Insulin and LPS led to a significant down-regulation of C6orf62 mRNA expression in HepG2 cells, whilst dexamethasone, T3, and TNF-α showed no effect. The topoisomerase inhibitors, camptothecin and etoposide, significantly up-regulated C6orf62 mRNA expression.

In a cell signaling array, C6orf62 over-expression caused an up-regulation of pathways involved in cytokine signaling, leukocyte attraction, endothelial leukocyte activation, and chronic inflammatory states, including COX-2.

In summary, C6orf62 is ubiquitously expressed but subject to tissue-specific regulation; it is modulated in response to the activation of insulin and TLR-4 signaling, and after apoptosis induction. Its over-expression activates cytokine signaling and cellular pathways associated with adaptive immunity.

031

Simultaneous Occurrence of Marine-Lenhart Syndrome and a Papillary Thyroid Microcarcinoma

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Background The Marine-Lenhart syndrome is defined as the co-occurrence of Graves' disease and functional nodules. The vast majority of autonomic adenomas are benign, whereas functional thyroid carcinomas are considered to be rare. Here, we describe a case of simultaneous occurrence of Marine-Lenhart syndrome and a papillary microcarcinoma embedded into a functional nodule.

Patient Findings A 55-year-old man presented with overt hyperthyroidsm (TSH < 0.01 µIU/l; FT4 3.03 ng/dl), negative thyroid peroxidase and thyroglobulin autoantibodies, but elevated thyroid-stimulating hormone receptor antibodies (2.6 IU/l). Ultrasound showed a highly vascularized hypoechoic nodule (1.1 × 0.9 × 2 cm) in the right lobe, which projected onto a hot area detected in the ^{99m}technetium thyroid nuclear scan. Overall uptake was increased (4.29 %) while the remaining thyroid tissue showed suppressed tracer uptake, supporting the notion that both Graves' disease and a toxic adenoma were present. After normal thyroid function was reinstalled with methimazole, the patient was thyroidectomized. Histological work-up revealed a unifocal papillary microcarcinoma (9 mm, pT1a, R0) embedded into the hyperfunctional nodular goiter.

Conclusions Neither the finding of an autonomously functioning thyroid nodule nor the presence of Graves' disease rules out papillary thyroid carcinoma.

032

Genetische Variationen im Gen Meis1 und Knochendichte

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Einleitung Die Knochendichte, eine wichtige Messgröße der Osteoporose, wird abhängig vom Messort im Ausmaß zwischen 50 % und 80 % vererbt. Zahlreiche Kandidatengene sind in die Vererbung von Knocheneigenschaften involviert. Wir untersuchten ein polymorphes Gen (Meis1) aus der HOX-Familie („homeobox-containing genes"), das evolutionär hochkonserviert ist und regulatorische Aufgaben in der Entwicklung zahlreicher Gewebe u. a. auch des Knochens hat.

Studiendesign 1975 Personen (77 % ♀) wurden auf Anamnese, Lifestyle-Faktoren, Frakturen, Routine- und Knochenstoffwechsel-Labor (Crosslaps, Osteocalcin, Kalzium, Phosphat, 25(OH)Vitamin D, PTH intakt) und auf ihre Knochendichte sowie weitere Knocheneigenschaften untersucht. Aus Leukozyten wurde genomische DNA gewonnen und mittels „High-throughput"-Taqman-PCR die beiden Meis1-Loci rs2049019 (rs204) und rs6716792 (rs671) mit Wildtyp (WT, grün), Heterozygotie (HE, blau) und Homozygotie (HO, grau) genotypisiert.

Ergebnisse Die Frequenz der polymorphen Genotypen betrug für rs2049019 WT 45,5 %, HE 44,7 % und HO 9,9 %, rs6716792 wies in dieser Bevölkerungsstichprobe eine Frequenz von WT 31,2 %, HE 50,6 % und HO 18,3 % auf. Bei jungen Probanden zeigte sich eine signifikante Assoziation mit BMD, Körpergröße und Testosteron, allerdings nur bei Männern für den rs2049019-Genotyp. Ältere Männer mit homozygotem Genotyp hatten an allen Messorten eine signifikant höhere Knochendichte als die beiden anderen Genotypgruppen.

