S = contribution of a student

01

Late-night urinary free cortisol in a 2 hour-timed urine sample in patients with adrenal tumors

Author/Address of institution:

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Background/Introduction:

Most adrenal incidentalomas are benign, non-secretory tumors. A mild autonomous cortisol secretion is the most common secretory pattern in functionally active adrenal tumors. As clinical signs and symptoms related to mild cortisol hypersecretion are mostly absent, the diagnosis is based on biochemical screening. Overnight dexamethasone suppression test (DST) and late-night salivary cortisol (LNSC) are used as screening tests. 24-hour urinary free cortisol is less sensitive. Shiwa et al reported higher late-night urinary free cortisol to creatinine ratio in patients with autonomous cortisol secretion compared to non-secretory tumors. We evaluated late-night free cortisol corrected for creatinine in a 2 hour-timed urine sample from 21-23 pm in addition to DST and LNSC.

Methods:

50 patients presenting with adrenal tumors were enrolled in the study. The diagnosis of adrenal tumor was based on imaging (CT, MRI or 18F-FDG-PET/CT). Testing was undertaken with baseline morning ACTH/cortisol levels and standard screening for primary aldosteronism and pheochromocytoma.
Patients were instructed to collect a timed urine sample for free cortisol from 21-23 pm and collect a salivary sample for LNSC (23 pm) on the same day. Patients then took 1mg dexamethasone at 23.15 pm: a morning blood sample was taken on the following day.
Data are expressed as median and interquartile range (IQR).

Results:

50 patients presenting with adrenal tumors were enrolled in the study. In our study, one patient had primary hyperaldosteronism, one had pheochromocytoma. Overall, 33 patients (age 56 (26-80 years; 15 males) had no cortisol excess. 17 patients (age 62 (39-84 years; 5 males) had cortisol hypersecretion, two of them with adrenocortical carcinoma with overt cortisol excess and 15 with cortisol >50 nmol/l in DST.
As expected (by definition), cortisol after DST was higher in 15 patients with (114, 74-203 nmol/l) than in 33 patients without cortisol excess (36, 27-45 nmol/l).
LNSC was 3.2 (1.75-12.25) in patients with vs. 1.5 (1.5-3.35 nmol/l) in those without cortisol excess. We also found higher median late-night urinary free cortisol values (without or with correction for creatinine expressed as cortisol to creatinine ratio) in patients with cortisol hypersecretion, 13 (8-36.5) µg or 14.52 (7.65-40.4) ug/mmol vs. 8 (5-11) µg or 7.59 (5.69-9.62) ug/mmol. The latter appears to discriminate at least as good as LNSC.

Conclusion:

Late-night urinary free cortisol could complement the available screening tests to detect autonomous cortisol secretion. Our results need to be confirmed in further studies.

02

GRAVES´ DISEASE AND MARINE-LENHART SYNDROME:

An unusual correlation.

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Background/Introduction:

The aim of this study is to review and discuss the clinical features and treatment options of the rare clinical presentation of the "Marine-Lenhart Syndrome", which is the coexistence of thyroid autonomy (Plummer's disease) and Graves' Disease has been termed .
Described in 1911 by Marine and Lenhart, the clinical features of the Marine-Lenhart Syndrome
refer to the development of autonomous thyroid nodules in patients with toxic adenoma and / or toxic multinodular goiter. Considering all the systematics involving the etiology, pathogenesis,
clinical manifestations and the treatment of Marine-Lenhart syndrome and their relationship with Graves' Disease , this study aimed to review and discuss its characteristics, clinics and treatment options aimed at improving the quality of practice involving metabolic disorders correlated with the autoimmune cause.

Methods:

The methodology adopted is a bibliographical research and case description.

Results:

The results of this study evidenced that different mechanisms are implicated in the pathogenesis of Graves' disease and in the nodular formation of thyroid tissue with functional autonomy. Graves' disease is caused by an autoimmune process involving the entire thyroid gland and is characterized by the presence of TSH receptor stimulating antibodies.
Studies on Marine-Lenhart Syndrome are scarce in the literature, but its development has been related to the treatment of Graves´ Disease employing a therapy with radioiodine, which leads to the formation of autonomic bifocal nodules. The Marine-Lenhart syndrome is a rare disease that gathers characteristics of both Graves´ Disease and Plummer's disease. However, among the described cases on this syndrome, only two of them involved positive TRAb titers.

Conclusion:

The present study concludes that caution should be exercised in the interpretation of thyroids in Graves' disease. Treatment of thyrotoxicosis requires high doses of oral antithyroid therapy or relapse occurs soon after oral antithyroid therapy is discontinued, this should alert the physician about the existence of toxic nodules, thus Marine-Lenhart Syndrome.

03

Macro-TSH as a rare differential diagnosis of subclinical hypothyroidism

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Background/Introduction:

Macro-TSH is a high molecular weight form of TSH (Thyroid Stimulant Hormone) formed by the binding of TSH to an immunoglobulin G (IgG). The molecular weight of macro-TSH is 150 kDa, while monomeric TSH is 28 kDa. The presence of the anti-TSH antibody hinders the clearance of TSH and consequently these patients have elevated serum TSH levels, accompanied by thyroid hormone levels within the normal range. This laboratory presentation is typical of subclinical hypothyroidism. But unlike this nosological entity, macro-TSH is biologically inactive, does not bind to the TSH receptor on thyroid cells and therefore does not stimulate thyroid hormone synthesis or goiter formation. In addition, patients with high molecular weight TSH will not have decreased TSH levels in response to levothyroxine replacement doses and may only evolve with elevated serum thyroid hormone levels after medication.

Methods:

We describe in this poster the case of an asymptomatic patient with no history of autoimmune diseases or use of exogenous levothyroxine, who sought the endocrinology service of the Military Hospital of Brasilia, for presenting very high levels of TSH and normal levels of anti thyroperoxidase antibodies and anti thyroglobulin. The echographic thyroid images were normal, and there was no drop in TSH levels despite the use of levothyroxine replacement doses. The patient was than submitted to a laboratory Macro TSH research by the gel filtration column chromatography method.

Results:

The result of the TSH analysis by gel filtration column chromatography identified the presence of a high molecular weight-TSH, confirming the suspected diagnosis of macro-TSH as a cause of the disease.

Conclusion:

The Diagnostic suspicion of macro-TSH is important in patients with a typical laboratory presentation of subclinical hypothyroidism in whom, when indicated for levothyroxine replacement, do not evolve with a normalization of TSH levels after hormone replacement. The Differential diagnosis is of paramount importance in populations at higher risk of inadequate levothyroxine replacement, such as pregnant women and children, especially during neonatal screening for congenital hypothyroidism.
p

04

Overweight, Obesity and its comorbidities: metabolic profile of patients at an Endocrinology Service in the State of Mato Grosso, Inland of Brazil.

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Background/Introduction:

Overweight and Obesity are chronic diseases associated with serious comorbidities. They pose one of the most important public health hazards worldwide. Its diagnosis and therapeutic approach should be done as early as possible in the history of the disease, to avoid complications. In 2025, 2.3 billion overweight adults and 700 million obese adults are projected worldwide. In Brazil, according to some surveys, more than 50% of the population is overweight. Large epidemiological studies have established an inverse relationship between BMI and the prevalence of diseases such as diabetes mellitus (DM), hypertension and dyslipidemia. The Abdominal circumference (AC) is highly correlated with abdominal fat and when altered denotes an increased risk for metabolic diseases.

Methods:

The purpose of this study is to characterize 67 overweight patients treated at an endocrinology clinic in Várzea Grande, Mato Grosso, from August 2016 to December 2017, defining the presence of the Metabolic Syndrome (MH) according to the criteria proposed by International Diabetes Federation (IDF).

Results:

Of the 67 patients studied, 55 were female and 12 were male, with ages varying from 20 to 74 years of age. Only 1 patient had CA within normal values, which reinforces their correlation with the presence of abdominal fat. Regarding weight, 34.3% were overweight and 65.6% obese, based on BMI. 43.1% presented grade I obesity (BMI ≥ 30 kg / m2), 43.1% obesity grade II (BMI ≥ 35 kg / m2) and 13.6% grade III obesity (BMI ≥ 40 kg / m2). Regarding blood pressure (BP), 35.8% presented altered BP, 16.4% had a diagnosis of hypertension or were already undergoing treatment. 34.3% of the patients with altered fasting glycemia (≥ 100 mg / dL) were 14.9% pre-diabetic and 19.4% diabetic, with 53.8% being new diagnoses of DM. In 31.3% of the patients, triglyceride levels ≥ 150 mg / dL and 44.7% HDL [low] values were found. Analyzing the criteria proposed by the IDF, 43.2% had a diagnosis of the Metabolic Syndrome. Patients with BMI ≥ 30 kg /m2 were questioned about current or previous treatment for obesity, and up to 50.7% reported never having been treated for Obesity.

Conclusion:

Overweight and obesity are health hazards with an increasing prevalence, along with its comorbidities such as hypertension, Diabetes and the high prevalence of Metabolic Syndrome in the studied group. Screening and early diagnosis should be recommended for this population, as well as adequate treatment and prevention. Lifestyle changes and a multidisciplinary follow-up with medications may become necessary. Such health problems need to be recognized as potentially hazardous for health.

05

Efficacy, Effectiveness and Safety of Nasal Glucagon as a Rescue Therapy for Severe Hypoglycaemia in Adults with Type 1 Diabetes

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Background/Introduction:
Injectable glucagon is one of the therapeutic options for severe hypoglycaemia which involves prior reconstitution. Nasal glucagon (NG), containing 3mg of glucagon dry powder absorbed through thep nasal mucosa, is a ready-to-use drug-device combination. NG is under development to treat severe hypoglycaemia in adults, children and adolescents with diabetes. This abstract presents the efficacy, effectiveness and safety of NG in adults with Type 1 diabetes (T1D).

Methods:
The randomised non-inferiority trial compared NG with injectable glucagon administered intramuscularly (IMG) for treatment of insulin-induced hypoglycaemia. The real-world use study evaluated the effectiveness and tolerability of NG 3mg to treat moderate/severe hypoglycaemic events (HEs).

Results:
In the randomised trial, NG 3mg was non-inferior to IMG in treating insulin-induced hypoglycaemia (98.7% versus 100%; difference: 1.3%, upper end of 1-sided 97.5% CI: 4.0%). NG 3mg was effective in a real-world setting in treating moderate/severe hypoglycaemia in adults with T1D, resolving 96.2% HEs including moderate and severe hypoglycaemia. Importantly, all 12 severe HEs resolved, and participants regained consciousness, stopped convulsions or achieved normalcy within 15 minutes of administration, as assessed by caregivers. NG and IMG showed consistent safety profiles for nausea and vomiting. Headache and nasal symptoms occurred more frequently with NG versus IMG, but most symptoms were transient.

Conclusion:
NG appears to be an efficacious and well tolerated ready-to-use nasal dry powder with potential to substantially ease severe hypoglycaemia rescue treatment in adults with T1D. It may also expand the community of people who could quickly render aid in a rescue situation.

06

Incidence of Iodine-induced Hyperthyroidism after Administration of Iodinated Contrast during Radiographic Procedures: a Systematic Review and Meta-Analysis of the Literature

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Background/Introduction:

Iodine induced hyperthyroidism (IIH) was a common issue in the early twentieth century after introduction of iodine supplementation in dietary salt. Currently, IIH is mostly encountered in western countries as a consequence of radiographic procedures involving the administration of iodinated contrast media (ICM). However, little is known about the magnitude and clinical relevance of this issue. To assess the incidence of hyperthyroidism after ICM exposure, we performed a systematic review and meta-analysis of the literature.

Methods:

MEDLINE, Embase and the Cochrane Library were systematically searched for trials published between 1946 and May 2018. Studies were considered eligible if they investigated the association between hyperthyroidism and iodinated contrast. Data on study design, baseline characteristics and outcome were extracted independently by two reviewers.

Results:

30 out of 1493 retrieved studies were included in the analysis. The time endpoint to assess thyroid hormone levels after ICM exposure varied between 1-541 days among studies. The overall estimated prevalence of overt hyperthyroidism after ICM exposure was extremely low (0%, 95% CI 0-0,3%), and did not change after adjustments for baseline thyroid status (0.3% in euthyroid patients at baseline, 95% CI 0-1,7%). There were no overt hyperthyroidism cases at 7 days after ICM exposure (0%, 95% CI 0-0%), and the incidence was very low at 30 days (0,2%, 95% CI 0-0,8%).

Conclusion:

The incidence of iodine induced hyperthyroidism following ICM administration during radiographic procedures is extremely low and does not seem to be higher in individuals with subclinical hyperthyroidism at baseline. Thus, prophylactic administration of thyrostatics or perchlorate prior to radiologic procedures involving ICM administration does not seem to be justified in most cases.

07 S

Analysis of the mixed-meal tolerance test for β-cell function after islet-transplantation in type 1 diabetes: a retrospective study

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Background/Introduction:

Mixed-meal tolerance tests (MMTT) are used to monitor graft function in patients with type 1 diabetes after islet transplantation. A peak concentration of blood glucose and C-Peptide within 180 minutes is expected in healthy individuals with normal glucose tolerance in MMTTs, but there is no data about the metabolic response in patients with type 1 diabetes after islet transplantation. This study focuses on analyzing the dynamics of MMTTs with respect to the time point of highest blood glucose and maximally stimulated C-peptide levels in this cohort.

Methods:

Data were gathered between 2000 until 2017 from patients that received islet allotransplantations at the University Hospital Zurich. We retrospectively analyzed liquid MMTTs (6kcal/kg bodyweight, 54% carbohydrates, 29% fat and 17% proteins) after 3, 6, 12 and 24 months after transplantation. Blood glucose and C-peptide levels were measured before ingestion and then in intervals of 30 minutes for a total of 180 minutes. Based on the need of exogenous insulin the cohort was divided into two groups, one with a lower (≤ 0.3 IU kg-1 d-1) and one with a higher dose of insulin.

Results:

MMTTs were conducted in 50 participants after islet transplantation. There was no distinct time point within 180 minutes after the start of the test when peak levels of glucose and C-peptide typically occurred. This was similarly true for patients with high and with low requirements of exogenous insulin. The group with a lower need of exogenous insulin showed a higher peak and a more rapid response in C-peptide levels in general. There was a negative correlation between levels of HbA1c and peak levels of C-peptide after an MMTT.

Conclusion:

When we assessed C-peptide and blood glucose levels during 180 minutes in an MMTT in a cohort of patients with type 1 diabetes after islet transplantation, there was no time when most maxima occurred. As expected, the need for only low amounts of exogenous insulin is associated with better islet funtion. In summary, the assessment of the endogenous insulin production after islet transplantation cannot be restricted to certain time points after meal ingestion.

08

EU-TIRADS ultrasonographic criteria modulate malignancy risk in cytologically indeterminate thyroid nodules but cannot reliably identify benign lesions

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Background/Introduction:
Thyroid cytopathology following ultrasound-guided (US) fine needle aspiration (FNA) is the key diagnostic tool to guide the treatment of thyroid nodules. However, up to 30% of cytopathological reports classify nodules into indeterminate categories with an increased risk of malignancy and further workup is required. Diagnostic surgery, repeat fine needle aspiration and molecular testing are currently recommended strategies, depending on the cytopathological result, local symptoms, patient preference and the availability of molecular panels. Our study explores whether the post-hoc application of ultrasound criteria can improve the risk stratification of cytologically indeterminate nodules.

Methods:
Data of patients admitted to the outpatients departments of the endocrine clinics of the Kantonsspital St. Gallen (n=292) and Aarau (n=27) for the workup of thyroid nodules were prospectively collected. Only patients/nodules with a definite diagnosis (i.e. benign or malignant cytopathology (Bethesda II and VI) and/or histology) were included in the final analysis (319 patients, 358 nodules). Selection for FNA took place according to the EU-TIRADS criteria and cytopathology was reported according to the Bethesda (B) system. Data are reported as medians and IQR and proportions and 95% CI. Chi-square, Fisher's exact and z-tests for 2 proportions were used to test for statistical significance. A $p<0.05$ was considered significant.

Results:
103/358 (29%) nodules were cytologically indeterminate (BIII 30%, BIV 70%) and 15% were finally malignant (10 papillary cancers 5 follicular cancers). 27% of the indeterminate nodules had low-risk US features (EU-TIRADS 2,3) and 23% had a high-risk US pattern (EU-TIRADS 5). An intermediate pattern (EU-TIRADS 4) was observed in the remaining 50%. The presence of a high-risk pattern significantly increased the malignancy risk (OR 3.65, 95%CI 1.2-11.1, p=0.021). This was mainly driven by the presence of irregular margins (OR 7.71, 95%CI 2.22-26.84, p=0.001). Despite the high positive predictive value of 92% for a benign lesion, a low-risk US pattern did not significantly lower the malignancy risk of indeterminate nodules (OR 0.39, 95%CI 0.09-1.61, p=0.343). 7.7% (95%CI 0.0-17.9), 11.5% (95%CI 2.9-20.2) and 29% (95%CI 11.0-47) of the nodules in the low, intermediate and high risk US group were malignant (p=0.130). All but one cancer identified conferred a low risk according to the American Thyroid Association risk stratification algorithm.

Conclusion:
Cytologically indeterminate thyroid nodules with a high risk EU-TIRADS US pattern carry an increased malignancy risk and diagnostic surgery may be an appropriate approach. Different strategies, such as molecular testing, should be explored to reliably identify benign lesions that may be safely followed or require no follow-up at all in indeterminate nodules with low and intermediate risk US pattern.

09

Ultra Rapid Lispro (URLi) Improves Postprandial Glucose (PPG) Control and Time in Range (TIR) in T1D Compared to Humalog® (Lispro): PRONTO-T1D Continuous Glucose Monitoring (CGM) Sub-study

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Background/Introduction:
URLi is a novel prandial insulin lispro formulation developed to more closely match physiological insulin secretion. This sub-study aimed to compare 24-hour glucose profiles using CGM during treatment with URLi or lispro used in combination with basal insulin glargine or insulin degludec in adults with T1D.

Methods:
Ambulatory glucose profiles were evaluated in 269 (22%) patients (pts) in PRONTO-T1D assigned to double-blind URLi (n=97) or lispro (n=99) given at the start of the meal, or open-label URLi (n=73) given 20 min after the meal (URLi +20). Primary endpoint was incremental $AUC_{0\text{-}2h}$ (iAUC) after breakfast. Blinded CGM (Dexcom G4 Platinum) was worn for 14 days before baseline and week 26. Pts reflected main study population: mean A1C at week 26 was 7.15% - URLi, 7.12% - lispro, 7.35% - URLi+20.

Results:
Compared to lispro, URLi had significantly smaller breakfast $iAUC_{0\text{-}2h}$ with estimated treatment difference (ETD) -28.1 mg.h/dL, p=0.048; more daytime TIR (71-180 mg/dL) ETD +43.6 min, p=0.020; and similar nighttime TIR. Time <50 mg/dL and >180 mg/dL were both numerically lower with URLi in daytime, with less time <50 mg/dL at nighttime vs. lispro: 7.0 vs. 12.6 min, p=0.023. PPG control in pts who marked meal times improved with URLi, while URLi +20 showed greater PPG variability. For all meals combined, URLi+20 showed less optimal PPG control compared to mealtime URLi ($iAUC_{0\text{-}2h}$ ETD: +1.7 mmol.h/L, p=0.001 and $iAUC_{0\text{-}3h}$ ETD: +1.8 mmol.h/L, p=0.049) but iAUCs were not significantly different compared to mealtime lispro. Glucose variability via CV and SD metrics was similar between groups, but less glucose variability was noticeable in CGM profiles of pts treated with URLi.

Conclusion:
When injected at the start of the meal, URLi resulted in significantly better PPG control and increased daytime TIR vs. lispro without increasing time in hypoglycemia. CGM results augment findings from PRONTO-T1D.

10

Copeptin kinetics and its relationship to osmolality during rehydration for diabetic ketoacidosis in children: an observational study

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Background/Introduction:
Copeptin is a surrogate marker for arginine vasopressin (AVP) release in response to hyperosmolal stimuli such as diabetic ketoacidosis (DKA). We aimed to characterize the temporal course (kinetics) of serum osmolality and copeptin during rehydration and insulin therapy in children with type 1 diabetes (T1D) and DKA, and the relationship between both (dynamics).

Methods:
An observational multi-center study was conducted including pediatric patients with T1D admitted for DKA and aged 1-18 years. Serial serum copeptin and osmolality measurements were taken at 14 time points from the start of rehydration therapy to 72 hours post rehydration start. Clinical parameters such as age, severity of DKA (mild = pH<7.3, moderate = pH<7.2, or severe pH<7.1) and Glasgow Coma Scale (GCS) were documented. Copeptin and osmolality kinetics and dynamics were further characterized using linear and non-linear mixed-effect regression modelling.

Results:
Twenty-eight children with T1D (20 newly diagnosed) and DKA (mild: n=3, moderate: n=12, severe: n=13) were included in the study. Median [IQ range] age was 11.5 years [8, 14], GCS was 15 points [15, 15], no patient had GCS <12 or suffered from cerebral edema. 275 paired serum copeptin and osmolality measurements were obtained (median: 10 per patient). Kinetics were described by a mono-exponential decline (95%CI) [inter-individual variability, expressed as coefficient of variation]: Copeptin decreased from 98 pmol/L (58.4-137.6) [142%] to 10.3 pmol/L (8.8-11.8) [25%] with a 50% recovery time (t1/2) of 6.0 h (5.1-11.5) [98%]. Serum osmolality decreased from 321 mosmol/L (315-327) [4%] to 294 mosmol/L (292-296) [1%] with t1/2 of 4.3 h (3.0-5.6) [64 %]. Bi-exponential decrease was also tested, but did not show clear improvement compared to mono-exponential decline given available data (large standard errors in parameter estimates). Dynamics were described as exponential increase: copeptin levels doubled with each osmolality increase by 15 mosmol/L (10-27) [50%], baseline copeptin levels were 9.2 pmol/L (8.0-10.4) [2%] at 280 mosmol/L.

Conclusion:
In this first data set with sequential copeptin levels in a hyperosmolal state in children, copeptin and osmolality decreased in parallel during rehydration therapy in patients with DKA. Physiologic maximum copeptin response was not observed despite wide osmolality range, suggesting a large synthesis and release capacity of AVP in children. This underlines the usefulness of copeptin as a surrogate marker of hyperosmolar triggered AVP release and as a potential marker to guide rehydration therapy

11

Health-care burden of hypopituitarism in adult medical inpatients - a population based matched cohort study

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Background/Introduction:

It is well-established that patients with hypopituitarism of various etiologies face excess mortality in the long-term outpatient management. However, data on the impact of pituitary dysfunction on clinical outcomes in acutely hospitalized patients is lacking.