Schlussfolgerung Morphogenetische Regulatoren haben einen entwicklungsbetonten Einfluss auf zahlreiche Knocheneigenschaften. Wir fanden einen auffälligen Zusammenhang der untersuchten SNPs im Meis1-Gen mit männlichen Hormonen. Die klinische Relevanz von Meis1-Genotypen und ihr Zusammenspiel mit Umweltfaktoren werden im Rahmen der Erstellung von individuellen Risikoprofilen für Osteoporose und andere Knochenerkrankungen in Diagnostik und Therapie untersucht.

033

Metformin Use and Lactose Intolerance in Patients with Polycystic Ovary Syndrome (PCOS)

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Metformin is the most common oral antidiabetic drug used in the treatment of polycystic ovary syndrome (PCOS). The substance inhibits lipogenesis and stimulates SHBG synthesis in the liver. A variety of metformin preparations from different pharmaceutical companies are used, some of them containing considerable amounts of lactose. Primary adult lactose intolerance (adult-type hypolactasia [ATH]) is based on a genetic variance in the MCM6 gene and affects about 20–25 % of the Austrian population. Less frequent secondary forms may be acquired by intestinal surgery, gastroenteritis, or other causes. We included 285 female PCOS patients with recommended metformin medication in our study and examined side effects and compliance by questionnaire. Additionally, we investigated the effect of the intronic SNP rs4988235 in the MCM6 gene

leading to lactose intolerance in Caucasians. Out of these patients, 39 had decided not to use metformin because of pregnancy, dissuasion by another physician, or too severe side effects. The remaining 246 patients were stable on metformin treatment.

Gastrointestinal problems were the main side effect reported, affecting 17.1 % of our PCOS patients. When assigning all patients to either a lactose-tolerant or a lactose-intolerant group, 28.9 % of lactose-intolerant versus 14.4 % of lactose-tolerant patients showed gastrointestinal side effects.

In conclusion, our PCOS patients with ATH showed more gastrointestinal side effects during metformin treatment. In view of a more personalized medicine, it might be of interest to select metformin preparations according to ATH status in order to obtain more stable therapy adherence in PCOS patients.

034

Organic Cation Transporter (Oct) Genotyping and Metformin Treatment in Patients with Polycystic Ovary Syndrome (PCOS)

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Metformin, a well-known oral antidiabetic drug, is commonly used in the treatment of polycystic ovary syndrome (PCOS). It acts in the liver where it decreases lipogenesis and activates SHBG production. It is widely known that there is a great variability in the clinical response to metformin. In humans, metformin is marginally metabolized and eliminated by the kidney. Metformin is a substrate of organic cation transporters (Octs), especially Oct1 (liver-specific) and Oct2 (kidney) with a considerable genetic variation.

We investigated the effect of 5 allelic variants (single-nucleotide polymorphism [SNP]) in Oct1 (rs12208357 [Oct1-1], rs34059508 [Oct1-2], rs34447885 [Oct1-3], rs34104736 [Oct1-4], and rs36103319 [Oct1-5]) and one SNP in the Oct2 gene (rs316019 [Oct2]) in 340 female PCOS patients. Each of these variants leads to the formation of an inactive transporter allele.

The SNPs Oct1-3, Oct1-4, and Oct1-5 (originally identified in Asian cohorts) did not contribute to metformin resistance in our Caucasian cohort based on a minor allele frequency (MAF) < 0.001. However, the other SNPs Oct1-1, Oct1-2, and Oct2 showed an inactive allele in 33.6 % of female PCOS patients, 2.3 % of PCOS patients carried more than one.

Oct SNPs influence the bioavailability of metformin by its hepatic uptake and renal clearance, contributing to variances in metformin efficacy. It is of increasing interest to know more about individual medication in common metabolic diseases such as diabetes or PCOS to improve therapy outcomes.

035

Osteocalcin upon Oral Glucose Load in Non-Insulin-Resistant and Insulin-Resistant Women

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Background Osteocalcin (OC) is known as a marker of bone turnover. Recently, a role in the regulation of energy metabolism has been revealed in murine models. Clinical studies have shown controversial findings.

Aim The aim was to evaluate the effect of a standard 75-g oral glucose tolerance test (OGTT) on serum total OC, cOC, and ucOC at 30', 60', and 120' in non-insulin-resistant (non-IR) as well as insulin-resistant (IR) women.

Methods OGTTs were performed in 70 premenopausal women. Insulin resistance was defined as HOMA-IR (homeostatic model assessment-insulin resistance) > 2. Total OC was determined by EIA (Roche, Mannheim); ucOC was measured after adsorption of cOC on hydroxyapatite.