Methods:

In this retrospective population based matched cohort study of all hospalizations in Switzerland from 2012 to 2017, adult (> 18 years) patients with a history of hypopituitarism hospitalized for acute medical reasons were compared with propensity-matched (1:1) controls. The primary outcome was a composite of in-hospital death, ICU admission and readmission within 30 days. Secondary outcomes included the single components of the primary outcome, length of index hospital stay, 30-day, and 1-year all-cause hospital readmission rates.

Results:

In total, 3280 patients with hypopituitarism were matched (1:1) with controls. Within 30 days of hospital admission the primary endpoint occurred in 944 (28.8%) of patients with pituitary dysfunction and in 782 (23.8%) of matched controls (odds ratio 1.29, 95% CI 1.15 to 1.44, P<0.001). There was a trend towards increased all-cause 30-day mortality among patients with pituitary dysfunction (mortality rates 5.9% vs. 4.9%; OR 1.21 (95% CI 0.97 to 1.49), P=0.09.
Compared to matched controls, length of index hospital stay was prolonged by 1.9 days in patients with hypopituitarism (9.6 vs. 7.6 days [95% CI 1.44 to 2.45], P<0.001).One year after the index hospitalization the risk of hospital readmission was still significantly higher among patients with hypopituitarism (OR 1.24 (95% CI 1.12 to 1.37), P<0.001.

Conclusion:

Patients with hypopituitarism carry a higher risk of adverse clinical outcomes when hospitalized for acute medical conditions.This study stresses the need for careful in-hospital management of patients suffering from the complex endocrine diagnosis of pituitary dysfunction.

12

Thyroid Involvement as the Initial Presentation of Sarcoidosis: a Case Report

Author/ Adress of institution
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Background:
Sarcoidosis is a systemic disorder typically characterized by the formation of non-necrotizing epithelioid cell granulomas. Several organs can be affected including the lungs, lymph nodes, eyes and skin. Thyroid infiltration is rare, affecting only a minority of patients. We herein report the case of a patient where thyroid involvement was the initial presentation of sarcoidosis.

Case report:
A 29 year-old man originally from Sri Lanka presented with hoarseness, night sweats and nasal obstruction. On clinical examination, the thyroid gland was slightly enlarged but not tender. Laboratory exams revealed a subclinical hypothyroidism (TSH 10.9 µU/mL) and a slightly eleva
ted CRP 18 mg/L with normal WBC count. Thyroid ultrasonography showed scattering of hypoechoic areas. Hence, silent thyroiditis was suspected. Due to the atypical presentation, FNA of one of the hypoechoic areas was performed; on cytopathology, necrotizing granulomas were observed. Tbc, HIV, Lues, Toxoplasmosis, Bartonella and Brucella infection were ruled out. Blood tests further revealed elevated levels of angiotensin converting enzyme (ACE), so that sarcoidosis was suspected. Albumin-corrected calcium was at the upper limit of normal range (2.51 mmol/l) with normal 1,25-DiOH-Vitamin-D levels. Chest X-ray showed mild bilateral hilar lymph node enlargement. Thoracic CT-scan revealed an enlarged inhomogeneous thyroid gland. Several enlarged hilar, mediastinal and axillary lymph nodes were found in the chest region, which reflected the characteristic distribution of sarcoidosis. The diagnosis could not be confirmed on bronchoalveolar lavage but granulomas were also found on biopsies of nose and vocal chords, thus explaining the patient's symptoms and confirming the diagnosis of sarcoidosis. A topical therapy with nasal corticosteroids was initiated. Subclinical hypothyroidism was treated with Levothyroxin.

Conclusion:
Thyroid involvement is rare in sarcoidosis: to date, only 65 cases of systemic sarcoidosis with thyroid gland involvement have been reported in the literature. We report a case of sarcoidosis with multiorgan involvement (thyroid, nose, vocal chords) that was initially suspected based on thyroid FNA results. Whereas granulomas in sarcoidosis are typically *non necrotizing*, cytopathology surprisingly revealed *necrotizing* granulomas in our patient: to date, this atypical characteristic has been reported only in 103 cases in the literature. Hence, sarcoidosis should be considered as a differential diagnosis of silent thyroiditis, even in the presence of necrotizing granulomas.

13

Poster: Hemangiopericytoma mimicking a pituitary adenoma - a case report.

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Background/Introduction:

The differential diagnosis of sellar masses is broad and includes - apart from the most common pituitary adenomas - other neoplasms such as craniopharyngiomas, germinomas, gliomas, meningiomas, and others. Hemangiopericytoma (HPC) is a rare vascular tumor arising from pericytes that may appear at any site of the body. We report an unusual case of an intrasellar HPC.

Methods:

A 63-year-old woman was admitted to our hospital complaining about headaches for twelve, frequently occurring orthostatic dizziness for six and progressive visual field defects for two months. Kinetic perimetry confirmed bitemporal hemianopia, and magnetic resonance imaging (MRI) revealed a sellar mass (27mm) which compromised the optic chiasm. On admission, pituitary insufficiency was diagnosed. Cortisol and thyroxine were replaced. The patient underwent transsphenoidal resection. Intraoperatively, the tissue had an unusual consistency with an increased bleeding tendency as compared with typical pituitary adenoma. After surgery, bitemporal hemianopia disappeared but adrenal insufficiency and hypothyroidism persisted. The final histo-pathological examination revealed a pleomorphic, highly vascular and cellular tumor (immune-positive fot STAT6, negative for CK8a/synaptophysin/TTF1). The diagnosis of a HPC grad 2 was made.

Results:

HPC are very rare intracranial tumors (<2.5% of all meningeal and <1% of primary intracranial tumors). However, a few cases of HPC presenting as a sellar mass have been described. Often they mimic a pituitary adenoma. The reported patients presented with visual field defects (reported in seven of twelve, just one with normal visual field) and headaches (reported in six of twelve). Data on pituitary function was available in six of twelve: two with normal pituitary profile; one with elevated prolactin; one with hypogonadism and adrenal insufficiency; one with adrenal insufficiency. In five of twelve cases visual field defects and pituitary insufficiency improved after surgery. Anyway, surgical resection is mandatory due to a high risk of progression, metastasis and relapse rates (up to 70%). Postoperative radiotherapy might be discussed in tumor boards with decision based on imaging and histopathological findings, and clinical aspects.

Conclusion:

HPC are very rare intrasellar tumor.

14

Improvement of Growth and Projected Adult Height by using a GnRH Inhibitor and an Aromatase Inhibitor in a Patient with Carney Complex Not Eligible for GH Treatment

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Background:

Carney complex is an autosomal dominant disease most frequently due to mutations in the gene for the protein kinase A type I-alpha regulatory subunit (PRKAR1A). One quarter of cases are de novo mutation. It is characterize by skin-pigmented lesions, cardiac myxomas,endocrine tumors and neuroendocrine tumors as PRKAR1A has the function of a tumor suppressor gene. 75% of male patients develop large cell calcifying Sertoli cell tumors (LCCSCT). These tumors may overexpress sex hormones, which leads in prepubertal boys to accelerated growth, advanced bone age and precocious pseudopuberty.

Patient description:

We report on growth of a boy with Carney complex (heterozygous PRKAR1A mutation p.V164DfsX5) who presented at 8 years with precocious pseudopuberty (G3, P3-4), height of 142.1 cm (SD +2.67), growth spurt and massively advanced bone age (+4 years) due to a hormonally active LCCSCT. After one-sided gonadectomy, he developed central precocious puberty and treatment with GnRH-blockage was therefore necessary. HGA axis suppression was successful, but projected adult height at this timepoint was 172 cm only with an parental target height of 182 cm +/- 8.5 cm. Because GH treatment with the genetic defect in a tumor suppressor gene seemed contraindicated, we started him on an aromatase inhibitor (letrozole) to stop further advancement of bone maturation. GnRH and aromatase inhibitor therapy were continued until the age of 13.5 years and after discontinuation spontaneous pubertal development occurred. At age of 14.5 years, height is 164.2 cm (SD -0.29), weight 50 kg (SD -0.50), growth velocity 3.1 cm/year (P3), bone age 14 years, pubertal stage Tanner 3 (P3, G3, A2). Projected adult height improved to 178 cm.

Discussion:

Boys with a Carney complex and a LCCSCT often present with precocious puberty with poor growth outcome. For puberty blockade they can be treated with GnRH-inhibitors, but this treatment mostly does not improve height. In this situation, a relative GH deficiency occurs but cannot be substituted for the underlying genetic defect in a tumor suppressor gene. In this situation, an aromatase inhibitor to block maturation in the growth plat may be an option to improve adult height as shown in our patient and few others in the literature.

Conclusion:

Treatment with an aromatase inhibitor in patients with Carney complex and LCCSCR improves predicted adult height by declining bone age advancement.

15

Early cardiovascular risk reduction under SGLT-2-inhibitors in high-risk patients (The Early CRUSH analysis of the PUSH Study)

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Background/Introduction:

There is no specific information on early cardiovascular risk reduction under treatment with SGLT-2-inhibitors. The purpose of this predefined sub-analysis of the PUSH study was to evaluate the extent of early cardiovascular risk reduction in patients with high cardiovascular risk during in-patient rehabilitation.

Methods:

The sub-analysis population included, as of June 2019, 76 high risk patients between the age of 40 and 79 treated during a period of 28 days in an in-patient rehabilitation setting. The patients were divided in 2 groups: the first group consisted of patients with inadequately controlled type II diabetes who were newly administered an SGLT-2-inhibitor of either canagliflozin 100 mg, or dapagliflozin 10 mg, or empagliflozin 10 mg. The second group was made of patients with adequately controlled type II diabetes mellitus patients with high cardiovascular risk without SGLT-2-inhibitors in their medication. In both groups, the blood pressure or lipid lowering medication were established according to recommended standards of medical care (1). High cardiovascular risk was arbitrarily defined as a ten year cardiovascular risk score above 20 % upon admission (baseline) using the ACC/AHA cardiovascular risk assessment (ASCVD) equation (2).

Results:

Mean age of the SGLT-2-inhibitor group was 70.9 ± 8.7 years vs. 70.3 ± 8.7 years of the non-SGLT-2-group. Baseline cardiovascular risk assessment using the ASCVD equation in percentage showed no significant difference between the 2 groups; SGLT-2-inhibitor group (n= 41): 41.4 ± 14.8 % vs. 41.3 ± 13.9 % of the non-SGLT-2-group (n = 35); p = 0.97 for inter-group difference. After 4 weeks of regular planned physical activity during in-patient rehabilitation, the absolute cardiovascular risk reduction between admission and 4 weeks was - 6.9 ± 3 % (p = 0.026) in the SGLT-2-group vs. - 4 ± 3.4 % in the non-SGLT-2-group (p = 0.24); see figure 1. This significant reduction in cardiovascular risk in the SGLT-2-group was more likely associated with a treat-to-target reduction in systolic blood pressure (reduction of mean systolic pressure from 139.4 mmHG to 127.5 mmHG; p = 0.0001) than with decrease in total cholesterol levels (reduction of mean total cholesterol from 4.4 mmol/l to 4.0 mmol/l; p = 0.15); see figures 2 and 3.

Conclusion:

The Early CRUSH analysis found that the addition of an SGLT-2-inhibitor in the medication of high-risk patients undergoing regular physical activity is associated with a measurable reduction in the cardiovascular risk in the short term. This reduction was more associated with a reduction in systolic blood pressure than with a decrease in total cholesterol levels.

16

Oncocytic variant of medullary thyroid carcinoma: an extremely rare entity to be misdiagnosed as benign follicular nodule - A Case Report

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Background/Introduction:

Medullary thyroid carcinoma (MTC) accounts for 2-3% of all thyroid carcinomas. The oncocytic variant of MTC is an extremly rare diagnosis (with less than 20 cases reported in the literature) and defined, when 60–70 % of the tumor cells are oncocytic in nature. Cells show a loose-granular eosinophilic (oncocytic) cytoplasma with “salt and pepper” chromatin. Oncocytic changes are common findings in benign as well as in malignant thyroid entities such as follicular adenomas, follicular carcinomas, papillary thyroid carcinomas and poorly differentiated thyroid carcinomas.

Methods:

A 75-year-old woman was diagnosed with a multinodular goitre at the ultrasound. The largest node (21 mm diameter) was described as slightly hypoechogenic, vascularized and with macrocalcifications (initially microcalcifications were reported).

Results:

Cytology of a fine needle aspiration (FNA) showed a regressively altered goitre with partial oncocytic transformation, classified as benign (according to Bethesda II). However, due to a certain size progression and the ultrasonographic aspect of the nodes, a total thyroidectomy was performed 8 months later. The histopathological examination revealed an oncocytic variant of a MTC, which could be confirmed by immunohistochemistry. Calcitonin blood levels were evaluated after surgery and the preoperative value of CEA could be ordered retrospectively. Both were markedly elevated. A cytological reevaluation of the initial FNA confirmed the diagnosis of an oncocytic variant of MTC. A Congo red staining showed amyloid (which was initially interpreted as colloid) and further immunohistochemical examinations showed positivity for calcitonin, chromogranin and synaptophysin.
A postoperative computer tomographic and ultrasound examination revealed no lymphadenopathy and no metastasis. We conducted biochemical follow up and no additional lymphadenectomy was performed. The biochemical screening for a MEN2 was negative.

Conclusion:

MTC and its oncocytic variant is known to be a mimicker of several thyroid lesions. The diagnosis of an oncocytic variant of MTC by means of FNA-cytology can be extremely difficult and information about ultrasonographic node patterns (typically solid, hypoechogenic, with ovoid to round shape and calcifications) as well as the measurement of calcitonin levels in plasma can lead to the correct diagnosis.

17

Mental health and its association with glucose-lowering therapy in GDM pregnancy. A prospective clinical cohort study

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Background/Introduction:

Women with gestational diabetes mellitus (GDM) have a fourfold increased risk of depression. Depression is related to both decreased adherence to lifestyle changes and to worsened metabolic health and could thus lead to an increased need for medical glucose-lowering therapy. In addition, the need for medical treatment by itself may impact on mental health (well-being and depression). To fill this knowledge gap, we aimed to investigate if reduced mental health (higher depression and lower well-being scores) in women with GDM predicts a need for medical treatment and if the need for medical therapy independently predicts subsequent reduced mental health during and after pregnancy.

Methods:

We included 342 pregnant women with GDM followed up at the GDM clinic at the Lausanne University Hospital. Patients completed two self-report questionnaires: The World Health Organization well-being index (WHO-5) at the first (29 weeks of gestation) and last prenatal GDM visit (37 weeks of gestation) and at the first postpartum visit (6 weeks postpartum) and the Edinburgh Postnatal Depression Scale (EPDS) at the first prenatal and the first postpartum visit. Medication use was extracted from medical charts. We used linear and logistic regressions and tested for mutual interactions between clinically-relevant depression scores and medical therapy.

Results:

Overall, 25.2 % of women were clinically depressed at the first GDM visit. In all women mental health improved during pregnancy and was higher in the postpartum period compared to the first GDM visit (both p≤0.001). Neither depression nor well-being at the first GDM visit predicted the need for medical glucose-lowering treatment during pregnancy (all p≥0.29). Furthermore, medical therapy or different forms of medication intake (metformin, basal or rapid-acting insulin) did not predict wellbeing at the end of pregnancy or depression or wellbeing in the early postpartum period, independent of their mental health at the first GDM visit (all p≥0.06). However, the impact of medical therapy on well-being in the postpartum period was significantly different in women who were clinically depressed at their first GDM visit compared to the others (i.e while medical therapy improved well-being in the non-depressed, it decreased it in the clinically depressed women, p for interaction=0.013). There were no other interaction effects (all p≥0.27).

Conclusion:

Overall, this prospective clinical cohort study did not find that mental health predicts need for glucose-lowering medication or that medical therapy impacts on mental health, neither during nor after pregnancy. However, the interaction analysis demonstrated that in women that are clinically depressed at the first GDM visit, medical therapy has a negative impact on well-being. Thus, preventive strategies should focus on these women.

18

Brunner's glands hyperplasia in a patient after Roux-Y gastric bypass – an important pitfall for GLP-1 receptor imaging

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Introduction: A 50-year old female patient was referred to our endocrine outpatient clinic because of frequent and severe episodes of postprandial hypoglycemia despite dietary modification and acarbose, DPP4-inhibitor treatment. Seven years earlier Roux-Y gastric bypass was performed for the treatment of morbid obesity followed by substantial weight loss.

Methods:
Continuous glucose monitoring revealed typical postprandial hyperglycemic peaks followed by recurrent hypoglycemic episodes and excluded fasting hypoglycemia. A standardized mixed-meal test confirmed hyperinsulinemic hypoglycemia requiring intravenous glucose administration with immediate remission of clinical symptoms. Due to the symptoms' severity of our patient a ^{68}Ga-DOTA-Exendin4 PET/CT (GLP-1 receptor imaging) was performed to exclude an untypical presentation of an insulinoma or nesidioblastosis, which would be a surgical target.

Results and clinical course:
^{68}Ga-DOTA-Exendin-4 PET/CT showed an intense signal between pars 1 and 2 of the duodenum with SUVmax 10.0 whereas the pancreas exhibited a homogenous physiological signal distribution. Double-balloon enteroscopy was performed which showed macroscopically unremarkable duodenal intraluminal structures. Biopsies of pars 2 duodenii revealed normal mucosa with hyperplastic Brunner's glands strongly positive for GLP-1 receptor and negative for insulin on immunohistochemistry. No histological signs of malignancy or inflammation were observed. Off-label therapy with empagliflozin was initiated followed by less hypoglycemic episodes and lower necessity for strict dietary adherence followed by a relevant subjective improvement of life-quality.

Conclusion:
1. 1. GLP-1 receptor positive Brunner's glands are a differential diagnosis of positive ^{68}Ga-DOTA- Exendin-4 PET/CT and a potential pitfall.
2. 2. Brunner's gland hyperplasia may occur in patients after gastric bypass, possibly due to increased GLP-1 levels, which, in turn, may lead to an upregulation of GLP-1 receptors.
3. 3. Whether the upregulation of GLP-1 receptors by GLP-1 and Brunner's glands hyperplasia are critical for the occurrence of postprandial hypoglycemia after bypass-

19

Postprandial hypoglycemia in patients after bariatric surgery is mediated by glucose-induced IL-1β

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Background/Introduction:

Postprandial hypoglycemia is an increasingly recognized important complication of bariatric surgery for which the underlying mechanisms still remain unclear. So far, no approved medical therapy exists. Based on pre-clinical data, we hypothesized that glucose-induced IL-1β triggers an exaggerated insulin response in this condition.

Methods:

We conducted a placebo-controlled, randomized, double-blind, double-dummy cross-over study with the SGLT2-inhibitor empagliflozin and the IL-1 receptor antagonist anakinra in 12 patients with confirmed postprandial hypoglycemia after gastric bypass by using a standardized liquid mixed-meal test and regular assessment of hypoglycemia and immunometabolic parameters.

Results:

Both drugs reduced significantly postprandial insulin release and prevented hypoglycemia without influencing GLP-1 or glucagon. Moreover, analysis of monocytes ex-vivo revealed a hyper-reactive inflammatory state.

Conclusion:

Our study proposes a role for glucose-mediated IL-1β in postprandial hypoglycemia after bariatric surgery and suggests that inhibition of SGLT2 and IL-1 may improve post bariatric hypoglycemia.

20

Taking advantage of liquid-chromatography mass spectrometry for mathematical modelling of insulin pharmacokinetics

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Background/Introduction:

Mathematical modelling of insulin pharmacokinetics requires highly specific quantification of plasma insulin levels. This is due to the structural similarity between endogenous and exogenous insulin, pro-insulin and its split products that may co-exist in human plasma. The widely used immunoassays for the measurement of plasma insulin concentrations lack specificity and/or do not allow multiplexing different insulins. Liquid-chromatography coupled to mass spectrometry (LC-MS) has the potential to circumvent this analytical shortcoming by providing molecular weight information. We sought to apply an in-house developed LC-MS insulin assay to for pharmacokinetic modelling of faster insulin aspart (FA) versus conventional insulin aspart (A) in patients with type 2 diabetes.

Methods:

We analyzed data obtained in a double-blind randomized cross-over trial contrasting fully closed-loop insulin delivery using FA and A in 15 adults with insulin-treated type 2 diabetes. All patients had residual endogenous insulin production and had long acting insulin on board during the experiment. Blood was collected every 15-30 min over a 10h period (07:00:17:00) to quantify plasma insulin levels (n=1000 samples). Sample work-up consisted of immunoextraction combined with LC-MS (UHPLC-Q-Orbitrap HRMS, Thermo Scientific, Waltham, MA, USA). Pharmacokinetics of FA and A were determined using a two-compartment model in SAAMII (V2.0, Epsilon Group and the University of Washington, Seattle, USA).

Results:

The LC-MS insulin assay accurately quantified human and analogue insulin with inter and intra-assay CVs ≤ 12 % and bias < 15 %. In a total of 1000 plasma samples, the assay successfully multiplexed insulin aspart, any residual long-acting insulin, endogenous insulin and pro-insulin. Using two-compartmental pharmacokinetic modelling, we found that time-to-peak plasma aspart concentration (Tmax) was 68.7±21.6min for FA and 89.7±31.8min for A (mean paired difference FA minus A 15.5min, 95% CI [-0.6, 31.6min], p=0.06) in line with the available literature. Metabolic clearance rate was comparable between the two insulins (ratio of FA over A 0.87, p=0.47).

Conclusion:

We hereby present a LC-MS approach that offers multiplexed, high-throughput, specific and precise quantification of human and analogue insulin. Its clinical feasibility was shown by assessing the pharmacokinetics of FA and A in type 2 diabetes. LC-MS has the potential to set a new standard in the quantification of insulin and opens new avenues for research.

21

Treatment Pattern in Neuroendocrine Tumors: Analysis of the SwissNET Database

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Background/Introduction:

Treatment options for neuroendocrine tumors (NETs) include mainly surgery, antiproliferative drugs and peptide receptor radionuclide therapy (PRRT). Virtually no high-level evidence exists addressing the optimal treatment sequence. Therefore, we aimed to analyze the treatment modalities and their sequence based on the Swiss NeuroEndocrine Tumor registry (SwissNET).

Methods:

SwissNET is a national registry, which prospectively documents patients with NETs since 2008, covering the entire area of Switzerland. We reviewed the data of all patients included in the registry. Currently, more than 40 participating hospitals are providing SwissNET with their patient information. All patients with a NET of the aerodigestive tract with the exclusion of small and large cell neuroendocrine carcinoma of the lung are included in SwissNet.