Results Total OC and cOC levels at baseline were significantly lower in IR women (n = 25) with a median HOMA-IR of 3.72 (2.88–6.39). In non-IR subjects (n = 45, HOMA-IR = 0.52 [0.42–0.82]), a significant decrease was observed for total OC (17.6 ng/ml [12.7–22.0] to 14.1 ng/ml [10.3–17.7]), ucOC (2.9 ng/ml [2.0–3.7] to 2.1 ng/ml [1.6–2.6]), and cOC (15.0 ng/ml [11.5–19.4] to 11.0 ng/ml [8.7–14.6]) ($p < 0.001$, respectively) during OGTT from baseline to 120'. In IR patients, no decrease was observed.

Discussion Non-IR women showed a decrease of all forms of OC after glucose load, whereas IR women did not. Baseline levels of OC, cOC, and ucOC in IR women were comparable to those in non-IR women after 120'. In IR women, OC, cOC, and ucOC levels seem suppressed by constantly elevated insulin levels, suggesting a down-regulation of osteoblastic insulin receptors. The reduction of bone formation by elevated leptin levels in IR might contribute to lower OC levels.

036

Untersuchungen zur antihyperglykämischen Wirkung von α_2-Antagonisten in der Maus

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Wir haben zuletzt Hinweise präsentiert, dass die blutglukosesenkende Wirkung des Imidazolins Efaroxan einer antagonistischen Wirkung an adrenergen α_2-Rezeptoren zuzuschreiben ist. Diese Hypothese wurde nun durch vergleichende Untersuchungen mit einem α_2-Antagonisten überprüft, der nicht zur Klasse der Imidazoline gehört (Yohimbin). Hierzu wurden C57BL/6J-Mäuse oral mit Yohimbin oder mit (+)-Efaroxan behandelt (das +-Enantiomer des Razemats Efaroxan ist hauptverantwortlich für dessen glukosesenkende Potenz). Dann wurde durch pharmakologische Hemmer der Insulinsekretion ein Anstieg der Glykämie induziert und über 180 Min. die inkrementale Fläche unter der Glukosekurve berechnet (AUC, Angaben in min*g/dl). Eine moderate Dosis von Yohimbin (0,1 mg/kg p. o.) wirkte einer Hyperglykämie entgegen, die durch einen α_2-Agonisten induziert worden war (AUC unter 0,1 mg/kg UK13,403 i. p.: Yohimbin 15,0 ± 2,1 vs. Kontrolle 26,0 ± 1,2; $p < 0,001$). Yohimbin zeigte aber keinen vergleichbaren Effekt, wenn der Glukoseanstieg durch einen K_{ATP}-Kanalöffner, also über einen anderen Mechanimus als den α_2-Antagonismus, induziert worden war (AUC unter 250 mg/kg Diazoxid p. o.: Yohimbin 35,7 ± 2,2 vs. Kontrolle 37,3 ± 3,3; n. s.). Dieses Wirkprofil, das offenkundig die α_2-antagonistischen Eigenschaften von Yohimbin widerspiegelt, wurde auch für eine moderate Dosis von 1 mg/kg (+)-Efaroxan festgestellt (AUC unter 0,1 mg/kg UK13,403 i. p.: (+)-Efaroxan 15,3 ± 1,4 vs. Kontrolle 20,9 ± 0,6; $p = 0,003$; AUC unter 250 mg/kg Diazoxid p.o.: (+)-Efaroxan 26,4 ± 1,9 vs. Kontrolle 27,6 ± 2,8; n. s.). Parallel dazu durchgeführte Experimente zur Insulinfreisetzung aus isoliert perifundierten Langerhans'schen Inseln ergaben ein ähnliches Bild. Die festgestellte Ähnlichkeit des Wirkprofils von Yohimbin mit jenem von (+)-Efaroxan untermauert unsere Hypothese, dass die blutglukosesenkende Wirkung von Imidazolinen entgegen weit verbreiteter Annahmen ihrer antagonistischen Wirkung an α_2-Rezeptoren der β-Zellen zuzuschreiben ist.

037

Die Rolle der Schilddrüse beim polyzystischen Ovarialsyndrom

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Einleitung Das polyzystische Ovarialsyndrom (PCOS) ist eine der häufigsten endokrinologischen Störungen bei Frauen im gebärfähigen Alter. Neben den klassischen Diagnosekriterien dieses Syndroms wie Hyperandrogenismus, Oligo- bzw. Anovulation und polyzystischen Ovarien, leiden auch viele der Betroffenen unter Schilddrüsenerkrankungen.

Ziele Ziel der Studie war es, die Prävalenz von Schilddrüsenerkrankungen bei Patientinnen mit PCOS zu untersuchen. Weiters wurde analysiert, ob es einen Unterschied bei endokrinen und metabolischen Parametern bei PCOS-Patientinnen mit und ohne Schilddrüsenerkrankung gibt.

Methoden Bei 762 Patientinnen mit diagnostiziertem PCOS wurde retrospektiv erhoben, ob eine Schilddrüsenerkrankung besteht. Zudem wurden > 50 Frauen, die zur PCOS-Abklärung vorstellig wurden, prospektiv laborchemisch und sonographisch hinsichtlich Schilddrüsenerkrankungen gescreent.

Ergebnisse 29,3 % der retrospektiv untersuchten Frauen wiesen eine Schilddrüsenerkrankung auf, wobei 82 % davon unter einer Hashimoto-Thyreoiditis oder einer Hypothyreose anderer Ursache litten. PCOS-Patientinnen mit Schilddrüsenerkrankung wiesen eine signifikant höhere Nüchtern-Insulinkonzentration (9,1 mU/l vs. 7,5 mU/l; p = 0,022) sowie einen höheren HOMA-Index (2,2 vs.1,8; p = 0,04) auf als PCOS-Patientinnen ohne Schilddrüsenerkrankung. Auch Bauchumfang (90,7 cm vs. 85,3 cm; p = 0,002) und BMI (28 kg/m² vs. 26 kg/m²; p = 0,001) waren bei PCOS-Frauen mit Schilddrüsenerkrankung höher als bei Patientinnen ohne Schilddrüsenerkrankung. Keine signifikanten Unterschiede konnten hinsichtlich der Nüchtern-Blutglukose festgestellt werden.

Conclusio Frauen mit PCOS weisen eine hohe Prävalenz an Schilddrüsenerkrankungen auf, weshalb jede Frau mit PCOS zumindest laborchemisch und eventuell mittels Ultraschall hinsichtlich Schilddrüsenerkrankungen untersucht werden sollte. Ebenso sollten Patientinnen mit Immunthyreopathie Hashimoto und charakteristischer Anamnese sowie Phänotyp auf das Vorliegen eines PCOS gescreent werden.

038

Vitamin D and Mortality: A Mendelian Randomization Study

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Background and Aim Decreased 25-hydroxy (25-OH) vitamin D levels have been associated with mortality rates, but it is unclear whether this association is causal. Therefore, we performed a Mendelian randomization study and analyzed whether 3 common single-nucleotide polymorphisms (SNPs) associated with 25-OH-vitamin D levels are causal for mortality rates.

Methods Genotypes of SNPs in the group-specific component gene ([GC] rs2282679), 7-dehydrocholesterol reductase gene ([DHCR7] rs12785878) and cytochrome P450 IIR-1 gene ([CYP2R1] rs10741657) were determined in a prospective cohort study of 3316 male and female participants (mean age 62.6 ± 10.6 years) scheduled for coronary angiography. 25(OH)vitamin D levels were determined by radioimmunoassay. The main outcome measures were all-cause deaths, cardiovascular deaths, and non-cardiovascular deaths.

Results In a linear regression model, baseline 25(OH)vitamin D levels were predicted by age ($p < 0.001$), gender ($p < 0.001$), GC genotype ($p < 0.001$), CYP2R1 genotype ($p = 0.036$), and DHCR7 genotype ($p = 0.001$). During a median follow-up time of 9.9 years, 955 persons (30.0 %) died, including 619 deaths from cardiovascular causes. In a multivariate Cox regression adjusted for classical risk factors, GC, CYP2R1, and DHCR7 genotypes were not associated with all-cause mortality, cardiovascular mortality, or non-cardiovascular mortality.

Conclusion We conclude that genetic variants associated with 25(OH)-vitamin D levels do not predict mortality. This suggests that low 25(OH)vitamin D levels are associated with, but unlikely to be causal for higher mortality rates. Other factors therefore need to be investigated. Whether 25(OH)vitamin D supplementation can reduce mortality needs to be analyzed in adequately sized randomized clinical trials.