Results:

The SwissNET registry comprises 1366 patients with documented therapies in 1063 cases. The median follow-up time was 1.86 (IQR 0.35 to 4.03) years. 149 different therapy sequences were observed. Out of these only 37 (25 %) were used more than once. In 708 (67 %) patients surgery was the only treatment performed. Well-differentiated NETs of appendical origin represented the most common entity in patients treated only by surgery (22 %). The sequence of surgery followed by chemotherapy was most frequently documented in poorly (G3) differentiated (67 %) and pancreatic (33 %) NETs. Tumors treated with surgery followed by biotherapy were predominantly well-differentiated (G1) NETs of the small intestine, whereas the sequence of initial surgery followed by PRRT was most frequently chosen in well-differentiated (G2) small intestinal NETs.

Conclusion:

(1) Surgery is the treatment of choice in most NETs irrespective of tumor stage.
(2) Only a small part of NET patients receive other treatment modalities in their disease course.
However, when received, an impressive variety of treatment sequences could be observed.
(3) PRRT represented a treatment option irrespective of primary tumor site
(4) PRRT was used prior to systemic therapy mainly in small intestinal NETs
(5) Chemotherapy and molecular treatment is more commmonly in pancreatic NETs

22

Pre-exercise intake of fructose reduces the risk of exercise-induced hypoglycaemia in individuals with type 1 diabetes on ultra-long acting insulin

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Background/Introduction:

Maintaining euglycaemia during aerobic exercise and physical activity in type 1 diabetes imposes high demands on patients and health care providers. The risk of exercise-induced hypoglycaemia is mainly rooted in the exposure to excess exogenous insulin. Whilst patients on insulin pump therapy can mitigate this by lowering insulin delivery before exercise, patients on ultra-long acting insulins do not have this option. Preventive pre-exercise intake of glucose-based carbohydrates, as an alternative strategy, often causes hyperglycaemia. Fructose is a monosaccharide without immediate glycaemic impact due to extensive splanchnic first-pass uptake and conversion to subsidiary energy substrates such as glucose and lactate and may therefore provide a more suitable glycaemia-stabilising nutritional strategy. The present study investigated whether pre-exercise ingestion of fructose reduces the risk of hypoglycaemia during aerobic exercise.

Methods:

Eleven male adults with type 1 diabetes on ultra-long acting insulin (age 27.9±8.4 years, HbA1c 7.0±0.7 %, BMI 24.2±2.2 kg/m2, daily insulin dose 0.6±0.2 UI/kg) were recruited for this two-period randomised single-centre cross-over study. In random order, participants consumed 20g of fructose (diluted in 200ml water) or water (200ml) 30min before a 60min cycling session (45% VO2max). Participants' diet and activity were standardised for 48h before the exercise visit. Participants maintained their usual insulin dose throughout the study. During the study visit, plasma glucose and lactate levels were assessed every 5 min before and during exercise. Substrate oxidation was measured immediately before and between 15 and 25min of exercise. The primary outcome was time to occurrence of hypoglycaemia (plasma glucose ≤3.9mM) during 60min of exercise, while event occurrence was also considered as a binary outcome.

Results:

The risk for a hypoglycaemic event occurring at any time during a 60min aerobic exercise session was reduced by 87.5% with intake of fructose compared to water (hazard ratio 0.13 [95CI 0.02-0.64; p=0.01]). With pre-exercise intake of fructose compared to water, one participant (after 60min) vs 5 participants (after 27.0±10.4min) experienced hypoglycaemia.
Glucose levels before intake of fructose/water were comparable (6.1±0.2 vs 5.7±0.3mM, p=0.3). The mean exercise-induced decrease in glucose did not differ between the interventions (p=0.06). Lactate levels were higher during the 30min after intake of fructose and did not differ between the two conditions during exercise (p=0.17). Fructose intake increased carbohydrate and reduced fat oxidation before exercise (both p<0.01), whereas no difference in substrate oxidation was noted during exercise (p=0.87and p=0.45). No gastrointestinal side effects occurred.

Conclusion:

Pre-exercise intake of fructose is a novel, easily feasible and well-tolerated strategy to alleviate the risk of exercise-induced hypoglycaemia in adults with type 1 diabetes treated with ultra-long acting-insulin.

23

First experience with the hybrid-closed-loop system Minimed 670G in a Swiss tertiary referral centre – A retrospective data analysis

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Background/Introduction:

In November 2018, the first commercially available hybrid-closed-loop system (Minimed 670G [MM670G], Medtronic) has been launched in Switzerland. The aim of the present study was to analyse glycemic control after the transition to the new MM670G and to compare it to the preceding treatment in patients at our tertiary referral center.

Methods:

A structured training programme consisting of a device-instruction and a carbohydrate refresher course was set up for the transition to MM670G. The training was carried out 2x monthly in groups of 3-5 participants. We retrospectively evaluated diabetes history, HbA1c values and CGM data of all patients receiving the MM670G system between November 2018 and June 2019 at our centre. Diabetes history and HbA1c values were obtained from medical records. CGM data were downloaded from the proprietary manufacturer's software and analyzed with the open-source Glyculator-2 script. To assess change in glycaemic control, we compared CGM data in two 30day-periods before and after the transition to the MM670G system. Within 8 months 29 patients (28 DM1, 1 DM2; 16 male, 13 female; mean age 28.0±14.9y) switched to the new MM670G system. Insulin therapy before switching to MM670G was performed with MM640G in 17 (59%), with other CSII in 8 (27%) and with MDI in 4 (14%) patients.

Results:

CGM data after change to MM670G was available for 25 patients: average time CGM-sensor was in use after change to MM670G was 78%, and meantime in auto mode was 75%. HbA1c was 6.9±1.1%, mean glucose 8.2±0.8mmol/L, CV 31.4±5.8%, time in range (TIR, 3.9-10mmol/L) 76.1±11.6%, time > 10mmol/L 21.6±11.5% and time < 3.9mmol/L 2.3±2.2%, respectively. HbA1c significantly decreased using MM670G (7.4±1.5% vs 6.9±1.1%, p=0.002). Paired CGM data prior and post switch to MM670G was available for 14 patients. TIR was higher after change to MM670G (77.4±11.7% vs 70.0±14.5%, p=0.024), whereas time > 10.0mmol/L was lower (19.6±11.3% vs 26.4±15.3%, p=0.013). Coefficient of variation [CV], amplitude of glycaemic excursion [MAGE] and interday-variability (MODD) were lower under MM670G compared to the preceding treatment (CV 32.7±6.2% vs 35.6±6.2%, p=0.013; MAGE 6.5±1.5mmol/L vs 7.6±1.6mmol/L, p=0.003; MODD 2.7±0.8 vs 3.2±1.1mmol/L, p=0.04; respectively). No difference was found for total daily insulin dose (47.0±14.8U [MM670G] vs 48.2±15.9U [pre-change], p=0.23). Two patients stopped the therapy with MM670G (1 not satisfied, 1 perioperative ketoacidosis).

Conclusion:

After switching to the new MM670G system, glycaemic control significantly improved in an already well-controlled cohort of diabetic patients at our tertiary referral center. This improvement is reflected in particular by a higher time in range, decreased HbA1c and reduced glycemic variability.

24 S

Introduction of an Interdisciplinary Fine Needle Aspiration Service with Rapid On Site Evaluation: The Bern Experience

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Background/Introduction:

2-29% of all thyroid FNAs are non-diagnostic (Bethesda I). Contributing factors for non diagnostic results are small nodules, cystic features, lack of operator's experience, insufficient number of needle passes and a faulty sample preparation. A tested method for reducing the non-diagnostic rate of FNA is the application of rapid on-site evaluation (ROSE), which was introducted at the Interdisciplinary Thyroid Clinic of the Inselspital in January 2017. Aim of this study was to assess the performance of the Interdisciplinary Thyroid Clinic before and after the implementation of ROSE by comparing the rate of non-diagnostic and cytologically indeterminate FNAs in 2015 (before ROSE) and 2017 (with ROSE).

Methods:

The study was a retrospective analysis of data of all FNAs performed in the years 2015 (before ROSE implementation) and 2017 (after ROSE implementation). The primary outcome was the cytological non-diagnostic rate (Bethesda I).

Results:

116 ultrasound-guided FNA were performed without ROSE in 2015. In 2017, a total of 280 FNAs (152 FNAs with ROSE and 128 FNAs without ROSE) were performed. The overall non-diagnostic rate was 39 % (52/135) in 2015 and 15 % (46/280) in 2017. In 2015, Re-FNP without ROSE was performed on 19 nodules, and 9 remained non-diagnostic (Bethesda I), whereas 10 were benign (Bethesda II). The remainder 24 nodules were followed up by ultrasound. Out of the Non-ROSE FNAs in 2017, 43/128 (34 %) were non diagnostic. Of these, Re-FNA was perfomed with ROSE on 32 nodules and revealed Bethesda II. Surgery was performed for 5 nodules, whereas 6 patients were followed up by ultrasound. Only 3/152 (2 %) of ROSE-FNAs in 2017 were non diagnostic, due to cystic features. These patients were followed up by ultrasound.

Conclusion:

This study showed that the implementation of ROSE considerably improved the adequacy rate of FNAs results at our institution. However, the rate of non-diagnostic FNAs remained unchanged in the Non-ROSE group, probably due to the fact that in our tertiary center FNAs are performed not only by experienced physicians but also by physicians still in formation. Based on these results, ROSE was expanded to all FNAs in 2019.

25 S

Untargeted plasma metabolomics identifies broad metabolic perturbations in glycogen storage disease type I

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Background/Introduction:

The primary metabolic defect in glycogen storage disease type I (GSDI) results in fasting hypoglycemia and typical secondary metabolic abnormalities (e.g. hypertriglyceridemia, hyperlactatemia, hyperuricemia). The aim of this study was to broadly assess further perturbations of the metabolic network by using untargeted plasma metabolomics.

Methods:

Plasma samples of 14 adult GSDI patients (11 GSDIa, 3 GSDIb. Mean age 26.4y, range 16-46y) on standard treatment were compared to a cohort of 31 healthy controls utilizing ultra-high performance liquid chromatography (UHPLC) in combination with high resolution tandem mass spectrometry (HR-MS/MS) and subsequent statistical multivariate analysis. Significantly altered features were identified by mining against an internal library as well as online databases Metlin and mzCloud.

Results:

The metabolic profile showed numerous alterations of metabolites in different areas of the metabolic network, e.g. in central pathways of energy generation such as the tricarboxylic acid cycle, in the metabolism of creatine, in the urea cycle, in the amino acid and purine/pyrimidine metabolism, but also changes of cofactors such as biotin. These metabolic alterations were consistently seen in patients of both GSD subtypes (Ia and Ib).

Conclusion:

The metabolic defect of GSDI has profound effects on a variety of metabolic pathways in both GSDI subtypes, in addition to the known typical metabolic abnormalities (e.g. in lipid metabolism). The effect of glycemic control on these metabolic alterations, as well as the mechanisms behind these observations remain to be further elucidated.

26

Arithmetical comparison of insulin adaptions calculated by a do-it-yourself artificial pancreas system with actual insulin delivery of the Medtronic 670G hybrid closed loop system.

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Background/Introduction:
Do-it-yourself (DIY) artificial pancreas systems (APS) represent open source closed-loop-systems which consist of a compatible insulin-pump, a CGM sensor and a third-party microcomputer. The latter holds a system-specific algorithm calculating insulin dose adaptions and bridges communications between the separate devices. DIY APS are not approved for human use but gained considerable interest in a technique-affine diabetes-community. The present analysis describes differences in calculated insulin doses issued by DIY APS with calculations obtained from the Medtronic 670G hybrid closed loop system (M670G) in patients with type 1 diabetes.

Methods:
A cohort of 5 patients used the M670G together with a DIY APS in parallel for 7 consecutive days. DIY APS comprised a Dexcom G6 CGM sensor, a Medtronic 522 Paradigm insulin pump filled with saline, an Intel Eddison microcomputer holding the algorithm, and a smartphone for data exchange with a cloud database. CGM records and insulin pump histories of DIY APS were exported from the cloud database, respective data from M670G were exported from the Carelink-database. Total daily insulin dose (TDD) was calculated as the sum of basal rates and microboli as calculated by the system-specific algorithm together with manual boli. Insulin on board (IOB) was calculated as the sum of basal rate and microboli corrected by the exponential absorption of Insulin FIASP over a time period of 6 hours. Difference in IOB was subsequently analysed in 8 separate time periods of 3-hours per day and for CGM records measured within the range <3.9 mmol/L, 4.0-10.0 mmol/L, and >10.1 mmol/L.

Results:
Ratio of TDD issued by DIY APS vs. M670G was 1.51. Analysis observed an increased IOB of 1.52 international units (IU) from 00:00-3:00, 1.94 IU from 03:01-06:00, 2.4 IU from 06:01-09:00, 1.60 IU from 09:01-12:00, 1.73 IU from 12:01-15.00, 1.61 IU from 15:01-18:00, 1.46 IU from 18:01-21:00, and 1.19 IU from 21:01-00:00 using DIY APS vs. M670G, respectively. After dividing CGM records in separate glycemic ranges, difference in IOB was 0.36 IU for <3.9 mmol/L, 1.23 IU for records within 4.0-10.0 mmol/L, and 1.15 IU for records > 10.1 mmol/L as calculated by DIY APS vs. M670G, respectively.

Conclusion:
Use of DIY APS translated into higher IOB during day- and nighttimes as compared with M670G. Moreover, DIY APS would have issued a higher IOB throughout different ranges of CGM records compared with M670G. The analysis was limited by the fact that only M670G infused insulin which might have deteriorated calculations of the DIY APS. The study provides the first comparison of a DIY APS algorithm with an approved hybrid closed loop system in Switzerland.

27

Effect of glucose control on outcomes in hospitalized patients with glucocorticoid-induced hyperglycemia – a retrospective analysis

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Background/Introduction:

Glucocorticoid (GC)-induced hyperglycemia is a frequent side effect in hospitalized patients. Guidelines recommend treat-to-target treatment of GC-induced hyperglycemia between 6-10 mmol/l with insulin, but patient-specific outcome has not been well-studied.

Methods:

In a retrospective data analysis, hospitalized patients at the medical ward receiving GCs between January 2014 to April 2018 were included. We evaluated the effect of glucose values, glucose control and treatment regimen for hyperglycemia on outcome. Mortality, cardiovascular events, and infections until 30 days after admission were evaluated.

Results:

16% of all patients hospitalized at the medical ward (n=25183) received systemic GCs. 2424 patient data sets were available for analysis. 36% did not have any glucose measurement, and 50% had 2 measurements per day. 824 (34%) developed GC-induced hyperglycemia. 511 patients (21%) had a previous diabetes diagnosis. Patients with GC-induced hyperglycemia had a higher rate of adverse events (OR 1.4, 95% CI 1.1-1.9) than normoglycemic patients, but coefficient of glucose variation and time in range were not independent predictors for outcome. This effect remained significant after adjusting for age, gender, BMI, preexisting comorbidities, GC dose (mg/kg KG per day), reason for hospitalization and for GC administration (adj. OR 1.3, 95% CI 1.0-1.7). For patients with new-onset GC-induced diabetes, results were similar (OR 1.4, 95%CI 1.1-1.9), but after adjusting for cofactors, these results were no longer significant (OR 1.3, 95% CI 0.96-1.8). When comparing patients with previous diabetes, now hyperglycemic, and new-onset GC-induced diabetes, there was no significant difference (OR 1.2, 95% CI 0.9-1.7; adjusted OR 1.2, 95%CI 0.8-1.6). In sensitivity analysis, both coefficient of glucose variation and time in range were potential predictors for outcome..

Conclusion:

Mortality, cardiovascular events and rate of infections were higher in patients with GC-induced hyperglycemia than in normoglycemic patients, independent of previous diabetes diagnosis. Whether the treatment of GC-induced hyperglycemia has an effect on outcome remains to be shown.

28

Evaluation of Malignancy Rate of Nodules according to the Bethesda System: The Bern Experience

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Background/Introduction:

Thyroid ultrasound and fine needle aspiration (FNA) help to stratify the risk of malignancy rate of thyroid nodules. At our Interdisciplinary Thyroid Clinic, the Bethesda System is implemented, which details malignancy risk for each cytopathological category. As standard of care we analyzed our data with reported malignancy risk of Bethesda system.

Methods:

The study was a retrospective analysis of data of all FNAs performed in the years 2015 and 2017. We collected data to determine the malignancy rate of investigated nodules at our clinic and compared our data with those of the established Bethesda reporting system.

Results:

404 ultrasound-guided FNA were performed (116 in 2015 and 288 in 2017). 60 nodules (15 %) were resected, of which 22 were proven to be malignant on histopathology (5 %). Looking closer into the different categories, we alligned following results: Bethesda I: 58 nodules, 10 resected, 2 histopathologically malignant (3 %). Bethesda II: 319 nodules, 39 resected, 1 histopathological malignant (0,3 %), Bethesda III: 4 nodules, 2 resected, 2 histopathologically malignant (50 %), Bethesda IV: 5 nodules, 5 resected, 1 histopathologically malignant (20 %) Bethesda V: 3 nodules, 3 resected, 3 histopathologically malignant (100 %) Bethesda VI: 15 nodules, 14 resected (1 anaplastic thyroid carcinoma), 15 histopathological malignant (100 %).

Conclusion:

Our results are similar to those of the established Bethesda reporting system. We found discrepancies only for the Bethesda III and V categories, with our malignancy rates being higher than those reported in the Bethesda classification. This could be attributed to the small number of cases in these categories. Another reason could be the very restrictive use of the Bethesda category III in our cytology laboratory.

29 S

Clinical characteristics of adult patients with inborn errors of metabolism in French-speaking Switzerland: the challenge continues after transition

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Background:
Inborn errors of metabolism (IEMs) are a group of rare disorders caused by genetic mutations that affect enzymes of intermediary metabolism. Number of patients with IEMs reaching adulthood has been continuously increasing in the past few years due to better diagnosis techniques, effectiveness of treatments and management of metabolic decompensations. Because adult with IEMs has become an emerging and challenging group in Switzerland, this study was intended to report the clinical characteristics of adult patients with IEM followed in the Adult Metabolic clinics in French-speaking Switzerland.

Methods:
This was a retrospective cohort study conducted in two University Hospitals in Geneva and Lausanne, Switzerland, both clinics being supervised by the senior author (CT). All adult patients with a biochemical and/or genetic diagnosis of IEM followed at the adult metabolic clinic from the CHUV and HUG since 2013 to 2018 were included in the study. Electronic patient records were reviewed for clinical features, biochemical investigations, neuroimaging, treatment and long-term outcome. The patients were subdivided in three categories according to the pathophysiology; small molecule disorders, energy defects and storage disorders.

Results:
We analyzed the data of 126 patients. The most prevalent group of IEM was small molecule disorders with 84 patients (67%), followed by energy defects disorders with 27 patients (21%) and storage disorders with 15 patients (12%), except for patients with Fabry disease who are followed by a specific and separate clinic. Classical phenylketonuria was the most represented disease with 23 patients. 81% of all the patients were transitioned from the pediatric metabolic clinic whereas 19% were referred from other specialty. 61% of the patients suffered from complications directly linked to their disease and 37% were hospitalized at least once during the time of the study, 74% of them for a metabolic decompensation. 97 patients (77%) were receiving a specific treatment (including specific diet) for their disease, which was efficient for 69 (75%) of them.

Discussion:

IEM constitutes a group of conditions with great clinical heterogeneity. A multidisciplinary and coordinated approach is necessary to monitor target organs as more than half of our patients presented with medical complications. Despite regular follow-up some of our patients were susceptible to metabolic decompensation and required specific management. Given the burden of disease, this study highlights the necessity to train specialists in adult EIMs to meet these care needs including up-to-date clinical and therapy monitoring and expertise to carry acute decompensation. This study should be extended to the other parts of Switzerland to obtain a basis for training programs and increase awareness of this matter.

30 S

Oral disposition index in patients with cystic fibrosis

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Background/Introduction:

Cystic fibrosis (CF) is characterised by inflammation, wasting and multi-organ failure. Not only CF related diabetes (CFRD) but also milder forms of dysglycemia (detected by oGTT) are associated with increased morbidity and mortality. We evaluated indices of insulin secretion and sensitivity in CF patients with severe lung disease awaiting lung transplantation (LTX).

Methods:

Over 10 years, consecutive CF patients were included during evaluation regarding LTX. Patients (excluding those known for previous fasting plasma glucose (FPG) >7mM and those treated with insulin) and a control group of healthy subjects underwent an oGTT to assess insulin secretion (insulinogenic index, IGI, Wareham), insulin sensitivity index (ISI, Matsuda); as a measure of beta-cell function adjusted for insulin sensitivity, we also calculated the oral disposition index (DI). Results were expressed as median and interquartile range

Results:

oGTT was performed in 56 CF patients (age 26 (21-36) years; 29 males) and 22 healthy controls (age 32 (25-35) years; 11 males). BMI was lower in CF patients than in controls (18.2 (16.5-20.5) vs 22.0 (20.6-25.1) kg/m2). FPG was similar in patients and in controls (4.8 (4.4-5.3) vs 4.5(4.2-4.7) mM), whereas 1h and 2h plasma glucose were higher in CF patients than in controls (1h: 11.5 (9.6-13.0) vs 7.6 (6.4-9.1) mM; 2h: 9.5 (7.1-13.8) vs 5.7 (4.4-7.0) mM). As defined by post-challenge venous plasma glucose concentrations, CF patients could be assigned to one of 4 categories: 22 (39.2 %) to CFRD, 11 (19.6 %) to impaired glucose tolerance (IGT), 8 (14.3%) to indeterminate glucose tolerance (INDET), and 15 (26.8%) patients to normal glucose tolerance (NGT).
IGI was lower in CF patients than in controls (14.2 (7.4-21.8) vs 58.1 (43.6-81.3) pM/mM), whereas ISI was comparable (8.6 (6.8- 10.9) vs. 9.4 (7.5-11.0) (mMpM)-1). DI was lower in CF patients than in the control group (0.29 (0.18- 0.55) vs. 1.53 (1.10-1.98).
Importantly, both IGI and DI were already (and comparably) reduced within the 2 subgroups of CF patients with normal FPG and impaired tolerance but no CFRD; to 15.8 (14.0-23.5) pM/mM and 0.35 (0.19-0.52) in patients with IGT and to 13.8 (8.1-18.8) pM/mM and 0.28 (0.17- 0.39) in those with INDET.