039

Indirect Evidence of a Thyroid Protective Effect of Selenium in the Postpartum Period

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A recent clinical observation substantiates in my view the usefulness of selenium (Se) to prevent postpartum hypothyroidism.

The patient was diagnosed to have chronic autoimmune thyroiditis at the age of 25. Hypothyroidism developed 3 years later. Substitution with L-thyroxine (T4) was initiated and euthyroidism was achieved with 100 µg/day. Two years after the start of T4 treatment she started to take 100 µg Se/day additionally. Her pre-treatment Se blood level was 87.6 µg/l (normal 70–130 µg/l).

Two months later she became pregnant for the first time. Thyroid function and thyroid autoantibodies were controlled every 4 weeks. The dose of L-T4 had to be increased to 125 µg/day in order to achieve TSH values below 3 mU/l. She delivered a normal euthyroid girl and continued to take Se until 7 months after delivery. Thyroid autoantibodies and TSH increased after 3 months without Se in the hypothyroid range (TPO: 878 U/ml, TSH: 14.7 mU/l) in spite of the continued intake of 100 µg L-T4/day. After a transient increase of the L-T4 dose TSH levels returned to normal and L-T4 could be reduced again.

Three years later the patient became pregnant again. During this pregnancy L-T4 had to be increased to alternative doses of 125/150 µg/day. She did not take any selenium. Three months after the uncomplicated delivery of a normal euthyroid boy she developed hypothyroidism (TSH: 14.7 mU/l, TPO: 484 U/ml). This hypothyroid phase was again transient.

The time course of the recurrent occurrence **(Figure 2)** of the hypothyroid phases in the postpartum periods of this L-T4-substituted patient with Hashimoto's thyroiditis suggests that her thyroid was protected after her first pregnancy as long as she took Se.

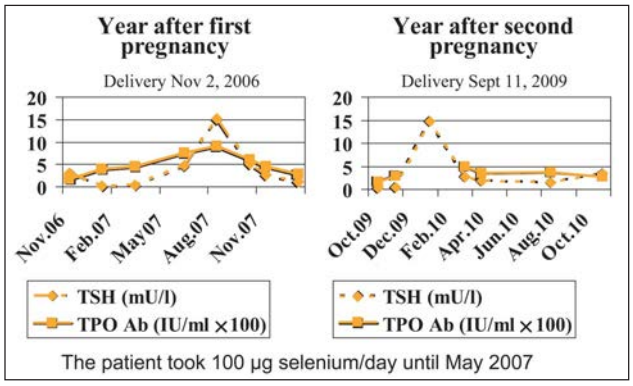

Figure 2. M. Weissel. TSH and thyroperoxidase antibody levels in the postpartum period of a hypothyroid patient with Hashimoto's disease: effect of selenium 100 mg/day.

040

Inhibition of Adipose Tissue Lipolysis Leads to Acute Depletion of Myocardial, but Not Hepatic Lipid Stores and Impaired Systolic Function

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Background In the myocardium, > 70 % of the total energy derives from fatty acid oxidation (FAO). Metabolic cardiomyopathy is characterized by increased FAO (~ 100 %), increased myocardial lipid content (MYCL), and the inability to adapt to changes in substrate availability under stress conditions.

It is unclear whether changes in adipose tissue lipolysis impact myocardial substrate metabolism (inter-organ cross-talk) and whether healthy subjects can compensate free fatty acid (FFA) deficiency by increasing carbohydrate oxidation. Therefore, the aim of this study was to investigate the impact of acute inhibition of adipose tissue lipolysis and consequent suppression of plasma FFA on myocardial lipid content and function in healthy subjects.

Subjects and Methods Five healthy male subjects were studied twice: once during inhibition of lipolysis by acipimox (administered at baseline and 180 minutes) and once during administration of placebo. Magnetic resonance spectroscopy for assessment of myocardial (MYCL) and hepatic (HCL) lipid content and MR imaging for measurement of left ventricular function were performed at baseline as well as at 180, 420, and 1440 minutes.