Conclusion:

Our data confirm a high number of newly diagnosed dysglycemic disorders in the group of CF patients awaiting LTX. It remains unclear whether IGI or DI (which identify subtle changes in beta-cell function) provide more sensitive disease progression-predictive and clinically useful (e.g. timely initiation of prandial insulin replacement therapy) information as compared to glycemic categories. Considering the 1 h in addition to the 2h glucose value appears to be well justified.

31 S

SwissHPN-II Study: Long Term Challenges and Complications

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Background/Introduction:

The incidence of home parenteral nutrition (HPN) for adults in Switzerland is about 4 per 1 million inhabitants per year1. Although necessary, no representative national registry exists to date to compare and evaluate HPN treatments with other countries and healthcare systems. The prospective SwissHPN-II study implements a first study from 2013/2014. The study aimed to characterize adult Swiss HPN-patients, their underlying diseases, HPN indications and complications, and living conditions. This preliminary study evaluation after two years focused on PN catheters-related complications and PN regimens used.

Methods:

Data from a structured questionnaire filled every 6 months by the patient and the treating physician of 70 HPN-patients (50% women) were analyzed.

Results:

The proportion of central venous accesses were: Hickmann (54%), Port-a-Cath (29%), and PICC (17%). Except two, all patients were infused with commercial multi-chamber all-in-one PN admixtures. Most patients (56%) manage HPN administration themselves or with help of family members. Most prevalent underlying diseases are cancer (30%), bariatric surgery (11%), and Crohn's disease (10%). Mechanical and infectious catheter-related complications were experienced by 66% and 36% of the patients, respectively. Catheter thrombosis occurred in 14% of the patients.

Conclusion:

The larger HPN-patient number compared to SwissHPN-I (+112%) gives a representative picture of the adult Swiss HPN cohort. Oncologic patients account for only one third. Mechanical complications affected every third patients while infectious complications were seen in two thirds of the patients. Venous thrombosis occurred in every sixth patient. More comprehensive data will be presented after completion of the data analysis.

32 S

Economic Challenges in Nutritional Management

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Background/Introduction:

Disease-related malnutrition (DRM) is a highly prevalent independent risk and cost factor with significant influence on mortality, morbidity, length of hospital stay (LOS), functional impairment and quality of life. The aim of our research was to estimate the economic impact of the introduction of routinely performed nutritional screening (NS) in a tertiary hospital, with subsequent nutritional interventions (NI) in patients with potential or manifest DRM.

Methods:

Economic impact analysis of natural detection of inpatients at risk and estimation of the change in economic activity after implementation of a systematic NS were performed.

Results:

The reference population for natural detection of DRM is about 20,000 inpatients per year. Based on current data, DRM prevalence is estimated at 20%, so 4,000 patients with potential and manifest DRM will be detected. The NI costs were estimated at CHF 0.693 million, with savings of CHF 1.582 million (LOS reduction) and CHF 0.806 million in additional revenue (SwissDRG system). Thus, the introduction of routine NS generates additional costs of CHF 1.181 million that are compensated by additional savings of CHF 2.043 million and an excess in additional revenue of CHF 2.071 million.

Conclusion:

NS with subsequent adequate nutritional intervention shows an economic potential for hospitals

33

Empagliflozin increases sodium levels in patients with the syndrome of inappropriate antidiuretic hormone secretion – a randomized, double-blind, placebo-controlled study

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Background/Introduction:

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the predominant cause of hyponatremia but its treatment options are unsatisfying. The SGLT2-inhibitor empagliflozin promotes osmotic diuresis via urinary glucose excretion and could therefore be a novel treatment option for SIADH

Methods:

From 09/2016 until 12/2018 we recruited 88 hospitalized patients with hyponatremia <130mmol/l due to SIADH in the University Hospital Basel. Patients were randomly assigned to either treatment with empagliflozin 25mg/day or placebo for four days in addition to standard fluid restriction of <1000ml/24h. The primary endpoint was the absolute change in plasma sodium concentration after four days of treatment

Results:

87 patients completed the trial of whom 43 (49%) received treatment with empagliflozin and 44 (51%) placebo. Severity of the SIADH was similar, with a median plasma sodium concentration of 125.5 mmol/l (IQR:122-127) and 126 mmol/l (IQR:123-127) in the empagliflozin and placebo group respectively.
Treatment with empagliflozin resulted in a significantly higher increase of median plasma sodium concentration of 10mmol/l (IQR:5–12) compared to placebo with 7mmol/l (IQR:3–11), p=0.038.
Severity of hyponatremia (<125 mmol/l) and baseline osmolality levels were predisposing factors for treatment response with empagliflozin. Treatment was tolerated well, no events of hypoglycemia or hypotension occurred.

Conclusion:

Empagliflozin in addition to fluid restriction leads to a higher increase in plasma sodium levels compared to placebo in patients with SIADH and is therefore a promising new treatment option.

34

Autosomal dominant growth hormone deficiency due to a novel c.178G>A mutation in the GH1 gene causing instability of the mutant GH protein (p.Ala34Thr)

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Background/Introduction:

Growth hormone (GH) is a member of the somatotropin/prolactin family of hormones and plays an important role in human physiology. Mutations in GH1 gene cause isolated growth hormone deficiency. Several disease-causing mutations from patients with IGHD have been reported. The most frequent cause of familial growth hormone deficiency (GHD) is Type II autosomal dominant GHD (isolated GHD type II) due to several heterozygous GH1 mutations. These mutations have been shown to (a) produce shorter isoforms of GH that does not bind to growth hormone receptor, (b) cause diminished secretion of GH or (c) result in misfolded GH protein.

Methods:

Method: Genomic DNA from patients with familial GHD was enriched for the coding exons using hybrid capture technology and GH1 was sequenced using Next Generation Sequencing technology. The p.A34T mutant protein was expressed in bacteria and binding to GHR was studied by surface plasmon resonance technology. Computational prediction of transcription indicated alternative splicing is likely to produce a shorter GH variant with skipping of exon 3 in GH1. Mammalian cell based studies incorporating transfection of whole GH1 gene containing exons/introns were used to study transcription effects. RNA was isolated from cells transfected with WT and mutant GH1 gene and analyzed by RT PCR using primers in 2nd and 5th exon of GH1 gene that could identify all possible isoforms of GH1 mRNA.

Results:

GHD was identified in three female siblings aged 3.25-6.33 years (Ht SDS -3.21 to -1.13, peak GH 2.9-6.6 ng/mL); their mother had previously been diagnosed with GHD at at age 12.33 years (Ht SDS -3.44, GH peak &lt 2 ng/mL). Sequencing of GH1 identified a heterozygous variant (c.178G>A; p.Ala34Thr) that had not been previously described, and was not found in the Broad ExAc dataset representing >60,000 children without severe childhood-onset disease. Functional studies using whole gene transfection shoed that this mutation leads to alternate splicing resulting in increased production of the smaller 17.5kD isoform of GH due to missing exon 3.

Conclusion:

The presence of a heterozygous GH1 variant (c.178G>A, p.Ala34Thr) in four individuals with GHD suggests that this is a novel cause of IGHD type II. Production of the smaller 17.5 kD GH isoform results in poor binding to GHR and competition with the normal GH protein, explaining the dominant negative phenotype.

35 S

Effects of alcohol consumption on copeptin and sodium-water homeostasis

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Background/Introduction:
Alcohol intake influences the sodium-water homeostasis; however, its exact effect remains unclear. Whether additional sodium and/or water intake can counteract these changes and the resulting hangover symptoms has not yet been investigated. The aim of this study was therefore to evaluate the physiological changes of alcohol consumption on the vasopressin surrogate marker copeptin and the sodium-water homeostasis. Furthermore, the effect of additional sodium and water intake with alcohol on hangover symptoms was investigated.

Methods:
Ten healthy men underwent four study nights in random order with the following interventions: a) beer consumption only, b) beer consumption with additional water or c) stock, d) water consumption only. The respective fluid intake was equal between the interventions and calculated to reach a blood alcohol concentration of 0.8 ‰ in the beer consumption groups. Blood and urinary samples including copeptin, sodium and osmolality measurements were taken at six timepoints over 720 minutes. The primary endpoint was the mean differences in copeptin levels 90 minutes after the start of fluid intake. Secondary endpoints were the mean differences in blood and urinary sodium and osmolality levels and hangover symptoms between the four interventions.

Results:
In all interventions plasma sodium levels decreased similarly from baseline to 60 minutes after fluid intake but increased significantly thereafter in the alcohol compared to the water consumption group (p<0.001). Additionally, alcohol consumption led to an increase in plasma osmolality levels 90 minutes after consumption, compared to a decrease with water consumption (p<0.001). Despite this osmotic stimulus, copeptin levels showed a similar decrease in all four groups after 90 minutes but resulted in significantly higher levels thereafter in the alcohol compared to the water consumption group (p=0.03). This led to a higher total urinary volume excretion after alcohol compared to water intake, p=0.01. Additional water or sodium intake did not counteract the effects observed consuming alcohol. Also, no differences between the four groups in regard to hangover symptoms the morning after were observed.

Conclusion:
Alcohol consumption inhibits copeptin secretion upon osmotic stimulation resulting in increased fluid loss and dehydration. Additional water or sodium intake did not change dehydration state nor hangover symptoms.

36

Model-Based Assessment of C-peptide Metabolic Clearance Rate in Post-Bariatric Individuals Experiencing Postprandial Hyperinsulinemic Hypoglycemia during OGTT

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Background/Introduction:

The Oral Minimal Models (OMMs) [Cobelli et al. 2014] are useful tools which allow to quantify postprandial glucose metabolism in humans. In particular, the C-peptide OMM (OCMM) [Breda et al. 2001] interprets plasma C-peptide concentration in relation to the observed changes in glucose concentration, thus providing an estimate of beta-cell responsivity to glucose. To do that, OCMM makes use of the knowledge of the C-peptide metabolic clearance rate (MCR) fixed to the values predicted by the Van Cauter population model (VCPM) [Van Cauter et al. 1992]. However, the VCPM was validated in normal, obese, and non-insulin-dependent diabetes individuals, hence it might not by applicable to different populations such as patients following bariatric surgery.
The aim of this study is to assess the validity of OCMM coupled with VCPM in post-gastric bypass individuals suffering from postprandial hyperinsulinemic hypoglycemia (PHH) as a late post-operative complication.

Methods:

Sixteen post-gastric bypass individuals suffering from PHH (11F; age = 43±8 y; BMI = 42.9±6.2 kg/m2 [pre-surgery] and 28.2±7.1 kg/m2 [post-surgery], normal glucose tolerance pre-surgery) underwent an OGTT (75g of glucose). Plasma glucose, insulin and C-peptide were measured for 210 min. The OCMM was identified on C-peptide data both by fixing the C-peptide MCR to that predicted by VCPM (PM approach) and by estimating it from the data using a Bayesian Maximum a Posteriori estimator (DB approach). Model performance was assessed based on model ability to predict the data.

Results:

Using the PM approach, the model was not able to well predict the data in 8/16 subjects showing a significant underestimation of C-peptide peak and overestimation of the tail. Conversely, using the DB approach, model prediction was able to satisfactorily predict the data. As a result, a significantly higher C-peptide MCR value (0.075±0.024 min-1 vs 0.060±0.002 min-1, p<0.05) was obtained when it was estimated (DB approach) vs. predicted by the VCPM (PM approach), respectively.

Conclusion:

Taken together, these results suggest that in our cohort of PHH subjects C-peptide MCR is higher than the values predicted by the VCPM. However, this hypothesis should be tested using the state of the art methodology for the measurement of C-peptide kinetics, requiring somatostatin infusion and exogenous C-peptide injection.

37

Pitfalls in the workup of PTH dependent hypercalcemia: Familial hypocalciuric hypercalcemia type 3 mimicking sporadic primary hyperparathyroidism

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Background/Introduction:

Familial hypocalciuric hypercalcemia (FHH) is a rare, heterogenous, autosomal-dominant disease, due to loss-of-function mutations in the CASR (calcium-sensing receptor; FHH type 1), GNA11 (G-protein subunit α11; FHH type 2) or AP2S1 (adaptor-related protein complex 2, sigma 1; FHH type 3) genes. Because of its benign nature and hence different treatment, it is crucial to distinguish FHH from other forms of primary hyperparathyroidism (pHPT), including both sporadic and other genetic etiologies such as MEN1, isolated familial HPT and jaw tumor-HPT syndrome. However, establishing a diagnosis of FHH may be difficult because of overlapping biochemical features, especially a poor specificity of the urine calcium-to-creatinine ratio (UCCR) with 20% of patients with sporadic pHPT presenting with values < 1% and recent guidelines suggest genetic testing in young subjects with a low urinary calcium excretion.

Case presentation:

A 43 year old man was admitted to the endocrine clinic for the workup of mild PTH-dependent hypercalcemia (Ca 2.7 mmol/l, PTH 55 ng/l, 25-OH-Vitamin D3 83 nmol/l). The fractional urinary calcium excretion was repeatedly low (0.43 and 0.87%) and DXA scanning revealed normal bone density. The family history was remarkable for urolithiasis in the patient's father, sister and niece at the young age of 12 years. Plasma calcium concentrations, however, were normal in both parents and the patient's niece and elevated at only one occasion in his sister. A genetic workup failed to detect a pathogenic variant of the menin gene. Cervical ultrasound and sestamibi SPECT-CT scanning were consistently compatible with a parathyroid adenoma dorsal of the left thyroid lobe and a diagnosis of spontaneous pHPT due to a singular adenoma was assumed. Because of the young age and compatible clinical symptoms the patient was referred for parathyroidectomy and a 153 mg left cranial parathyroid gland was removed. However, intraoperative PTH failed to decrease and hypercalcemia persisted on several follow-up visits. A subsequent choline PET-CT scan failed to detect a parathyroid adenoma. Further genetic testing (CASR, GNA11 and AP2S1 genes) revealed a pathogenetic heterozygous loss-of-function variant of the AP2S1 gene (c.44G>A; p.Arg15His) and a diagnosis of FHH type 3 was established. A genetic workup of the patients family is pending.

Conclusion:

This case report highlights several pitfalls in the workup and differential diagnosis of PTH-dependent hypercalcemia and FHH, including heterogeneous clinical presentation and false-positive imaging results and strongly advocates for the early use of genetic testing in the presence of any suspicious features.

38

Congenital generalized lipodystrophy: Early diagnosis by perianal eruptive xanthomas and therapy of metabolic complications during infancy

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Background/Introduction:

Lipodystrophy syndromes are rare diseases due to deficiency of adipose tissue in absence of a catabolic state. As a consequence of defient fat mass and low levels of leptin, lipid storage occurs in liver, muscles and heart, causing insulin resistance and diabetes, hypertriglyceridemia, polycystic ovarian syndrome (PCOS) and nonalcoholic fatty liver disease (NAFLD). Depending on etiology and distribution of deficient adipose tissue, there are four major categories: congenital generalized lipodystrophy (CGL), familial partial lypodystrophy (FPLD), acquired generalized lipodystrophy (AGL) and acquired partial lipodystrophy (APL).

The diagnosis is based on history, physical examination, body composition and metabolic status. Since there is no confimatory diagnostic test, genetic testing must be performed if CGL or FPLD is suspected. A curative therapy is not available, but we aim to describe, how early start of diet, exercise and metreleptin can prevent or ameliorate the comorbities..

Methods:

Case Report: A 6 week old female infant presented with perianal skin lesions and failure to thrive in the absence of subcutaneous adipose tissue. Pregnancy, delivery and perinatal period were unremarkable. She was very hungry and breast feeded every 2-3 hours. The ultrasound of the abdomen showed hepatomegaly and polycystic hypertrophic ovaries. Laboratory examinations revealed extreme hypertriglyceridemia (93 mmol/l) and elevated blood glucose (10.3 mmol/L) and liver enzymes (GGT 216 U/L and ALP 537 UI/L). The skin lesions were diagnosed as eruptive xanthomas. By suspicion of a genetic lypodystrophy syndrome, genetic testing was performed, which confirmed a mutation in AGPAT2-gene, responsible for de novo phospholipid biosynthesis and typical for CGL.

Results:

A low-fat diet containing 28% of total fat intake with added medium-chain triglyceride oil and essential fatty acids was started. After a few days under the diet, a reduction of triglycerides was seen (8.7 mmol/l) and normalization of blood glucose and liver enzymes, in the presence of normal growth and psychomotor development. Due to absence of adipose tissue and resulting leptin-deficiency a therapy with Metreleptin is being started to prevent comorbities.

Conclusion:

Lipodystrophy syndromes are rare diseases characterized by deficient adipose tissue, hypertriglyceridemia, insulin resistance and ectopic lipid storage. Their diagnosis is challenging because metabolic comorbidities usually associated with obesity are found in lean patients. Since risk for severe metabolic complications is high and response to conventional medication poor, early diagnosis and immediate start of low-fat diet are crucial; leptin anolog therapy is approved in CGL patients >2 years.

39

Hypertension and hyperkalemia: an unusual combination in a 20-year-old patient

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Introduction:

Gordon syndrome (GS) is a rare hereditary disease causing arterial hypertension combined with hyperkalemia and metabolic acidosis.

Case Report:

A 20-year-old patient with treatment-resistant arterial hypertension was admitted to our outpatient clinic for exclusion of secondary causes of high blood pressure. Despite therapy with a sartan, an alpha-blocker and a loop diuretic, systolic blood pressure remained over 150 mmHg. Pheochromocytoma, Cushing's disease and renal artery stenosis were excluded. However, laboratory findings were striking for recurrent hyperkalemia and a low transtubular potassium gradient. Further examinations revealed metabolic acidosis with suppressed renin levels. Suspecting Gordon syndrome, the previous antihypertensive treatment was changed to a monotherapy with hydrochlorothiazide which resulted in a complete normalization of the blood pressure. Genetic testing confirmed Gordon syndrome caused by a mutation in the KLHL3 gene.

Comment and conclusion:

Gordon syndrome – or Pseudohypoaldosteronism Type 2 – is a rare disorder leading to familial hypertension with manifestation in early adulthood and autosomal dominant inheritance. It may be caused by mutations in various genes (WNK1, WNK4, KLHK3, CUL3) encoding two serine/threonine kinases. These gain-of-function mutations lead to an activation of the sodium chloride cotransporter as well as the sodium potassium chloride cotransporter in nephrons of the distal tubulus, increasing sodium and water reabsorption and therefore causing hypertension. Additionally, the named mutations inhibit expression of ROMK (renal outer medullary potassium channels), hereby causing hyperkalemia. Thus, GS is characterized by hypertension at young age, hyperkalemia in spite of normal renal function and metabolic acidosis. Often, hyperkalemia, metabolic acidosis and failure to thrive occur before overt hypertension ("Spitzer-Weinstein-Syndrome"). The causative mutation defines the severity of the phenotype. Hypertension in GS can very effectively be treated with low-dose thiazide diuretics or salt restriction (< 20mmol/d).

40

Incidence of clinically relevant Pituitary Mass: a retrospective community-based study in Cantonal Hospital Fribourg, Switzerland

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Background/Introduction:

Pituitary masses are mostly benign adenomas and among the most common human neoplasms. Nevertheless, data on the incidence of pituitary mass are scarce. A population-based study in the sub-urban area of Fribourg reported a prevalence of 1 pituitary adenoma in 1241 people. However, the incidence of pituitary tumors in Switzerland is unknown.

Methods:

We retrospectively created a database of all patients with pituitary-related diagnosis followed by the Department of Diabetology-Endocrinology at the Cantonal Hospital Fribourg from January 1st 2010, to December 31th 2018.

Results:

A total of 50 patients were identified. The mean age at presentation was 49.70 years (SD 17.67), with an overall male preponderance (54%). During the nine-year follow-up, we found an incidence of 5.5 cases per year. The incidence rate (/100 000 inhabitants) increased over the nine years; from 0.36 in 2010 to 3.17 in 2018.
In our cohort there were 23 patients with a macroadenoma (46%), 14 with a microadenoma (28%), two with a pituitary apoplexy (4%), four with a craniopharyngiomas (8%), and three Rathke's cyst (6%). Two patients presented a clinical and radiological hypophysitis (4%) and another two patients an abnormally increased size of the pituitary gland without adenoma (4%).
Among the 39 pituitary adenomas, there were 25 nonfunctioning adenomas (64.1%), ten prolactinomas (25.6%), three growth hormone-secreting adenomas (7.7%) and one adrenocorticotropic hormone-secreting adenoma (2.6%).
At initial presentation, hormonal deficiencies were uncommon, present only in 24% of all patients. In these patients, hypogonadism was most commonly diagnosed (83%). Growth hormone deficiency, adrenal insufficiency, and secondary hypothyroidism were found in 58%, 58%, and 75%, respectively. No patient presented with diabetes insipidus at the initial diagnosis.
Sixteen patients (32%) were referred for surgery, 21 patients (42%) underwent clinical and radiological follow–up, and 11 patients (22%) medical treatment. An associated surgery-radiation therapy approach was done in two patients (4%).

Conclusion:

To the best of our knowledge, this is the first epidemiological study on the incidence of clinically relevant pituitary masses during a nine-year period in a community hospital in Switzerland. In contrast to previous studies, microprolactinomas are underrepresented, probably because most of them are diagnosed and followed by gynecologists. Interestingly, the incidence over the nine-year follow-up seems to increase. This confirms for Switzerland the trend already described by other studies. Multicenter prospective studies are needed to evaluate the real world incidence of these conditions and to help allocate appropriate resources. p

41

Serum β-glucuronidase activity and soluble α-Klotho before and after pituitary surgery in patients with acromegaly

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Background/Introduction:

Acromegaly is caused by excessive growth hormone (GH) secretion. Removal of the GHproducing
adenoma decreases insulin-like growth factor 1 (IGF-1) and soluble α-Klotho (sKlotho) serum levels. Klotho is structurally related to β-glucuronidase, and sKlotho exerts enzymatic (weak β-glucuronidase) activity. We aimed to test whether serum β-glucuronidase activity, like sKlotho, decreases along with GH activity after transsphenoidal removal of the GHsecreting pituitary adenoma.

Methods:

We determined IGF-1 and sKlotho levels (by commercial ELISAs) and β-glucuronidase activity (conversion of 4-methylumbelliferyl-β-D-glucuronide to 4-methylumbelliferone) in serum samples of 21 (11 female) patients with confirmed acromegaly, before (baseline) and after surgery. Data are shown as median(interquartile range).