Results Compared to placebo, administration of acipimox was associated with a significant decrease in MYCL ($p < 0.02$; **Figure 3**)

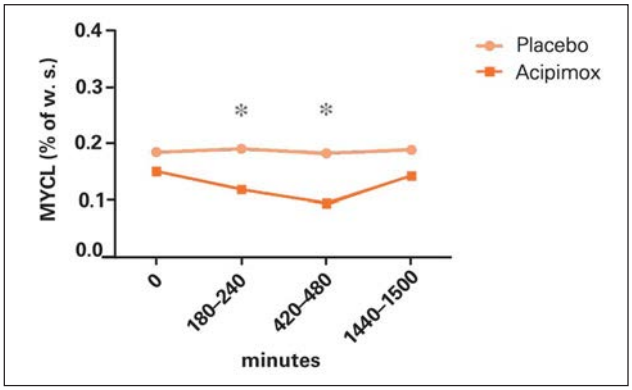

Figure 3. Y. Winhofer et al. (040). Concentrations of myocardial lipid content (MYCL, in % of water signal) after administration of acipimox (boxes) or placebo (circles). * $p < 0.05$

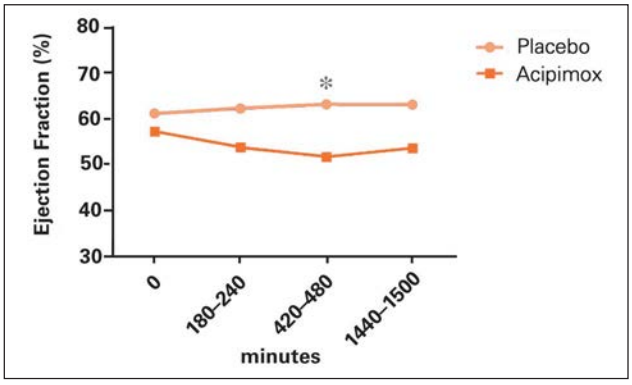

Figure 4. Y. Winhofer et al. (040). Changes of ejection fraction (EF) after administration of acipimox (boxes) or placebo (circles). * $p < 0.05$

and ejection fraction ($p = 0.03$; **Figure 4**), while HCL and plasma glucose concentrations remained unchanged during the experiments.

Conclusions Suppression of FFA is associated with a significant decrease in myocardial lipid content and ejection fraction, indicating that alterations in adipose tissue lipid metabolism (lipolysis) acutely affect myocardial function in healthy subjects.

041

Changes of Myocardial Lipid Metabolism, Cardiac Function, and Insulin Secretion 6 Months after Transsphenoidal Selective Adenectomy in Patients with Acromegaly

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Background Patients with acromegaly have an increased risk of developing metabolic (ie, diabetes) and cardiovascular complications, which mainly account for morbidity and mortality in this patient population. Hence, the aim of this study was to assess the impact of transsphenoidal selective adenomectomy on cardiac and metabolic parameters.

Patient Population and Methods So far, we have studied 6 patients with acromegaly (ACRO) before and 6 months after transsphenoidal adenomectomy and 16 healthy controls (CON), matched for age and Body Mass Index. All participants underwent an oral glucose tolerance test (for assessment of insulin secretion/sensitivity) and cardiac magnetic resonance (for assessment of myocardial lipid content and function). In addition, pituitary hormones were measured.

Results Before surgery, ACRO had significantly increased left-ventricular end-systolic (34.8 ± 8.4 vs 22.7 ± 7.7 ml/m²; $p = 0.004$) and end-diastolic volumes (90.5 ± 11.9 vs 68.8 ± 13.4 ml/m²; $p = 0.002$), increased left-ventricular mass (91.3 ± 10.4 vs 59.9 ± 12.6 g/m²; $p < 0.0001$), and wall thickness (9.7 ± 0.6 vs 5.8 ± 1.2 mm; $p < 0.0001$) compared to CON. Postoperatively, a significant decrease in the disposition index (-0.255 ± 0.007 [= –14.4 %]; $p = 0.01$), left-ventricular mass (-11.6 ± 6.4 g/m² [= –12.3 %]; $p < 0.007$), and wall thickness (-1.84 ± 0.76 mm [= –18.8 %]; $p < 0.006$) as well as the end-diastolic volume (-11.0 ± 10.4 ml/m² [= –12.2 %]; $p < 0.05$) was observed in ACRO. IGF-1 decreased by 404.5 ± 220.0 ng/ml ([= –47.6 %]; $p = 0.006$), while pituitary hormones and myocardial lipid content remained unchanged. In comparison to CON, left-ventricular mass and wall thickness remained increased, while cardiac volumes became comparable postoperatively.