Results:

Surgery decreased levels of IGF-1 in 20, sKlotho in all 21, and β-glucuronidase activity in 18 of the 21 patients, mean decreases were 59%, 64.5% and 32.3%, respectively. IGF-1 declined significantly from 841(620-994) to 266(185-383) ug/l, sKlotho from 4502(1264-6677) to 716(592-1177) pg/ml, and β-glucuronidase activity from 0.89(0.53-1.21) to 0.45(0.36-0.77) nmol/min/ml.

Conclusion:

IGF-1 and sKlotho are serum biomarkers reflecting disease activity and treatment effect in patients with acromegaly. β-glucuronidase activity was higher before than after surgery, suggesting that serum activity of this enzyme is also regulated by GH.

42

Elevated lactate in Mauriac syndrome: still a mystery

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Background

The "Mauriac syndrome" was originally described in 1930 and refers to poorly controlled diabetes mellitus type 1, stunted growth and glycogenic hepatopathy. A recently recognized consequence of glycogenic hepatopathy is lactic acidosis further enhanced by insulin treatment.

Case Report

A 17-year-old girl known for type 1 diabetes since childhood and history of Mauriac syndrome was admitted at the Emergency department of Lausanne University Hospital with a 4 days history of mild abdominal pain and nausea. She reported no change in urine or stools and no melena, dysphagia, anorexia, or change in her weight.

Results

Laboratory exams revealed a glucose level of 44.1 mmol/l (793.8 mg/dl) with a mild hyperosmolar hyponatremia (Na - 130 mmol/l, osm -316 mmol/kg H2O) without ketoacidosis. Management of hyperglycemia was initiated including fluid replacement and rapid acting subcutaneous insulin therapy at a dose of 0.1-0.15 U/kg, which lead to a fall in serum glucose from 44.1 mmol/l to 31.0 mmol/l (793.8 mg/dL to 558.6 mg/dL). While glycaemia decreased with insulin therapy, lactate levels increased from 1.65 mmol/l prior to insulin administration to 6.02 mmol/l seventy-five minutes after the injection of insulin aspart (8U). Following the next 12 hours, lactate levels progressively decreased to 2.16 mmol/l. As genetic variants at the *KJCN11* and *PHKG2* genes had been previously found in association with Mauriac syndrome, these genes were sequenced on a next generation sequencing (NGS)-based panel (*AGL, GYS2, PHKA1, PHKA2, PHKB, PHKG2, KCNJ11*), but no pathogenic or rare variants were identified.

Conclusion

The clinical and metabolic anomalies of Mauriac syndrome are typically seen in children suffering from poorly treated type 1 diabetes, and changes tend to normalize in adulthood, with intensification of insulin therapy. Monitoring of elevated lactate levels during insulin therapy for diabetic decompensation is suggested, as it appears to be part of the spectrum. What remains unclear is whether Mauriac syndrome is just a consequence of poor metabolic control of type 1 diabetes or if a predisposition may contribute to this clinical phenotype. The answer to this question is not trivial, as it may affect the therapeutic strategy for type 1 diabetes.
A better understanding of glycogen metabolism in Mauriac syndrome using non-invasive techniques coupled with a thorough genetic analysis of genes involved in glucose regulation may be revealing.

43 S

Vitamin B6 supplementation in patients after bariatric surgery - too much of the good thing?

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Background: A 30-year old male patient with severe obesity (initial BMI 75 kg/m^2) received subsequent bariatric procedures (sleeve gastrectomy, omega-loop bypass, biliopancreatic diversion) over four years, leading to substantial weight loss. (current BMI 45.7 kg/m^2). The patient presented in our endocrine outpatient clinic with a progressive, immobilizing fatigue as well as par- and dysesthesia in the fingers IV and V of the left hand with neurographically reduced amplitude of the sensory nerve action potential of the left ulnar nerve. Laboratory analysis revealed massively elevated vitamin B6 levels (up to 1600 nmol/l) for several years. Medical history of the patient unraveled an intake of 2-3 energy drinks per day in addition to his regular multivitamin supplementation. After complete withdrawal of the energy drinks, that contain high levels of vitamin B6 and change in the multivitamin supplementation towards supplement with lower vitamin B6 content, clinical symptoms improved substantially and vitamin B6 levels decreased to 400 nmol/l.

Methods:
We therefore, did a retrospective quality assurance analysis of our electronic patient data base (ISMED) of all endocrine post-bariatric outpatient cases at the University Hospital Basel in 2017, where vitamin B6 values are examined on a routine basis during regular follow-up visits. All findings were controlled and only post bariatric patients were included in the final analysis.

Results:
In total, data of 233 patients was analyzed of which only 41 % had normal vitamin B6 levels. Most of the patients had vitamin B6 levels 2- to 4-fold higher than upper normal limit and nine patients (3.8 %) had levels more than 4-fold above upper normal limit. None of the patients had vitamin B6 deficiency. We expect further results by November 2019 including in-depth analyzes of further vitamins, used multivitamin preparations, neurological symptoms and bariatric procedure.

Conclusions:
1. Vitamin B6 levels in patients after bariatric surgery are often elevated and can be asymptomatic but may also have complex neurological consequences
2. A thorough analysis and critical evaluation of vitamin B6 supplementation and neurological symptoms in patients after bariatric surgery is highly warranted

44

Baseline characteristics of Swiss acromegaly patients included in the German acromegaly registry

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Background/Introduction:

Patient registries are valuable tools to study long-term course of rare diseases. Acromegaly is a rare disease (incidence 3–4/mill/year, prevalence 40–80/mill; approx. 24-32 new patients/yr and up to 600 patients in Switzerland). The German Acromegaly Registry is an initiative of the Pituitary Study Group of the German Endocrine Society (DGE). The database has been established in 2003. Swiss centers have access to this database since November 2018.

Methods:

Files of patients with acromegaly (diagnosed in 2003 and later) were retrieved in three Swiss centers (Aarau, Lucerne, Basel). Initial clinical, biochemical assessment (IGF-1 concentrations expressed as standard deviation of age and gender normalized IGF-1 concentrations = z-score; random growth hormone (GH) concentrations), imaging (initial size of adenoma) and co-morbidities were analyzed and expressed as mean (SD), median (IQR) or in percentage as stated.

Results:

Data of 75 patients with acromegaly were recorded, 41 female (55%). Mean age at diagnosis was 50.3 years (± 14.4) (SD) and mean BMI was 28.0 kg/m2 (± 3.2). Male patients tended to be younger at diagnosis with a mean age (SD) 48.5 years (+ 13.7) compared to female 53.3 years (+14.9), p=0.06. Median (IQR) IGF-1 z-score was 11.8(8-17), median (IQR) random GH was 12 (4-28), ng/mL and the mean size of the pituitary adenoma accounted for 20.1 (±10.3), mm. Tumor size positively correlated with random GH levels at diagnosis (r=0.426 (95%CI; 0.178-0.623, p=0.001) as well as IGF-1 levels at diagnosis (r=0.312 (95%CI; 0.057-0.528, p=0.01). Co-morbidities occurred as follows: hypertension (60%), diabetes (35%), neoplasia (17%), carpal tunnel syndrome (17%), sleep apnea syndrome (9%), atherosclerotic disease (9%) and osteoporosis (5%), with no significant gender differences.

Conclusion:

Initial results from three Swiss centers demonstrate that patients can be included in this registry efficiently and with satisfactory data quality. The registry will be a valuable tool for assessment of disease-specific and health care-specific aspects of hGH excess in Switzerland. Comparison with data from the German acromegaly registry will provide important data on treatment outcomes under different health care systems.
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45

Low bone turnover is associated with functional hypoparathyroidism in type 2 diabetes

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Introduction:

Bone turnover is reduced in patients with type 2 diabetes (T2DM), however its determinants remain unclear. Within a cohort of patients with T2DM we examined the relationships between markers of bone turnover and glycaemic control, disease duration and calciotropic hormones.

Methods:

This case-control study included 110 patients with T2DM (mean±SD; age 63.7±6.0yrs; BMI 29.8±4.3 kg/m2, HbA1c 7.5±1.2%; median disease duration 13.5 years [IQR 8-20]; treatment with insulin 64 patients [58.2%]) and 92 non-diabetic controls (age 60.5±6.3 yrs, BMI 24.9±4.5 kg/m2, HbA1c 5.5±0.3%) who are prospectively followed in the DiabOS-Study (an ongoing observational cohort study evaluating skeletal health in T2DM). Biochemical markers of bone formation (PINP, bonespecific alkaline phosphatase [BAP]) and resorption (CTX), as well as measures of calcium homeostasis (iPTH, 25OHVD, calcium, magnesium), IGF-1 and HbA1c were assessed at baseline.

Results:

After adjustments for age, gender and BMI, patients with T2DM had lower serum levels of PINP (p<0.001), CTX (p=0.03), iPTH (p=0.03), magnesium (p<0.001) and higher HOMA-Index (p=0.03) as compared to non-diabetic controls. Serum calcium, creatinine, 25-OHVD, IGF-1 and nutritional calcium intake did not differ between groups. Intact PTH was positively correlated with magnesium levels (r=0.21, p=0.03). In multivariate logistic regression analyses, only serum iPTH remained an independent predictor of bone markers in T2DM (p=0.006 for PINP, p=0.002 for BAP and p<0.001 for CTX). In contrast, HbA1c, disease duration, age, HOMA-Index and BMI were not associated with bone turnover markers.

Conclusion:

We conclude that functional hypoparathyroidism is an important regulator of low bone turnover in
T2DM. Based on the relationship between serum levels of iPTH and magnesium, low bone turnover,
specifically in T2DM, might be mediated by hypomagnesemia-related hypoparathyroidism.

46

Estimation of 10-Year Cardiovascular Risk among Newly Diagnosed Type 2 Diabetes Patients in the "Evaluation of Effectiveness of Treatment Paradigm for Newly Diagnosed Type 2 Diabetes Patients in China (NEW2D)" Study Population

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Background/Introduction:

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with type 2 diabetes (T2D). This study aimed to estimate the distribution of 10-year predicted CVD risk among newly diagnosed T2D patients, using China-PAR (Prediction for Atherosclerotic cardiovascular disease Risk in China) model, in the NEW2D population.

Methods:

CVD was defined as the first occurrence of acute myocardial infarction, stroke, or death from cardiovascular causes. Risk factors included in the China-PAR model were age, geographic region, urbanization, smoking, waist circumference, systolic blood pressure, total cholesterol, HDL-C, and family history of CVD.

Results:

Of the total population of 5770 patients, 2301 fulfilled the inclusion criteria (e.g. no glucose-lowering therapy) and were included in the current analyses. The model-predicted mean CVD risk was 7.4%, with 54% of patients having a medium or high risk to develop CVD within 10 years (Table 1).

Table 1. Distribution of patient characteristics, in total and by predicted CVD risk levels.

Patient characteristics, mean ± SD or N (%)	Total N=2301	Predicted CVD Risk			P value
		Low (<5%) N=1050	Medium (5-9%) N=651	High (>=10%) N=600	
Age, year	54.3 ± 12.5	45.5 ± 9.3	58.0 ± 8.1	65.6 ± 9.8	<0.0001
Urban	2058 (89.4)	905 (86.2)	589 (90.5)	564 (94.0)	<0.0001
Current smoker	557 (24.2)	233 (22.2)	164 (25.2)	160 (26.7)	0.0978
Waist circumference, cm	88.1 ± 10.5	87.1 ± 10.9	88.0 ± 9.7	90.0 ± 10.2	<0.0001
Systolic blood pressure (SBP), mm Hg	128.6 ± 14.1	122.2 ± 10.6	129.6 ± 12.0	138.6 ± 15.4	<0.0001
Antihypertensive treatment	407 (17.7)	46 (4.4)	135 (20.7)	226 (37.7)	<0.0001
HbA1c, %	8.3 ± 2.4	8.5 ± 2.5	8.2 ± 2.4	8.0 ± 2.3	0.0004
HDL-C, mmol/L	1.2 ± 0.4	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.3	<0.0001
LDL-C, mmol/L	3.0 ± 1.0	3.0 ± 0.9	3.0 ± 0.9	3.0 ± 1.0	0.7944
Antidyslipidemia treatment	177 (7.7)	49 (4.7)	65 (10.0)	63 (10.5)	<0.0001
Cataract	30 (1.3)	3 (0.3)	12 (1.8)	15 (2.5)	0.0002
Serum creatinine, µmol/L	70.1 ± 21.9	66.1 ± 20.1	71.2 ± 22.4	75.7 ± 23.2	<0.0001

Conclusions:

Our study demonstrates that the majority of newly diagnosed patients with T2D in China have a medium or high risk to develop CVD. SBP appears to be a prominent driver of this elevated risk. These results underscore the importance of primary prevention and management of CVD in patients with T2D.

47

A glimpse into the starry sky

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Background/Introduction:

The thymus is the primary site of T-lymphocyte development and it arises from the third pharyngeal pouch during embryogenesis. After detachment from the pharynx the thymus lobes migrate caudally and eventually meet in the central compartment of the thoracic cavity (superior mediastinum). Cervical thymic tissue may result from disorders in pharyngeal detachment, organ separation and migration during organogenesis. Therefore, thymic tissue may be located anywhere along the pathway of normal thymic descent, from the mandibula to the mediastinum. However, cervical thymic masses are rare and mostly asymptomatic. The prevalence of intrathyroidal ectopic thymus is estimated to be around 1% in children.

Methods:

We describe the clinical presentation, imaging, cytopathological and histological findings of a pediatric patient with ectopic thymic tissue, which, at first glance, was suspicious for papillary thyroid carcinoma.

Case Report:

An 11-year old girl was referred to our pediatric endocrinology outpatient clinic for the evaluation of a newly diagnosed left sided cervical mass which had become symptomatic for the first time in gym lesson with a feeling of pressure in the thyroid bed and shortness of breath. The patient was euthyroid and cervical sonography revealed a cystically transformed nodule (15 x 19 x 19 mm) in the midregion of the left thyroid lobe with a benign appearance which probably had caused the acute symptoms. However, cranially and caudally adjacent to this nodule two suspicious and not certainly intrathroidal lesions (9 x 10 x 17 mm and 7 x 15 x 21 mm, respectively) were found. They both demonstrated irregular margins, showed a mainly hypoechoic pattern with numerous bright spots, compatible with microcalcifications. Based on the sonographic findings these two lesions were interpreted as highly suspicious for papillary thyroid carcinoma. Hence, fine needle aspiration (FNA) with rapid-on-site-evaluation (ROSE) of the cytologic specimens was performed at in our interdisciplinary thyroid consultation service. Cytology showed numerous benign appearing lymphocytes and no thyrocytes could be detected. Because of the malignant sonographic aspect left-sided hemithyroidectomy finally was performed and revealed ectopic thymus tissue and an oxyphilic thyroid nodule. Of note, the initial interpretation of the numerous bright speckles as microcalcifications per se was not wrong – however it must be kept in mind that in rare cases microcalcifications can correspond to calcified Hassall`s corpuscules of the thymus and not to papillary thyroid cancer .

Conclusion:

The ultrasound features of non-spherical hypoechoic intrathyreoidal lesions with uniform distribution of punctuated echogenic foci ("starry sky" pattern) and absence of a rim are characteristic for intrathyreoidal ectopic thymus and may mimic thyroid cancer, especially in children. Healthcare professionals should be aware of this rare entity to avoid unnecessary interventions and reduce psychological stress for patients and their families.

48

HEADWIND: Design and Evaluation of a Vehicle Hypoglycemia Warning System in Diabetes - a proof of principle study

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Background/Introduction:

Despite ongoing developments in the treatment of diabetes, hypoglycaemia remains one of the most relevant acute complications associated with this disease. During hypoglycaemia cognitive, executive and psychomotor abilities significantly deteriorate. Accordingly, hypoglycaemia has consistently been shown to be associated with an increased risk of driving accidents and is, therefore, regarded as one of the relevant factors in traffic safety. Today's cars continuously gather a broad spectrum of real-time information on various driving parameters. This may allow for an alternative approach to the problem of hypoglycaemia during driving. Using artificial intelligence constantly analyzing driving behavior it may be possible to timely detect changes in driving patterns characteristic for driving in hypoglycaemia. Based on these alterations in driving variables we aim at establishing algorithms capable of discriminating eu- and hypoglycemic driving patterns using artificial intelligence.

Methods:

In a proof of principle study we compared data regarding driving behavior of 5 individuals (3 non-diabetic and 2 with type 1 diabetes) tracking measurements in eu- and hypoglycemic condition while driving on a predefined route using a professional driving simulator (Carnetsoft BV). Over 60 driving parameters were assessed at a sampling rate of 30 Hz. Time series of car-based sensor data was then sliced into 5-minute windows and random forest machine learning classifier as well as deep neural networks were applied to build a system detecting hypoglycemia within 5 minute frames.

Results:

Car-based data provided 73'970 measurements in hypoglycemic condition (<3.9mmol/L) and 110'959 samples in euglycemic condition (4.0-10mmol/L). A simple linear logit model was used for reasons of interpretability, which confirmed statistical significance of key variables (e.g. "velocity" and "steering speed") at the 1% level. 1-fold cross-validation on subject level (i.e. training the model on all subjects except for one, which is used for testing and repeat this until every subject has been in the testing set) using random forest from machine-learning and deep neural networks, applied because of the highly non-linear relationship resulted in a ROC-AUC in hypoglycemia prediction of 0.72 and 0.74, respectively.

Conclusion:

Our preliminary evaluation applying machine learning models on driving simulator-based data show between-subject predictability of hypoglycemia even in a small dataset. This confirms the effectiveness of artificial intelligence in hypoglycemia detection while driving and may represent a promising novel approach to increase traffic safety in patients suffering from diabetes.

49

White coat adherence in patients with diabetes mellitus

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Background/Introduction:
White coat adherence (WCA) is defined as an increased adherence to treatment regimens in the days prior to the visit with a healthcare provider. In patients with diabetes WCA is reported in adolescents increasing the frequency of blood glucose measurements and carbohydrate documentation. However, there is little data on adult patients. The widespread use and reimbursement of continuous and flash glucose monitoring (CGM & FGM) devices in Switzerland provides an optimal framework for a detailed analysis of glycemia, and thus also an in-depth evaluation of WCA with consecutive impact on diabetes control in adult patients.

Methods:
We retrospectively analysed CGM- and FGM data of all patients treated at our tertiary referral center between January 2013 and July 2018. To assess WCA we compared the 3 days prior to the visit (d3) with the preceding 25 days (d25). Patients were included in the anaysis if CGM-/FGM-data were available for at least 50% of the two single time-periods. 279 patients (64% male, 36% female; Type 1 diabetes (DM1) 65.6 %, DM2 23.6 %, other 11.8 %) were finally included in the study, resulting in a total of 819 data sets (average 4.2 data sets per patient).

Results:
Sensor use was higher during d3 than d25 (89.8±10.7% vs 83.1±13.5%; p<0.001). Mean glucose [MG], coefficient of variation [CV] and amplitude of glycaemic excursion [MAGE] were lower in d3 compared to d25 (MG 9.27±2.49mmol/L vs 9.37±2.15mmo/L, p=0.046; CV 33.4±8.7% vs 36.0±7.1%, p<0.001; MAGE 7.57±2.24mmol/L vs 8.03±1.81mmol/L, p<0.001; respectively). Time in range (TIR 3.9-10mmol/L) was higher in d3 than d25 (60.2±22.1% vs 59.1±19.0%, p=0.014), wherease for d3 compared to d25 time above 10.0mmol/L (35.6±23.2% vs 36.8±20.4%, p=0.013) and time above 13.9mmol/L (12.5±17.1% vs 13.4±14.9%; p=0.018) were lower with no difference for time below 3.9mmol/L (4.1±6.6% vs. 4.1±4.7%, p=0.85).
Subgroup-analysis for HbA1c categories (≤7%, 7.1-9%,>9%) showed higher reduction of mean-glucose (p=0.02) and time > 13.9mmol/L (p=0.03) for HbA1c 7.1-9%. CSII compared to MDI resulted in higher reduction of mean glucose (delta 0.24mmol/L, p=0.026) and time > 13.9mmol/L (delta 1.8%, p=0.019) and greater increase of TIR (delta 2.1%, p=0.039). No significant differences were found for type of diabetes, gender, age or diabetes duration.

Conclusion:
When analysing CGM-/FGM-data and adjusting treatment-regimes based thereupon, healthcare providers should be aware that WCA may also occur in diabetes mellitus and is expressed in particular by an increase in sensor use and reduced glucose variability in the days prior to a clinical visit. WCA is more pronounced in patients with an intermediate level of glucose-control and less common in patients with multiple daily insulin injections compared to CSII.

50

Fructose exposure and extracellular ATP signalling induce intracellular fasting-like phenotype in the beta-cells, associated with AMPK activation

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Background/Introduction:
While the use of fructose as a sweetener is associated with increased hepatic fat storage and obesity, fructose alone does not acutely stimulate insulin exocytosis from the pancreatic beta-cell, as opposed to the chief secretagogue glucose. We recently reported the effects of chronic exposure to fructose on beta-cell function. Our results revealed that fructose induces extracellular ATP signalling, resulting in the potentiation of physiological glucose-stimulated insulin secretion (GSIS). This effect is mediated by the activation of the calcium-mobilizer purinergic P2Y1 receptor and is associated with the release of cellular ATP through pannexin-1 (PANX1) channels. Since fructose also induces AMPK activation, we have now investigated the effects of fructose on both the extracellular and the intracellular ATP signalling arms of beta-cells. INS-1E beta-cells, rodent and human islets were treated over days with fructose before assessment of their glucose response.

Methods:
We also analyzed the transcript levels of the components of extracellular ATP signalling. QT-RT-PCR for Pdx1, Pkraa2, the sweet taste receptors Tas1r2, Tas1r3, Panx1, the ecto-ATPase Entpd3 and P2ry1 was performed on insulinoma cells and isolated rodent (mouse and rat) islets, as well as FACS-purified beta-cells. INS-1E beta-cells or freshly isolated human islets were then exposed for 4 days to 5.5 mM fructose in their respective standard medium. At the end of this pre-treatment period, we measured AMPK phosphorylation and calcium levels. We also performed immunodetections of KIR6.2.

Results:
Panx1 was expressed in the whole islet, whereas Pdx1, Entpd3 and P2ry1 transcripts were enriched in purified beta-cells. Chronic exposure of INS-1E beta-cells and human islets to fructose induced AMPK phosphorylation. Correlating with AMPK activation, fructose pre-treatment of INS-1E beta-cells caused translocation of K+-ATP KIR6.2 channels to the cell membrane, exhibiting fasting-like phenotype. Stronger plasma membrane depolarization, faster cytosolic calcium oscillations and higher calcium levels were observed in the fructose-treated cells. Activation of hemichannels by removal of extracellular Ca2+ led to the activation of AMPK. Addition of acute fructose for 10 min or the P2Y1 agonist 2MeSADP to naive INS-1E cells activated AMPK, mimicking chronic fructose pre-treatment and pointing to the purinergic P2Y1 receptor for acute AMPK activation.

Conclusion:
Fructose treatment induced intracellular fasting-like phenotype in INS-1E beta-cells and human islets, uncovered by AMPK activation. In parallel, fructose activated extracellular ATP signalling, an effect mediated by the activation of purinergic P2Y1 receptors through increased release of cellular ATP. These results reveal a channel-mediated mechanism for the regulation of AMPK through purinergic signalling.

51 S

Inhibitory effects of Curcuma longa extracts on the steroid metabolizing cytochrome P450 enzymes

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Background/Introduction:

Turmeric, a popular ingredient in the cuisine of many Asian countries, is known for its use in Chinese and Ayurvedic medicine and comes from the roots of the Curcuma longa. Turmeric is rich in curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Curcuminoids have potent wound healing, anti-inflammatory and anti-carcinogenic activities but not much is known about their effects on steroid metabolism. Since many anti-cancer drugs target enzymes from the steroidogenic pathway, we tested the bioactivity of curcuminoids on cytochrome P450 CYP17A1, CYP21A2, and CYP19A1 enzyme activities.

Methods:

Curcuminoids were extracted from turmeric with organic solvents. We conducted a cell-based assay for CYP17A1 and CYP21A2 activities using human adrenal cell line NCI-H295R. Steroids were separated by thin layer chromatography and analyzed by phosphorimager analysis. For CYP19A1 activity, an in vitro assay using endoplasmic reticulum from JEG3 were used with 3H-androstenedione as the substrate.

Results:

When using 10 µg/ml of curcuminoids, both the 17α-hydroxylase as well as 17,20 lyase activities of CYP17A1 were reduced significantly. On the other hand, only a mild reduction in CYP21A2 activity was observed. Furthermore, CYP19A1 activity was also reduced up to ~20% of control when using 1-100 µg/ml of curcuminoids in a dose-dependent manner. Molecular docking studies confirmed that curcumin could dock into the active sites of CYP17A1, CYP19A1 as well as CYP21A2. In CYP17A1 and CYP19A1, curcumin docked within 2.5 Å of central heme while in CYP21A2 the distance from heme was 3.4 Å, which is still in the same range or lower than distances of bound steroid substrates.

Conclusion:

These studies suggest that curcuminoids may cause inhibition of steroid metabolism, especially at higher dosages. Also, the recent popularity of turmeric powder as a dilatory supplement needs further evaluation for the effect of curcuminoids on steroid metabolism. Molecular structure of curcuminoids could be modified to generate better lead compounds with inhibitory effects on CYP17A1 and CYP19A1 for potential drugs against prostate cancer and breast cancer.

52 S

The Fruit Fly, Drosophila melanogaster, as a model to elucidate human differences of sex development (DSD)

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Background/Introduction:

An activation cascade of specific genes sets up the initiation of sex determination leading in males to testes formation and synthesis of testicular hormones. Disruption of this gene cascade may cause a spectrum of disorders/differences of sex development (DSD) phenotypes. Here we describe for the first time two sisters suffering from 46,XY DSD, who by whole exome sequencing were shown to carry a mutation in the X-linked StAR-related lipid transfer domain protein 8 (STARD8) gene. STARD8, also known as deleted in liver cancer 3 (DLC-3) is a functional Rho-specific GAP protein, the loss of which enhances perinuclear Ras homolog gene family member A (RhoA) activity which in turn is known to be involved in SOX9 expression regulation. Additionally, STARD8 downregulation severely disturbs recruitment of β-catenin to sites of cell adhesion, this one being, moreover, a key pro-ovarian and anti-testis signaling molecule.

Methods:

To gain new insights in human sex development mechanisms, we aimed to analyze the functional consequences of STARD8 mutations. Since the STARD8 knockout NMRI mouse model we generated did not recapitulate the human clinical picture, we chose to use another in vivo model to study the mechanisms of disease. Interestingly, Crossveinless-c (Cv-c) the Drosophila homolog of DLC-3/STARD8, has similar location and function than its mammalian counterpart. We therefore chose to study the consequences of Cv-c mutations in the gonadal development of the fruit fly. Gonad development was analyzed in cv-c7, cv-cM62 and cv-cC524 alleles using Immunohistochemistry and confocal microscopy to visualize gonad specifics markers. Cv-c expression in the male gonad was confirmed by cv-c fluorescent RNA in situ and Cv-c-GFP TRAP construct.

Results:

We found defects affecting the germ cells (GCs) migration from the beginning of embryogenesis with different degrees of severity in the cv-c mutant embryos, preventing gonad coalescence in the most severe cases. We also observed a decrease in the number of GCs in male mutant gonads compared to wild type males.

Conclusion:

Our results indicate that cv-c is required for gonadal development in Drosophila embryos, suggesting that the defect in STARD8 is the most likely cause of DSD in our patients. We were able to exploit the fruit fly, Drosophila melanogaster, for functional investigation of findings from human whole exome sequencing, by creating a fly model of a defect in the protein STARD8 found in two patients with 46, XY DSD.

53

The transcriptional repressor Scrt1 regulates pancreatic β-cell proliferation and maturation

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Background/Introduction:
Glucose-induced insulin secretion, a unique feature of fully differentiated β-cells, is only acquired after birth and is preceded by a phase of intense proliferation. These events occurring in the neonatal period are critical for the establishment of an appropriate functional β-cell mass covering the insulin needs throughout life. However, key regulators of gene expression involved in the cellular reprogramming along maturation remain to be elucidated.

Methods:
This project addressed this issue by taking advantage of a new methodology called ATAC-seq permitting a fine genome-wide mapping of chromatin accessibility. ATAC-seq assay was used to compare open chromatin regions in newborn versus adult rat β-cells. These regions were then correlated with the expression profiles of mRNAs to unveil the regulatory networks governing functional β-cell maturation We obtained a genome-wide picture of chromatin accessible sites (~100'000) among which 10 % were differentially accessible during maturation. Half of these sites are in the proximity of genes displaying differential expression in newborn and adult rat islets. An enrichment analysis of transcription factor binding sites revealed that 35 transcription factors could explain these changes. While the importance of some of them, including REST, FoxO1 and JunB, is already known, the role of others remains to be determined. We focused on Scrt1 a transcriptional repressor whose expression is upregulated.

Results:
Downregulation of Scrt1 did not affect insulin secretion in response to glucose, but restored an elevated proliferation rate in adult β-cells, suggesting an involvement of this repressor in post-natal maturation. To further understand the role of Scrt1 in the regulation of the β-cell transcriptome, we performed an RNAseq on FAC-sorted β-cells from adult rats. Differential expression analysis between siScrt1 and control samples revealed 168 genes were significantly impacted (111 down-regulated and 57 up-regulated), including several genes related to proliferation and/or β-cell development (Notch1, Parp16, Ppp3r1, NFATc1 and NFATc2). Next, we compared genes affected by Scrt1 silencing and the ones differentially expressed upon maturation (in postnatal P10 versus adult rat islets) and found a set of 62 genes changing in both data set. Interestingly, a significant anti-correlation (correlation test p-value = 0,013) was observed between the fold-changes from the comparison between siScrt1 versus siCtl in adult rat beta-cells and P10 versus adult islets.

Conclusion:
In the present study, the comparison of open chromatin sites between newborn versus adult rat islets using ATAC-seq assay allowed us to found several known and unforeseen key transcriptional regulators acting at cis-regulatory sites during β-cell maturation. Among them, we could identify Scrt1, an important transcriptional repressors implicated in the switch between the proliferative and the functional state of β-cells along pancreatic islet maturation.

54 S

Regulation of CBX2 transcription in human development

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Background:

The process of sexual differentiation is critical for reproduction in nearly all metazoan. Defects in any of the genes involved in either testicular or ovarian development can result in disorders of sex development (DSD). CBX2/M33 is a chromatin modifier that plays an important role in sexual development and its disorders, highlighted by the fact that M33-deficient mice have male-to-female sex reversal and loss-of-function of CBX2 causes 46, XY DSD in humans. The promoter of CBX2 is unknown; however, there are hints of differential expression by its multiple isoforms across different cell lines and tissues.

Here we aim to characterize the CBX2 promoter in applicable cell lines using a custom reporter construct, to identify a regulatory network in gonadal development in which CBX2 takes part.

Methods:

To locate the CBX2 promoter, based on predicted binding sites two candidate regions targeting transcription and one the start of translation, were cloned into the promoterless pGL4.17 Vector upstream of the luciferase reporter gene *luc2*. The constructs were transfected in several cell lines (HeLa, KGN, HEK293, NT2-D1, and HSerC), with reporter activity established by performing a dual-reporter assay measuring firefly and *Renilla* luciferases. Through a screening experiment, dissection of the CBX2 promoter is done to determine essential transcription factor binding sites and investigate DNase I hypersensitive sites, along with related histone activity. Subsequently, ovarian, testicular and adrenal cell lines (KGN, HSerC, and NCI-H295R cells respectively) are challenged with the identified regulatory elements to determine the regulation of CBX2 expression.

Results:

Utilizing the dual-reporter assay system, we identified an optimal candidate CBX2 promoter construct (-479/+34) that exhibited a significant normalized fold change in activity across several cell lines tested (range from 3.6 – 14.65 fold) when compared to a negative control ($p<0.0074$ – $p<0.0001$). The results indicate substantial differences in transactivation potential among the various cells, allowing us the potential application of the promoter construct to explore and elucidate differential transactivation of CBX2, distinct from its known function as chromatin-modifier.

Conclusion:

The characterization of a candidate CBX2 promoter could provide insight into the functional role of CBX2 as transactivator. Further study of the impact of CBX2 activation and suppression may shed light on potential pathological mechanisms involved in DSD, and ultimately its diagnosis and management.

55

Depth Sensing and Computer Vision for Automated Macronutrient Quantification

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Background/Introduction:

Quantification of dietary intake is key to the prevention and management of numerous metabolic disorders. Conventional approaches are challenging, laborious, and, suffer from lack of accuracy. The recent advent of depth-sensing smartphones in conjunction with computer vision has the potential to facilitate reliable quantification of food intake.
We sought to evaluate the accuracy of a novel smartphone application combining depth-sensing hardware with computer vision to quantify meal macronutrient content.

Methods:

The smartphone application runs on a smartphone with a built-in, structured-light depth sensor (iPhone X). The app estimates weight, macronutrient (carbohydrate, protein, fat), and energy content of meals. We applied it to 48 randomly chosen meals (type of meals: breakfast, cooked meals, snacks) encompassing 128 food items.
We generated the reference weights for individual food items using a precision scale. The study endpoints were fourfold: i) error of estimated meal weight; ii) error of estimated macronutrient content and energy content; iii) segmentation performance; and iv) processing time.

Results:

The application's estimates had a mean±SD for the absolute error in overall weight of 35.1±42.8g (14.0±12.2%), in carbohydrate content of 5.5±5.1g (14.8±10.9%), in protein of 2.4±5.6g (13.0±13.8%), in fat of 1.3±1.7g (12.3±12.8%), and in energy of 41.2±42.5kcal (12.7±10.8%). While the viewing angle did not affect estimation accuracy, the type of meal mattered: estimates for breakfast and snack were more accurate compared to cooked meals. Segmentation required adjustment for 7 out of 128 items. The Mean±SD processing time for all meals was 22.9±8.6s.

Conclusion:

In the present study, we evaluated the accuracy of a novel smartphone application integrating a depth-sensing camera and computer vision technology. We found the application accurate for all macronutrients estimations, a performance paralleled by a high segmentation accuracy and low processing time, thus making the system highly usable.

56

Effects of high glucose exposure on the global transcriptome of human pancreatic islets

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Background/Introduction:

In the context of type-2 diabetes, the molecular mechanisms going from beta-cell adaptation, secondary to insulin resistance, to beta-cell failure that triggers the diabetic state, remain unclear. In particular, transcriptional reprogramming of the human islet in glucotoxic conditions is of crucial importance but remains poorly characterized. Here we explored the effect of chronic high glucose exposure on human islets and their adaptation in terms of transcriptomics.

Methods:

Human islets were isolated from pancreases of deceased multiorgan donors, who had provided written informed consent (ECIT consortium). Freshly isolated islets were then exposed to high glucose conditions (25 mM) for 3 days, while the physiological 5.6 mM glucose served as control (in CRML-1066 medium). RNA was isolated from whole islets following standard procedures. RNA was fragmented and cDNA synthesis was performed according to the manufacturer's instructions (TruSeq 2, Illumina). Read quantification and differential expression analysis of all RefSeq genes was performed using the RUVSeq package. Log-transformed and normalized counts of all genes with padj ≤ 0.1 were selected for enrichment analysis and visualization using Reactome and Cytoscape tools.

Results:

Exposure to chronic high glucose conditions induced a pronounced reprogramming of the human pancreatic islet transcriptome. We identified 926 genes being upregulated and 924 genes downregulated (FDR≤0.1). Among the pathways enriched upon glucotoxic conditions, we identified some related to ER homeostasis, such as up-regulation of XBP1-mediated activation of chaperone genes involved in ER stress (key genes XBP1, SYVN1, MYDGF) or COPI-mediated vesicular transport between ER and Golgi, a post-ER sorting station for anterograde and retrograde protein trafficking within the early secretory pathway (key genes TMED9/3, FKBP11, COPE). We also observed up-regulation of SREBF, whose activation has been implicated in beta-cell dysfunction caused by glucolipotoxicity (key genes SREBF1/2, SMARCD3, FASN). In addition, we identified downregulation of HSF1-mediated heat shock response, which plays a fundamental role in protecting against numerous cellular stresses including metabolic perturbations (key genes HSPA1A, HSPBP1, HSPA6, ST13).

Conclusion:

This human islet transcriptome reveals functional gene networks which are relevant for islet function and possibly for diabetes pathogenesis.

57 S

About the hepatic contribution of glutamate dehydrogenase in hyperammonemia of the HI/HA syndrome.

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Background/Introduction:

Clinically, the hyperinsulinism/hyperammonemia syndrome (HI/HA) is characterized by elevated plasma ammonia levels accompanied by severe hypoglycaemia and epilepsy in about 40% of cases. It is a rare genetic disease caused by gain-of-function mutations in the GLUD1 gene encoding for the enzyme glutamate dehydrogenase (GDH). Mammalian GDH catalyses the reversible reaction of glutamate to α-ketoglutarate (α-KG) plus ammonia. HI/HA syndrome gives rise to increased (3-5 times) plasma ammonia levels, presumably due to systemic expression of mutant GDH. To explore the effects of GDH-S445L mutation on hepatic ammonia metabolism, we transduced in vivo liver-specific GDH knockout mice with adenoviruses carrying human mutant GDH. We performed challenges of gluconeogenic amino acids, both in vivo and ex vivo, in order to assess ammonia homeostasis. This study aims to elucidate the contribution of the liver in the elevated circulating ammonia levels associated with the GDH-S445L mutation.

Methods:

We used tamoxifen induced liver specific GDH null mice (Hep-Glud1-/-, Karaca et al. Diabetes 2018) for in vivo expression of human mutant GDH following retroorbital injection of 10^9 PFU of adenovirus (Ad-GDHmut). Control Glud1fl/fl floxed mice were injected with saline. The efficiency of transduction was controlled by immunoblotting on liver extracts. After an overnight fast, amino acid-induced gluconeogenesis was stimulated by i.p. glutamine and alanine challenges. To assess the systemic turnover of ammonia, blood samplings at different sites of the vasculature were performed (abdominal aorta, portal vein, hepatic vein, renal vein) and ammonia, urea and glutamate levels were determined.

Results: p

Immunoblotting indicated that the levels of Ad-GDHmut expression in the liver of Hep-Glud1-/- mice accounted for approx. 70% of endogenous Glud1fl/fl control mice. Alanine and glutamine are important substrates for gluconeogenesis. The ammonia production from glutamine is contributed by deamidation to glutamate by glutaminase and subsequent deamination to αKG by GDH. However, alanine solely relies on GDH for ammonia production. Upon in vivo amino acid challenges, there was no difference in glucose production between Glud1fl/fl control and Hep-Ad-GDHmut. Although urea concentrations were stable throughout the study, circulating glutamate increased in Hep-Ad-GDHmut, up to 350% of the values of control mice. The efficiency of ammonia clearance from the portal vein was substantially decreased in Hep-Ad-GDHmut versus control mice (-83%, $p<0.05$). In parallel, ex vivo challenge with glutamine and alanine in perfused liver indicated ammonia intolerance in Hep-Ad-GDHmut mice at the expense of urea production.

Conclusion:

Our study shows that Hep-Ad-GDHmut livers were less efficient at ammonia disposal in vivo. Ex vivo, Hep-Ad-GDHmut livers acutely challenged with amino acid were ammonia intolerant. Overall, GDH-S445L mutation impaired the efficiency of hepatic nitrogen disposal.

58

Investigation of differences in clot-formation between patients with type 1 diabetes, type 2 diabetes, and healthy volunteers using a microvascular whole blood flow model

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Background/Introduction:

Diabetes is assocaited with an increased high risk for macrovascular complications and an increased cardiovascular mortality. Endothelial dysfunction, activation of blood cells, and changes in plasma proteins have been shown to contribute to the development of thrombotic complications. However, in vitro experiments mostly focused on individual aspects without taking into account the complex interactions between each contributoring factor. The aim of the present study was to investigate differences in clot formation between patients with type 1 diabetes, type 2 diabetes, and healthy volunteers. For this purpose, a microvascular whole blood flow model was developed that illustrated interactions between endothelial cells, blood cells and plasma proteins.

Methods:

Primary cardiac microvascular endothelial cells from healthy volunteers (control cells), patients with type 1 diabetes (T1D cells), and patients with type 2 diabetes (T2D cells) were grown to confluence in parallel channels of transparent silicone chips. Freshly drawn whole blood was obtained from healthy volunteers as well as from T1D and T2D patients with an HbA1c >8%. Microvascular flow chips were coated with either control cells, T1D or T2D cells and were perfused with the respective whole blood samples at physiological flow rates. Clot formation within the channels of the microvascular flow chips was assessed in real-time by confocal microscopy measuring the fluorescence signal over time of immobilised fibrin.

Results:

Clot formation showed a tendency to occur faster and to a higher extent in the presence of diabetic endothelial cells and diabetic whole blood as compared with healthy controls. The area under the curve (AUC) for clot formation was highest among microvascular flow chips coated with T2D cells and perfused with T2D whole blood as compared with the T1D setup and healthy controls.

Conclusion:

T2D was associated with the highest extent of clot formation in the microvascular flow model. The model observed a strong contribution of endothelial cells to clot formation, whereas the interindividual variability was considerable. The present study might contribute to a better understanding of mechanisms associated with the increased risk for macrovascular complications in diabetes.

59 S

Adipocyte-specific gp130 signalling mediates exercise-induced weight reduction

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Background/Introduction:

Repetitive physical activity is a well-established intervention to reduce obesity and to ameliorate obesity-associated insulin resistance. Besides increased energy expenditure, reduced caloric intake may contribute to exercise-induced weight loss in obesity. Using adipocyte-specific glycoprotein (gp130) knockout (gp130Δadipo) mice, we recently unravelled that obesity-induced interleukin-6 (IL-6) signalling in adipose tissue contributes to circulating levels of the two anorectic hormones leptin and insulin. Herein, we aimed to investigate the role of adipocyte-specific IL-6 signalling in exercise-mediated appetite control and, hence, weight reduction in obesity.

Methods:

gp130Δadipo and control littermate mice (gp130F/F) were regularly exercised (60 minutes/day, 5 days/week) during a 12-week period of high fat diet (HFD)-feeding. As sedentary controls, HFD-fed gp130F/F and gp130Δadipo mice were handled 5 days/week without undergoing exercise training. Thermogenesis was determined using thermography and food intake as well as energy expenditure were assessed in metabolic cages. Insulin sensitivity was assessed by performing intraperitoneal insulin tolerance tests. Circulating IL-6, insulin and leptin levels were measured using immunoassays. Protein levels of phosphorylated STAT3, JAK2 and Akt were assessed in the hypothalamus to analyse leptin and insulin sensitivity.

Results:

Repetitive physical activity reduced food intake and HFD-induced weight gain in gp130F/F but not gp130Δadipo mice. In parallel, insulin sensitivity was ameliorated in HFD-fed control but not in knockout mice. In contrast, thermogenesis and energy expenditure were not different between the genotypes. Circulating insulin and leptin levels were significantly reduced in gp130Δadipo mice. Moreover, hypothalamic leptin and insulin signalling were enhanced in exercised gp130F/F but not in gp130Δadipo mice as demonstrated by elevated pSTAT3, pJAK2 and pAkt protein levels.

Conclusion:

Adipocyte-specific IL-6 signalling plays an important role in exercise-mediated reduction in food intake and weight gain in HFD-fed mice. As exercise-mediated appetite control in obesity is not only important for weight reduction but also for the prevention of weight regain, the herein identified pathway may be of importance for body weight management.

60

Loss of multiple enzyme activities due to the human genetic variation P284T in NADPH cytochrome P450 oxidoreductase.

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Background/Introduction:

Cytochromes P450 located in the endoplasmic reticulum require NADPH cytochrome P450 oxidoreductase (POR) for their catalytic activities. Mutations in POR cause multiple disorders in humans related to the biosynthesis of steroid hormones and also affect drug-metabolizing cytochrome P450 activities. Here we are reporting the effects of a POR genetic variant P284T which is located in the hinge region of POR that is necessary for the flexibility of domain movements.

Methods:

Human wild-type and P284T mutant of POR, as well as cytochrome P450 proteins, were expressed in bacteria, purified and then reconstituted for enzyme kinetic assays. Quality of POR proteins was checked by cytochrome c, ferricyanide and tetrazolium dye reduction assay and measurements flavin content.

Results:

We found that for the P284T variant of POR the cytochrome c reduction activity was reduced to 47% of the WT and MTT reduction was reduced to only 15% of the WT. No impact on ferricyanide reduction activity was observed, but a severe loss of CYP19A1 (aromatase) activity was observed (9% of WT). In the assays of drug metabolizing cytochrome P450 enzymes, the P284T variant of POR showed 26% activity for CYP2C9, 44% activity for CYP2C19, 23% activity for CYP3A4 and 44% activity in CYP3A5 assays compared to the WT POR.

Conclusion:

These results indicate a severe effect on several cytochrome P450 activities due to the P284T variation in POR which suggests a negative impact on both the steroid as well as drug metabolism in the individuals carrying this variation.