Conclusions Our findings indicate that cardiac changes related to growth hormone excess are partially reversible after transsphenoidal adenomectomy. In addition, improvement of insulin secretion may decrease the risk of developing metabolic complications.

042

Observing the Hepatic Metabolism by Non-Invasive Quantification: A ^{31}P-Magnetic Resonance Spectroscopy Feasibility Study

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Background The interplay between glycogen metabolism, glycolysis, and gluconeogenesis is essential for maintaining fasting plasma glucose concentrations. Several steps of these processes involve phosphorylation of glucose and metabolic intermediates. Advances in ^{31}P magnetic resonance spectroscopy (NMRS) allow for precise non-invasive measurements of concentrations of ^{31}P meta-

bolites in human liver. Therefore, the aim of the study was to analyze the time course of intrahepatic phosphorus containing metabolites during fasting and after glucose ingestion.

Methods All MR measurements were performed on the 7.0-T Magnetom MR system using a 10-cm 1H/31P double-tuned circular surface coil. 5 healthy volunteers participated in the study. They underwent 3 ^{31}P NMRS examinations at 8:00 am after an overnight fast, at 3:00 pm, and at 5:00 pm. Participants had to continue fasting from 8:00 am to 4:00 pm, when an oral glucose tolerance test was performed and blood samples were drawn to assess glucose concentration every 30 minutes. Metabolites were quantified as a ratio to γATP resonance line.

Results It was possible to quantify concentrations of the phosphomonoesters (PME) phosphoethanolamin and phosphatidylcholin, the phosphodiesters (PDE) glycerophosphocholine and glycerophosphoethanolamine, and inorganic phosphate. However, there were no significant changes in concentrations of PME and inorganic phosphate detected based on the duration of fasting, only PDE showed a slight decrease at the second measurement (8.02E-01 vs 9.32E-01), which turned back to 9.34E-01 after glucose intake.

Conclusions ^{31}P NMRS allows to quantify concentrations of intrahepatic ^{31}P metabolites. However, it was not possible to detect any changes in phosphorylated gluconeogenetic intermediate concentrations after fasting or glucose intake.

Short-Term Balneotherapy Is Associated with Changes in Salivary Cortisol Levels

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Objective Since ancient times, physicians have speculated that balneotherapy (therapeutic bathing in medicinal and thermal springs) has a stress-relieving effect. While bathers usually experience a sense of well-being and relaxation during balneotherapy, the stress-relieving effects of balneotherapy have not yet been scientifically established. Therefore, the aim of this study was to evaluate the stress-relieving effects of short-term (25 min) balneotherapy in a controlled trial. To evaluate the stress-relieving effects of balneotherapy we measured salivary cortisol as a sensitive stress marker. Additionally, we assessed 2 control groups: one employed a well-established technique for stress relief (muscle relaxation) and the other was simply asked to rest.

Methods 49 healthy probands were randomized into 3 intervention groups. Interventions were either balneotherapy, resting, or progressive muscle relaxation (PMR). Group 1 performed bathing in a thermal spring (Bad Loipersdorf, Styria Thermal Region, Province of Styria, Austria), group 2 (control group 1) relaxed in deckchairs in order to rest, and group 3 (control group 2) performed PMR. In each group, the intervention lasted for 25 minutes. Saliva samples were collected immediately after getting up in the morning, before and after intervention, and participants rated their subjective relaxation levels on a quantitative scale. Salivary cortisol was determined by enzyme-linked immunosorbent assay. Additionally, the following psychological tests were employed: Perceived Stress Scale, Recovery-Stress Questionnaire, and Symptom List. One-way ANOVAs for repeated measures were performed to detect changes in salivary cortisol and subjective stress ratings between groups.

Results In all 3 groups, saliva cortisol decreased ($F = 23.532$; $p < 0.001$) and subjective relaxation ratings increased ($F = 132.178$; $p < 0.001$) after intervention. Interestingly, the increase of the participants' subjective levels of relaxation was significantly higher in the balneotherapy group compared to control groups ($F = 5.216$; $p = 0.009$).

Conclusion These findings suggest both objective and subjective stress-relieving effects associated with short-term balneotherapy, with respect to changes in saliva cortisol levels other stress reduction interventions seem to produce similar effects but may not be experienced as similarly beneficial as balneotherapy.

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