61

Effect of metformin on ACTH receptor activation and downstream signaling

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Background/Introduction:

The peptide hormone adrenocorticotropin (ACTH or Corticotropin) is a major component of the stress response system in the Hypothalamus-Pituitary-Adrenal (HPA) axis. Under stress, it is secreted from the anterior pituitary and stimulates cortisol production from the adrenal cortex. Changes in ACTH production or action are associated with multiple disease conditions. In clinical situations like Cushing's disease, ectopic ACTH syndrome and congenital adrenal hyperplasia, there is excess ACTH production and blocking the interaction of ACTH at its site of action would be a therapeutic option. Currently, effective therapy to block the action of ACTH is unavailable. Insulin-sensitizing treatment, such as metformin, has been used to ameliorate a few reported cases of adrenal disorders. However, the exact mechanism of how these insulin-sensitizing drugs affect the HPA axis is not known. Here we test whether an insulin-sensitizing drug, metformin have a direct effect on the activity of ACTH.

Methods:

Cell based in-vitro assays were performed to test the effect of metformin on ACTH receptor activation and signaling. For assays, OS3 cells transfected with ACTH receptor and luciferase reporter plasmids were used. Cyclic AMP (cAMP) generation upon receptor activation was measured by dual luciferase assay(Promega). The potential to shift the ACTH concentration-response curve (CRC) was evaluated to characterize the inhibitory activity of metformin on ACTH receptor activation. Detailed characterization was done to calculate the 50% inhibitory concentration (IC50) by varying concentration of metformin.

Results:

Metformin was found to inhibit the activation of the ACTH receptor and downstream signaling associated with ACTH response. Significant inhibition of ACTH induced receptor activation upon treatment with 10 mM metformin was observed. Metformin shifted the ACTH CRC towards the right by half log, indicating antagonism.

Conclusion:

Treatment of an insulin-sensitizing drug, metformin reduces ACTH induced receptor activation and signaling. This study could be useful in developing new strategies for management of hyperandrogenic states especially associated with excess ACTH.

62

Transcriptome analysis of novel Sertoli cell models to highlight potential genes involved in DSD mechanism of disease.

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Background/Introduction:

Determination of the gonads in men is closely dependent on Sertoli cells differentiation and maturation. Many cases of differences of sex development (DSD) are caused by variations in these processes. The study of the mechanisms underlying these complex conditions is crucial for optimal clinical management and Sertoli cells would be an ideal model for this purpose. Our human Sertoli-like cell model (SLCs) may shed some light on the identification of new genes and common pathways involved in the mechanism of disease in DSD.To explore the transcriptomes of three Sertoli cell models Ntera2 (NT2d1), primary human Sertoli cells (HSerCs) and the new SLCs in order to find significant expression differences and similarities that prove the quality of SLCs as a human Sertoli cell model and highlight new potential genes involved in the development of human Sertoli cells.

Methods:

We used RNA-Sequencing to analyze the transcriptome of NT2d1, HSerCs and SLCs. Gene Ontology (GO) enrichment of the significantly regulated genes ($p<0.05$, $FC>=2$) in NT2d1, HSerC and SLCs, compared to induced pluripotential stem cells (iPSCs) using ToppCluster. Similarities and differences in the transcriptome of the three Sertoli-like cell lines were visualized using Cytoscape.

Results:

This approach revealed that SLCs and HSerCs are much more similar among each other than NT2d1 cells or the KGN female gonad cell model. SLCs showed an expression of genes related to urogenital development while several genes involved in WNT signaling pathway and male infertility are downregulated. Anong those genes, we observed an expression of Pax2 and several Hox genes, both linked to multiple steps of urogenital development and bipotential gonad formation. The functional redundancy among members of this large family may be masking a role in sex developmental defects. We compare this SLCs expression pattern with Whole exome sequencing data from DSD patients in collaboration with the groups under the Sinergia project "identification of new factors implicated in abnormal gonadal development in humans"(FN 7315). We can highlight the expression of POLD1, which has a critical role on DNA repplication and repare. Although there is no previous evidence of its implication in sex development, mutations in these gene were found in 5 different DSD patients presenting 46 XY, gonadal dysgenesis.

Conclusion:

Sertoli-like cells have proved to be a better model than the commonly used NT2d1 cells to study human Sertoli cells. Moreover, the comparison of high quality Sertoli cell models highlighted several common genes that may conceal a not yet known role in male gonadal development.

63

The GLP-1 receptor agonist liraglutide impacts hepatic lipid and gut microbiota composition in a mouse NASH model.

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Obesity reaches epidemic proportions worldwide, increasing the prevalence of type 2 diabetes (T2D). T2D is associated with various complications including non-alcoholic fatty liver disease (NAFLD). NAFLD can evolve to hepatic inflammation and fibrosis [non-alcoholic steatohepatitis (NASH)], possibly leading to cirrhosis and hepatocellular carcinoma. Pharmaceutical treatments for NAFLD/NASH are still lacking. GLP-1 receptor agonists (GLP-1RAs) are currently widely used in the treatment of T2D. Therefore, our study aimed to assess potential beneficial effects of the long-acting GLP-1RA liraglutide on liver disorders associated with T2D.

Wild-type C57BL/6J male mice were fed a methionine-choline deficient (MCD) diet to induce NAFLD/NASH. After 3 weeks on a MCD diet, mice were infused with either liraglutide (16 µg/d) or saline solution for 4 additional weeks. In addition to steatosis, inflammation and fibrosis assessed by qPCR and histology, we studied hepatic lipid composition using Liquid Chromatography–Mass Spectrometry (LC-MS) and gut microbiota distribution using Next Generation Sequencing (NGS).

Liraglutide infusion decreased hepatic expression of markers of inflammation and fibrosis. Despite a similar degree of steatosis, liraglutide-treated mice exhibited a decrease in C16 and C24 ceramides/sphingomyelin lipid species in the liver. In addition, liraglutide treatment reduced hepatic content in saturated fatty acids. Liraglutide infusion reduced liver gene expression of Toll-like receptors 4 and 9 involved in bacterial recognition, suggesting a role in the gut/gut microbiota axis. Interestingly, liraglutide restored proportion of *Bacteroides*, *Coriobacteriaceae* and *Alloprevotella* genera, which were decreased on a MCD diet, and normalized proportion of *Clostridium*, *Turicibacter* and *Acetatifactor* genera, which were increased on a MCD diet.

In conclusion, liraglutide ameliorates hepatic inflammation and fibrosis. Liraglutide also changes qualitatively, but not quantitatively, hepatic lipid content in our experimental context, notably decreasing lipids involved in the development of insulin resistance. Moreover, liraglutide corrects some alterations in the gut/gut microbiota axis observed on a MCD diet. Taken together, these results suggest that beyond its known actions in T2D, liraglutide exhibits additional beneficial effects in the gut-liver axis.

64

Investigating Clinical and Genetic Effects of Human Steroidogenic Factor 1 Variants on Sex Development and Steroid Biology - An International Multicenter Study

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Background/Introduction:
Steroidogenic Factor 1 (SF-1/NR5A1) is an important factor for steroid hormone biosynthesis and sex development. Variants of SF-1 lead to a broad spectrum of phenotypes including adrenal insufficiency, disorders of sex development and primary ovarian insufficiency. Variants in additional genes might explain the broad phenotypes, but detailed mechanisms are unclear. This study aims at assembling a large group of individuals and families with SF-1 variants from the international I-DSD registry. In particular, we aim to describe their phenotype, investigate their genotype, define genotype-phenotype correlations and characterize identified SF-1 variants and candidate genes.

Methods:
Patients from the I-DSD registry are eligible if they have disorders of 46,XX or 46,XY gonadal development, disorders of androgen synthesis/action or non-specific disorders of undervirilization. We will exclude 46,XX individuals with disorders of androgen excess, disorders of Mullerian development or cloacal exstrophy, and 46,XY individuals with Leydig cell defects, Persistent Mullerian Duct Syndrome or cloacal exstrophy. We will collect data on general and disease-specific health, biochemical and genetic tests, therapy and surgery, organ abnormalities and family history. We will investigate families with SF-1 variants using TRIO+ WES analyses and filter genetic data with stata-of-the-art algorithms. We will describe phenotype-genotype clusters by linking data from phenotyping to data from genotyping. To characterize gene variants, we will test promoter activity, gene/protein expression and steroid production in established cell models and in human induced steroidogenic cells (hiSCs).

Results:
Of 71 clinicians with eligible patients in the I-DSD registry, 41 responded and 38 agreed to participate in our study by June 2019. The 38 clinical partners registered 1282 eligible patients. Of those, 1170 patients (91%) had no SF-1 screening or information on SF-1 screening was not available. Of 112 patients screened for SF-1, 37 (33%) were tested positive for SF-1 variants. The study will run from 2019-2024. We will describe phenotype patterns, expect to find new disease-causing variants in SF-1 and other genes, and describe genotype-phenotype correlations. We anticipate to show that multiple genetic variants together with SF-1 variants affect steroidogenesis and sex development.

Conclusion:
Individuals with SF-1 variants have special needs that are so far unknown and unmet. This study will complement these gaps and thereby improve standards of care. Planned basic studies will increase our understanding of sex development and steroidogenesis and will work towards cell-based therapeutic options.

65

WES analysis of a cohort of 94 patients presenting with 46,XY and 46,XX DSD

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Background/Introduction:

Differences of Sex Development (DSD) is diagnosed in approximately one out of 4'500 newborns. The presenting phenotype in children born with DSD is very diverse, and they and their families face considerable challenges, potentially including surgical intervention and gender assignment, as well as associated complications (e.g. infertility). Currently, causative genetic variants can be identified in about 50% of the analyzed patients, due to a lack of knowledge concering DSD and the pathways involved in sex development In order to advance our understanding of sex development and to uncover new genes potentially involved in DSD, we performed Whole Exome Sequencing (WES) on a cohort of 46,XY and 46,XX patients.

Methods:

WES was performed on a cohort of 94 46,XY and 46,XX patients. In order to provide a genetical explanation for the observed phenotypes, different filtering methods were applied to the WES data to identify rare variants in previously known DSD related genes as well as rare variants in new potential causative targets.

Results:

For 33 patients, causative genetic variants in previously known DSD genes could be identified and matched to the diagnosis made by physicians. Additionally, new potential candidate genes for DSD were identified based on the number of patients carrying variants, the similarity of phenotype, their expression in tissues important for sex development (i.e. gonads and pituitary) and the rarity (MAF<0.05%) of the variants.

Conclusion:

WES is an important tool that allows for the identification of new genes potentially involved in DSD, advancing our understanding of human sex development and our capacity to accurately diagnose, support and treat patients and their families.

66 S

Impact of common polymorphic variant A503V in POR on drug metabolism: Implications for POR deficiency

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Background/Introduction:

A broad spectrum of human diseases, including abnormalities in steroidogenesis, are caused by mutations in the NADPH cytochrome P450 oxidoreductase (POR) (1-2). Cytochrome P450 proteins perform several reactions, including metabolism of steroids, drugs and other xenobiotics. Therefore, genetic variations in POR can impact many different metabolic pathways by changing the activities of cytochromes P450. In 2004 the first human patients with defects in POR were reported with symptoms of ambiguous genetalia and bone malformations, and over 200 variations in POR are known.

Methods:

By analyzing the POR sequences from genomics databases, we focused on common variant in POR A503V which is often present in hetrozygous form in many PORD patients. We prepared the A503V variant and characterized it by functional studies using recombinant proteins. Proteins were expressed in bacteria and purified for activity assays. Activities of cytochrome P450 enzymes were tested with lipids into which P450 and P450 reductase proteins were embedded and assayed using fluorogenic substrates on a microplate spectrofluorometer.

Results:

We found a positive effect on many drug metabolizing enzyme activities due to A503V variant in POR. Activity of CYP2C9 was increased to 180% of the WT POR, and CYP2C19 showed 243% of WT activity with the A503V variant of POR. Most remarkable was the impact of A503V variant on CYP3A5 activity, which was increased by 421% compared to WT POR.

Conclusion:

Effect on drug metabolism in patients with PORD require careful considerations of cytochrome P450 mediated activities. While many PORD patients have low or reduced drug metabolism due to defects in POR, presence of A503V allele, can alter the overall effect on drug metabolism. Significantly, tacrolimus, a drug given during organ transplant, can be metabolized several fold faster due to presence of A503V variant of POR. It is likely that presence of A503V allele is beneficial in patients with POR

67

Mitochondrial diabetes is rare in Switzerland

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Background/Introduction: When young-onset (< 45 years of age) autoimmune antibody negative diabetes occurs in a non-obese individual, a monogenic form is suspected and even more so, if congenital malformations or disabilities are associated. We recently genetically analyzed a cohort of individuals with a suspicion of monogenic diabetes and identified a variant in a MODY gene in 40% of them. Recent data from the UK and France show that 12% with a genetically caused diabetes have a mitochondrial form (mDM). Surprisingly, the classical associated extra pancreatic features such as deafness, macular dystrophy, were often not present or missed because of a very mild clinical phenotype. So, the aim of our study was to assess how many mDM forms were present in the Swiss cohort.

Methods: The mitochondrial m.3243A>G mutation was analyzed by melting curve analysis of signals produced by fluorescence resonance energy transfer (FRET) in a real-time thermocycler (LC480; Roche). Although semi quantitative, the method provides a rough estimation of plasmy status of the sample. Analysis was calibrated using a set of wild-type and mutant samples.

Results: We have analyzed 228 probands (137 females, 97 males) living in Switzerland using a method combining FRET with qPCR. The mean age at diabetes diagnosis was 27.7 ±15.4 years. We identified the mitochondrial m.3243A>G mutation in a total of 3 individuals corresponding to 1.3 % of the total cohort and to 3.1% of the individuals with an identified genetic origin of diabetes. The clinical characteristics are described in table below.

Patient ID	Age at diabetes onset (years)	Sex	HbA1c at onset (mmol/l)/ (%)	Glycemia at diabetes onset (mmol/l)	Diabetes autoimmune antibodies	Maternal diabetes	Deafness	Complications	Treatment	Hetero-plasmy
1	51	f	49/ 6.6	-	No	Yes	Yes	Proteinuria, Muscular hypotonia	-	~30%
2	23	m	144/ 15.3	25.6	No	No	No	No	Metformin, repaglinide	~30%
3	16	f	-	54	No	No	No	Diabetes insipidus	Metformin, Insulin	<10%

Conclusion: Even if diabetes caused by a significant plasmic rate of mitochondrial mutation remains rather rare in Switzerland, we have started to routinely include the search for the m.3243A>G mutation when diagnostically analyzing probands for monogenic diabetes. The discrepancy with the French and UK data might be explained by 1) the inclusion of individuals with adult onset diabetes only (age >15 to 40 years) in comparison to the Swiss cohort harboring 33% of subjects with diabetes onset in childhood; 2) it is possible that due to limited sensitivity of the method used here, we might have underestimated the rate of heteroplasmic mitochondrial mutation in patients affected by mDM. The diagnosis of mDM has a direct clinical impact, since a thorough work-up for multisystem organ involvement is mandatory and treatment with metformin should be avoided and will be changed in the affected patients. Our future goal will be to understand the exact origin of each individual's diabetes, this will allow us to further implement precision medicine, and to offer the best possible care to our patients.

68

Air pollution mediates diabetes via oral exposure by disrupting innate mucosal immunity

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Background:

In recent years, air pollution has emerged as an additional risk factor for type 2 diabetes. So far, the mechanism has been poorly understood. Previous studies focused on the lung as the primary target organ of air pollution. However, air pollution particles also reach the gut by mucocilary clearance and ingestion of contaminated foods. The aim of this study was to elucidate whether air pollution particles induce diabetes via the gut and what mechanisms are involved.

Research Design and Method:

Male C57B6/N, CCR2-/-, Rag2-/- or C57B6/N mice treated with a CSFR1 inhibitor were exposed to diesel exhaust particles (DEP) by oral gavage (5 days/week; 12µg/day) for up to 6 months. Glycemia was monitored by glucose tolerance tests. Beta-cells were assessed by histology and immune cells characterized by flow cytometry. To address changes in the intestinal macrophages, we performed single cell RNA sequencing.

Results:

Mice orally treated with DEP developed impaired glucose tolerance with reduced insulin secretion. However, beta-cell mass was not affected, suggesting a functional beta-cell defect. We found a specific loss of anti-inflammatory/resident intestinal macrophages, creating an inflammatory milieu in the gut. Mechanistically, air pollutants up-regulated inflammatory- and interferon-response pathways in intestinal macrophages, hence promoting their inflammatory phenotype. Genetic or pharmacological depletion of macrophages protected mice from developing an inflammatory milieu in the gut, insulin secretion defect and diabetes. In contrast, adaptive immunity was not involved in air pollution-induced diabetes, as Rag2-/- mice, lacking B and T cells, became glucose intolerant upon oral air pollution exposure.

Conclusion:

Oral exposure to DEP results in impaired glucose tolerance, which is mediated by altered innate immunity: DEP disrupts the differentiation of intestinal macrophages, thereby creating an inflammatory milieu, which impacts on beta-cell identity and function. Our findings provide a new understanding on how air pollutants affect health, which is crucial if we want to find novel disease prevention and treatment strategies to lower the global burden of disease attributable to air pollution.

69 S

Management and outcome of pregnancies in women with adrenal insufficiency: experience from a retrospective multicenter study

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Background/Introduction:
Recommendations for the management of pregnancies in patients with adrenal insufficiency (AI) are scarce. The aim of this study was to analyse current clinical approaches in seventeen specialized centers across Europe with a particular focus on maternal and fetal outcome.

Methods:
95 pregnancies in 86 patients with AI of different aetiology [Addison's disease (n=37), secondary AI (n=20), congenital adrenal hyperplasia (CAH) (n=22), or other reasons of AI including bilateral adrenalectomy (n=5)] were followed since 2013. Clinical and biochemical parameters and treatment details were assessed before and during pregnancy and maternal and fetal outcomes were recalled.

Results:
66.3% (59/89) of the pregnancies were substituted with hydrocortisone in two or three daily doses while 14.6% (13/89) were treated with modified hydrocortisone, 9% with prednisolone, 5.6% with cortisone acetate and 6.7% with a combination of different steroids. The mean hydrocortisone equivalent dose before pregnancy was significantly lower in comparison to that during pregnancy (21.0±7.7mg/day before vs. 23.1±8.0 during 1st trimester, 25.5±10.6 during 2nd trimester und 25.9±8.3 during 3rd trimester) but did not differ significantly between trimesters. Fludrocortisone was used in 92.9% of the Addison's cases and in 39.1% of women with CAH before pregnancy and dosage was increased in 51% (23/45) of patients. Overall, in 63.1% of all cases glucocorticoid or mineralocorticoid dosage was adapted at least once during pregnancy. For delivery, in 55.3% (47/85) of all pregnancies caesarian section was performed while only in 8/47 cases the reason was clearly documented or was conducted as an emergency procedure. Hydrocortisone administration during delivery varied among different centers with no clearly standardized practice followed. Considering the outcome, 24 of 86 women (27.9%) had a documented history of at least one previous abortion with further three miscarriages taking place dur

Conclusion:
Overall, these retrospective data indicate good maternal and fetal outcome of pregnancies in AI patients. However, optimized treatment adjustments during pregnancy and appropriate approaches during delivery remain challenging, considering the lack of evidence-based guidelines. A remaining proportion of reported adrenal crisis during pregnancy and histories of abortion highlight the need for appropriate education of patients and treating physicians as well as early diagnosis of adrenal insufficie

70

Dynamics of fat oxidation from sitting to light exercise in sedentary humans

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Background/Introduction:

It is now recognized that societal erosion of daily life low-level physical activity - substituted with more sedentary (mostly sitting) behavior - has a greater influence on the obesity epidemic than moderate-to-vigorous intensity leisure-time pursuits. This has generated considerable interest for better monitoring, characterizing and promoting a plethora of low-level physical activities in daily life. Given the demonstration that low fat oxidation is also a risk factor for obesity, the aim of this study was to investigate, in sedentary young adults, the dynamics of fat and carbohydrate oxidation from the resting state to very low and low intensity exercise.

Methods:

The study was conducted in 26 healthy sedentary young subjects of normal BMI (12 men and 14 women) after a 10-12h of overnight fast, with women in the follicular phase of the menstrual cycle. Using facemask indirect calorimetry coupled with polar system (Cosmed Quark, Milan), energy expenditure (EE), respiratory quotient (RQ) as a measure of fat vs carbohydrate oxidation, as well as heart rate (HR) were assessed in the sitting posture at rest, during graded cycling exercise from no-load to 50 watts (W) on a bicycle ergometer, and also during passive (motor-driven) cycling exercise on an active/passive trainer (APT, Mettler, USA). During active cycling, perception of the exercise intensity was assessed using the Borg Scale for ratings of perceived exertion (RPE) between 'very very light' to 'very very hard'.

Results:

In response to active no-load cycling, EE increased by nearly 2-folds, while RQ dropped($p<0.01$). Subsequently, a linear increase in EE between 2-4 folds above resting levels was observed during cycling exercise across 10 to 50 W, while RQ remained close to levels found at rest. Both HR and RPE increased linearly across no-load to 50 W, but RPE did not exceed values corresponding to the exercise being perceived as 'light'. However, analysis of individual data at 50 W revealed two subgroups of subjects, with those having RPE values corresponding to the exercise being perceived as 'very light to light' showing no increase in RQ relative to resting levels, as opposed to an increase in RQ (i.e. less fat oxidation) in those who perceived the exercise as being 'somewhat hard to hard' (0.03 vs 0.08, $p<0.001$). In both subgroups, EE, RQ and HR did not change in response to passive cycling relative to the resting state. No gender differences were observed in the changes in EE, RQ, HR or perception in response to the active or passive exercise.

Conclusion:

During perceived light exercise, when EE is 2-4 times higher than at rest, RQ stays in the zone of high lipid oxidation, and a shift to increased carbohydrate oxidation only occur with a shift in perception from 'light' to 'somewhat hard'. Given that compliance to exercise diminishes when it is perceived to be hard, our study showing that high lipid oxidation is maintained during 'light-perceived' exercise reinforces the importance of light physical activity in obesity management.

71

Improving food literacy of patients with obesity or type 2 diabetes with the mobile app MySwissFoodPyramid

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Background/Introduction:

Mobile apps can be useful tools in the therapy of patients with obesity or type 2 diabetes. They should be evidence-based and guarantee data protection in order to be recommended by physicians. For patients, ease of use, cost, personalised features and attractive user interfaces are requirements when using apps. One important factor in the therapy of patients with obesity or type 2 diabetes is a healthy, well-balanced diet. It can support achieving a healthy body weight and good metabolic control. The app MySwissFoodPyramid aims to improve food literacy of individuals by providing information on a healthy, well-balanced diet and comparing individual habits with the food-based dietary guidelines of the Swiss food pyramid. These guidelines are generally suitable for adult patients with obesity or type 2 diabetes.

Methods:

Technical basis of the app is the open source behavioural intervention platform MobileCoach (www.mobile-coach.eu). The app was developed between 2017 and 2018 by the Institute of Technology Management, University of St. Gallen under a mandate of the Federal Food Safety and Veterinary Office. Registered dietitians and nutritionists were responsible for the elaboration of the nutritional content. Like other MobileCoach apps, MySwissFoodPyramid consists of a chat interface with a digital coach and a sidebar. In MySwissFoodPyramid, this sidebar gives access to a semiquantitative food diary, a chapter with information on a healthy, well-balanced diet and a map showing individual progress.

Results:

A semiquantitative food diary allows for comparison of individual dietary habits with the official guidelines of the Swiss food pyramid. Evaluation consists of an image of the user's own food pyramid and general explanations on which foods and drinks to consume in larger or smaller quantities. No indication on calorie or carbohydrate intake is made. Users are supported by a fully automated digital guide, who gives instructions on how to complete the food diary and informs about the principles of a healthy, well-balanced diet. The app is available for free on the App Store and Google Play Store in German, French and Italian and was published in June 2018. No comparable apps are available in Switzerland.

Conclusion:

The app MySwissFoodPyramid can support treatment of patients with obesity and type 2 diabetes by improving their understanding of a healthy, well-balanced diet and its implementation in daily practice. Physicians can rely on the evidence-based content, adequate data protection and free accessibility. Updates are planned to improve user-friendliness and include further topics. The app shall not replace professional counselling from a registered dietitian.

72

Effect of a high fructose diet on metabolic parameters in carriers for hereditary fructose intolerance

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Background:
High fructose intake can decrease hepatic insulin sensitivity, and increases uric acid concentrations, which may contribute to insulin resistance. Untreated hereditary fructose intolerance is associated with hyperuricemia. We hypothesized that asymptomatic carriers for hereditary fructose intolerance (HFI) would have increased fructose-induced uric acid responses and insulin resistance.

Methods:
6 subjects heterozygous for HFI (hHFI) and 6 age-, sex- and weight-matched Controls (C) were studied in a randomized, controlled, crossover trial. All subjects ingested according to a cross-over design two identical test meals containing 0.7 g/kg glucose and 0.7 g/kg fructose, once after a 7-day on a low fructose diet (< 10g/d) diet, on an another occasion after 7 days on a high fructose diet (1.4g fructose/kg/d). Uric acid, glucose, insulin concentrations were monitored in fasting conditions and over 2 hours postprandial. Postprandial data were expressed as incremental area under the curves (iAUC) and were analyzed using a mixed model with interaction.

Results:
Basal uric acid concentration were higher in hHFI than C ($P < 0.01$), but all other parameters were not different. On the low fructose diet, postprandial iAUCs for all parameters were not statistically different in hHFI compared to C (all $P>0.05$). Plasma uric acid was significantly higher in hHFI compared to controls ($P < 0.01$) but was not affected by dietary conditions in both groups. The postprandial increase in plasma insulin was higher in hHFI after a high fructose diet than in C ($P < 0.001$).

Conclusion
Consumption of a high fructose diet for 7 days increased postprandial insulin in hHFI, but not in C, suggesting that it induced insulin resistance in hHFI only. hHFI patients also had increased uric acid concentrations, which however were not altered by the fructose content of the diet. The mechanisms responsible for fructose-induced insulin resistance in hHFI remains to be further evaluated.

73 S

Adipose Tissue Fat Fraction as Determined by Magnetic Resonance Imaging as a Predictor of Thermogenic Capacity

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Background/Introduction:

Brown adipose tissue (BAT) is a thermogenic tissue and plays an important a role in energy homeostasis in adult humans. BAT contains a high amount of mitochondria and differs from white adipose tissue (WAT) in its lipid content. Currently, BAT activity is quantified by 18F-FDG-EPT/CT after a mild cold stimulus of at least two hours duration. This technique is cumbersome, expensive and associated with exposure to ionizing radiation. As the fat fraction (FF) of the adipose tissue compartment is lower if it contains a high amount of mitochondria, measuring the FF by magnetic resonance imaging (MRI) might provide a less expensive method to predict BAT activity.

Methods:

We performed a prospective, randomized interventional trial to evaluate the effect of glucocorticoids on human BAT. During this trial BAT activity was stimulated by mild cold-exposure and BAT activity was assessed by 18F-FDG-PET/CT. Further, we performed MRI of the adipose tissue in the cervical and supraclavicular region and calculated the fat fraction of the tissue. BAT activity, as determined by maximum (SUVmax) and mean (SUVmean) glucose uptake into the tissue, was compared to the fat fraction of the supraclavicular fat depot.

Results:

FF correlated positively with SUVmean in the supraclavicular area (R2 = 0.3091; P = 0.0390). In the cervical region there was no correlation detectable between FF intensity and SUV mean (R2 = 0.008117; P = 0.7594).

Conclusion:

Although MRI fat fraction could be correlated with SUVmean values in the supraclavicular area, the correlation remains rather weak. Furthermore, this correlation could not be found in the cervical areas. Thus, further research and development will be necessary to develop different MRI techniques which might eventually replace the current gold standard PET/CT to detect BAT and BAT activity.

74

First case report of pregancy under diazoxide therapy for hyperinsulinism-hyperammoniemia (HI/HA) syndrome

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Background

Hyperinsulinism-hyperammonemia syndrome (HI/HA) is a rare autosomal dominant disease caused by *GLUD1* variant and is the second most common cause of congenital hyperinsulinism in infancy. The disease is manifested by hypoglycemia and elevated ammonia. The mainstay of pharmacological therapy is diazoxide, however data related to its safety during pregnancy remains limited to high dose IV administration for maternal hypertension. We report here the case of a pregnant woman with HI/HA treated with diazoxide during pregnancy.

Case presentation

A 27 year-old female with congenital hyperinsulinism of unknown cause and treated with oral diazoxide 3x 50 mg daily, was admitted to the hospital to evaluate her current therapy as she was 11 weeks pregnant. Due to the potential embryotoxic effect of diazoxide, it was decided to interrupt the treatment and to introduce a diet with slow sugar-based snacks and reduced carbohydrate (40% of intake). With this diet she did not present any severe hypoglycemic episodes during the hospital stay. However, the day after she left the hospital, she developed a hypoglycemic coma at home with a glucose level at 1.6 mmol/l requiring intravenous glucose administration by the paramedics. A multi-disciplinary consensus with the endocrinologist, obstetrician and pharmacologists decided to resume diazoxide at the same dose for the rest of her pregnancy. She did not develop any other episodes of severe hypoglycemia during the rest of the pregnancy. We performed a metabolic work-up showing ammonia level that was elevated at 118 µmol/l. The association of hypoglycemia, hyperinsulinism and hyperammonia was in favor of a HI/HA syndrome. Genetic testing of the *GLUD1* gene was performed during pregnancy and revealed a heterozygous missense variant, c.1496G>T (p.Gly499Val) confirming the diagnosis of HI/HA caused by the *GLUD1* defect.
The foetus developed a moderate intrauterine growth restriction (IUGR). At 40 weeks of pregnancy, she was admitted because of prelabor rupture of membranes. Due to a failed labor induction, a C-section was performed. The newborn was confirmed as low-birthweight (2410 g at birth, <3th percentile), but without any congenital malformation and with a normal glucose level at 4.4 mmol/l. A genetic testing was subsequently performed in the newborn which showed the absence of *GLUD1* gene mutation.

Conclusion

To the best of our knowledge this is the first report of oral low dose diazoxide treament during pregnancy in a mother presenting HI/HA diagnosed in adulthood. In line with previous report of diazoxide treatment during pregnancy for other conditions, no major teratogenic effect was observed, except IUGR. In our case, IUGR could be attributed to repetitive maternal mild hypoglycemia related to HI/HA and to a potential reduction of fetal growth hormone secretion by the diazoxide. Carefull monitoring of fetal growth to detect IUGR is then mandatory.

75 S

Relation of Diet-Induced Thermogenesis to Cold-Induced Thermogenesis and Brown Adipose Tissue Activity in Healthy Men

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Background/Introduction:

Brown adipose tissue (BAT) is a thermogenic tissue which can dissipate chemical energy as heat if activated by the sympathetic nervous system in response to cold exposure. Active BAT increases insulin sensitivity and improves serum lipids by taking up glucose and lipid from the circulation. Furthermore, it leads to increased energy expenditure (EE) and can counteract overweight and obesity.
Ingestion of food leads to an increase in EE which is known as diet induced thermogenesis (DIT). Several animal studies have proposed a link between BAT and DIT. In this analysis we investigated the relationship between BAT and DIT in healthy human volunteers.

Methods:

We measured EE by indirect calorimetry in seventeen healthy male volunteers before and after a cold stimulus. Furthermore, we maximally stimulated BAT activity with the β3-adrenoreceptor agonist Mirabegron and two hours of mild cold exposure and assessed BAT activity by 18F-FDG-PET/MRI. DIT was assessed by indirect calorimetry before and during an oral glucose tolerance-test at 0, 60 and 120 min. Additionally, the skin temperature was measured by wireless sensors in 11 predefined locations of the skin.

Results:

Seventeen healthy men (mean age 23.4 years, mean BMI 23.2 kg/m2) participated in the study. EE increased from 1908 (±181) kcal/24 hours to 2128 (±277) kcal/24 hours (p <0.0001, +11.5%) after a mild cold stimulus of two hours duration. An oral load of glucose increased EE from 1911 (±165) kcal/24 hours to 2096 (±167) kcal/24 hours at 60 minutes (p < 0.0001, +9.6%). After 120 min EE decreased again by 6.8% to 1953 (±154) kcal/24 hours, (p = 0.0002 to EE60min). The increase in EE in response to cold was significantly associated with BAT activity in PET (R2=0.4337, p=0.004). However, DIT in response to an oral glucose load was not significantly associated with BAT activity (R2=0.015, p=0.64).

Conclusion:

DIT after an oral glucose load is not associated with BAT activity as determined by 18F-FDG-PET.

76

High Throughput in situ Metabolomics for Genotype/phenotype Correlation in Pheochromocytoma and Paraganglioma

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Background/Introduction:

The pathophysiology of pheochromocytoma and paraganglioma (PPGLs) has been investigated via genetic approaches and multi-steroid profiles for plasma, urine and tumor tissues. However, the pathophysiological mechanism that translate genetic alterations into functional autonomy have not been elucidated in detail. This study was undertaken to provide a comprehensive high-resolution mass spectrometry imaging (MSI) map of PPGLs in relation to immunohistochemical (IHC) profiles, mutational status and clinical annotation.

Methods:

Matrix-assisted laser desorption/ionization-Fourier transform-ion cyclotron resonance (MALDI-FT-ICR) MSI was conducted for quantification of metabolites including nucleoside phosphates indicative of oxidative phosphorylation, catecholamines, intermediates of glycolysis and the tricarboxylic acid cycle, lipids and fatty acids. Obtained metabolite profiles were analyzed with genotype/phenotype information.

Results:

Distinct metabolomic profiles of PPGLs were observed with respect to clusters based on genomic status between cluster 1 and 2 and metabolites of the inositol phosphate metabolism. Analysis focused on the clinical outcome of PPGLs revealed further distinct metabolomic profiles between benign and metastatic tumors with metabolites included in cardiolipin biosynthesis being significantly changed. Moreover, cox proportional hazards regression revealed that the distribution of 48 metabolites were significantly associated with metastatic behavior and multivariate analysis including SDHB mutation status defined 26 metabolites as independent factors for the development of metastasis. Lower peak intensity of threoninyl-cysteine (m/z 243.0415) was associated with metastasis-free survival (log-rank tests P = 6.73E-06) and as an independent factor from genetic status (hazard ratio, 27.6, P = 0.003).

Conclusion:

The present study demonstrates distinct metabolomic profiles of PPGLs in relation to tumor genotypes. In addition, we revealed significant changed metabolites in metastatic PPGLs, which can predict malignant status. Our study provides unprecedented insights into the pathophysiology, clinical features of PPGLs.

77 S

Predictors and differences in early and late postpartum weight retention in women previously diagnosed with Gestational diabetes; a clinical cohort study

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Background/Introduction:

Postpartum weight retention (PPWR) is the difference between weight at the postpartum period and weight prior to pregnancy. Increased PPWR is a significant risk factor of long-term weight gain and obesity and is highly predictive of future diabetes in women with gestational diabetes mellitus (GDM). In order to provide guidance for preventive strategies, this study investigated the predictors of early and late PPWR in a longitudinal cohort of women with previous GDM.

Methods:

We included 862 consecutive women with GDM during pregnancy and followed between 2015 and 2019. PPWR at 6-8 weeks and at 1-year were calculated by subtracting the pre-pregnancy weight from the weight at either 6-8 weeks or 1-year. Potential predictors including pre-pregnancy weight and BMI, weight during and after pregnancy were measured at the first GDM visit and at the postpartum visits. Gestational weight gain was calculated by subtracting pre-pregnancy weight from weight at the end of pregnancy. Other potential predictors were depression (Edinburgh Postnatal Depression Scale), physical activity and eating behavior (intuitive eating scale-2) during the perinatal period. We then modeled the odds of PPWR at 1 year PP using multivariable logistic regression models with backward elimination which included variables that had p<0.2 in an initial univariate regression analysis.

Results:

Mean pre-pregnancy BMI was 25.6±5.4kg/m2, gestational weight gain (GWG) was 12.7±5.9kg and PPWR at 6-8 weeks and 1 year PP were 4.6±5.7kg and 4.0 ±7.4kg respectively. At these two PP time points, only 18.8% and 33.6% of the women had no PPWR. Among women with PPWR at 6-8 weeks PP, a fourth (27.4%) had no PPWR at 1-year PP whereas only 55.2% of those who had no PPWR at 6-8 weeks maintained this at 1-year PP. At 6-8 weeks PP, women without PPWR had significant higher mean pre-pregnancy BMI (29.3±6.2 vs 24.7±4.6 kg/m2) and lower GWG (6.6±5.3 vs 14.2±5.1kg) compared to those with PPWR (both p<0.001), without differences in their metabolic profile. At 1-year PP, however, women without PPWR had no significant difference in pre-pregnancy BMI compared to their counterparts (both BMI 25 kg/m2, p=0.8). Women without PPWR had significantly lower GWG (10.1±5.7 vs 14.16±6.1kg), reduced BMI at 6-8 weeks (26.6±4.6 vs 28.1±5.36 kg/m2) and lower fasting glucose (5.3±0.5 vs 5.6±0.7mmol/l, all p≤0.04) at 1-yr PP. In the multivariate analysis, higher GWG (OR: 1.1, 95% CI: 1.04-1.21) predicted weight retention at 1-year PP.

Conclusion:

Our findings indicate a substantial weight retention in the early and later PP period; however, only half of the women without PPWR at 6-8 weeks PP maintained their status at 1-year PP. Pre-pregnancy BMI and GWG are significant predictors of weight retention in the early and/or late postpartum periods in our cohort of women with previous GDM. Interventions targeting GWG can help prevent weight retention in PP period in these women.

78 S

High fat diet-induced activation of colonic macrophages is linked to glycemic control

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***Background**:*

Intestinal macrophages originate from circulating blood monocytes, subsequently enter the lamina propria of the gut and differentiate through phenotypically distinct subpopulations (inflammatory: P1-P2; intermediate: P3) to resident/ anti-inflammatory macrophages (P4-P5). Not much is known about the role and activation status of these macrophage subpopulations in metabolic disease. Therefore, we aim to elucidate the role of intestinal macrophage subpopulations in glucose metabolism.

Methods:

Intestinal macrophages were characterized by flow cytometry and single cell RNA sequencing in mice fed a high fat diet (HFD) or standard diet. Macrophages were depleted systemically by oral CSF-1R inhibitor BLZ945 (50, 100, 200 µg/g/d) or colon-specifically by intrarectal clodronate liposomes (500 µg every other day). Local inhibition of mTOR was achieved by intrarectal rapamycin (3 mg/kg every other day). Glucose metabolism was assessed by insulin and glucose tolerance tests.

Results:

We found that mice on HFD exhibit increased inflammatory macrophage subpopulations P1 and P2. Macrophage depletion – systemically or colon-specifically – restored glucose metabolism, suggesting a link between intestinal macrophages and glycemic control. The transcriptional profile of colonic macrophages of HFD fed mice showed significantly up-regulated interferon-γ and -α responses, oxidative phosphorylation and mTOR signaling. Up-regulation of mitochondrial function and mTOR was confirmed on protein level. Moreover, preliminary data suggest that local inhibition of mTOR activation by rectal injections of rapamycin can reduce the activation status of intestinal macrophages in HFD-fed mice.

Conclusion:

HFD induces a phenotypical switch towards pro-inflammatory colonic macrophages, which is linked to impaired glycemic control. This macrophage activation involves mTOR, oxidative phosphorylation and interferon signaling pathways and could be prevented by colon-specific mTOR inhibition. Thus, gut-specific attenuation of macrophage activation could emerge as a novel therapeutic strategy to improve glycemic control.

79

Postbariatric patients receiving ferric carboxymaltose are at high risk for developing hypophosphatemia in a FGF23 dependent manner: A prospective cohort study

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Background/Introduction:
Iron deficiency is a common finding in patients following bariatric surgery and parenteral supplementation is frequently required. Ferric carboxymaltose (FCM) is among the preferred compounds used but may be associated with new-onset hypophosphatemia. This study was undertaken to study the prevalence of hypophosphatemia following FCM in post-bariatric surgery patients, a population that may be at particular risk due to highly prevalent secondary hyperparathyroidism.

Methods:
Post-bariatric surgery iron depleted patients (ferritin≤30 mcg/l) scheduled for FCM supplementation (≥500mg) were eligible for this prospective cohort study. A clinical and biochemical assessment was performed before and one week after FCM application. The primary endpoint was new onset of post-FCM hypophosphatemia (<0.8mmol/l). Relevant hypophosphatemia (≤ 0.6mmol/l) was supplemented and patients were followed until plasma phosphate levels were restored.

Results:
52 patients (40 female) following Roux-Y gastric bypass (n=50) or Sleeve Gastrectomy (n=2) completed the trial. The median age and BMI were 46 years (range 22-68 years) and 32.2 kg/m^2 (IQR, 27.5-37.3 kg/m^2), respectively. 15 subjects (28.8 %) developed new-onset hypophosphatemia, 11 of whom requiring oral phosphate supplementation for a median duration of 14 days (IQR, 14-25 days). Plasma phosphate decreased by 0.3 mmol/l (IQR, -0.5- -0.2 mmol/l), p<0.0001). The decrease in plasma phosphate was associated with a significant increase in plasma intact FGF23 (+30% (IQR, -3.8-90.0%); p<0.0001) and a decrease in 1,25(OH)2 vitamin D (-37.6% (IQR, -53.3- 11.6%); p<0.0001) concentrations. Fractional urinary phosphate excretion increased by 55.5% (IQR, 21.6-153.6%); p<0.0001) during follow-up.

Conclusion:
Post-bariatric surgery patients receiving FCM are at considerable risk of developing significant hypophosphatemia secondary to increased renal phosphate wasting through a mechanism involving FGF-23. Our data suggest that plasma phosphate should be monitored after parenteral iron supplementation with FCM in patients following bariatric surgery.

80

GLYCAEMIC PROFILE OF PROFESSIONAL CYCLISTS WITH TYPE 1 DIABETES OVER A 7-DAY UCI-WORLD CYCLE TOUR

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Background:

Professional road cycling is recognised as one of the most physically demanding sports, combining extremes of exercise duration, intensity and frequency. Living with type 1 diabetes (T1D) presents considerable challenges, particularly around exercise. Therefore, individuals with T1D wishing to compete in professional cycling stage races have the monumental task of managing their blood glucose during races and the recovery periods between stages. This observational study aimed to examine the in-ride and nocturnal glycaemic profiles of professional cyclists with T1D over a 7-day UCI-World Tour race.

Methods:

Six male professional cyclists with T1D on multiple daily injections (age 29±3 years, duration T1D 13±7 years, body mass 70.0±5.3 kg, HbA1c 6.4±0.6%) cycled between 3 and 7 h, covering 78 to 136 km on seven consecutive days during the Tour of California. Time spent in pre-specified glycaemic ranges was assessed in-ride and subsequent nocturnal periods (22:00-06:00) throughout the Tour using Dexcom G6. Frequencies were compared with Pearson's chi-square test of independence and odds ratios. Results are presented as mean±SD and statistical significance was accepted when P<0.05.

Results:

Participants spent a high proportion of races in euglycaemia (63±13%) with low percentage of rides spent in Level 1 (1±2%) and 2 (0±0%) hypoglycaemia. However, there was a high proportion of time in the hyperglycaemic range during the rides (36±13%). During the nocturnal periods, the riders spent progressively greater time in Level 1 and 2 hypoglycaemia from day 1 (Level 1 = 6±12%; Level 2 = 0±0%) to day 7 of the tour (Level 1 = 12±12%; Level 2 = 2±4%) (χ^2 (1) >4.78, P<0.05). Overnight, the odds of being in hypoglycaemia increased by 32% (odds ratio = 1.32) from day 1 to day 7.

Conclusion:

Professional cyclists with T1D spent a high proportion of races in target glycaemic range, with little time in hypoglycaemia over a stage tour. Of concern, is the progressively greater time in hypoglycaemia during the nocturnal period after each stage of the Tour. Future research should investigate strategies to reduce the risk of nocturnal hypoglycaemia and to study the impact that this has on recovery between stages.

81

Assessing the surgical footprint of the “chopsticks” technique with intraoperative 3T MRI in endoscopic transsphenoidal adenoma surgery. Clinical experience and surgical results

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Background/Introduction:

The “chopsticks” technique has been recently introduced as a mean to reduce the impact (also defined as surgical footprint) of endoscopic transsphenoidal pituitary surgery (TSS) on the endonasal mucosa. The aim of the current study is to present our experience with this technique, and to offer to neurosurgical literature a first benchmark of its morbidity with particular focus on nasal morbidity.

Methods:

Cohort analysis of prospectively collected data on 130 TSS operations using the “chopsticks” technique. All patients had at least 3 months postoperative neurosurgical, endocrinological and rhinological follow-up. The surgical technique is described and the results as well as the surgical footprint of the procedure on the nasal mucosa (quantified with SNOT-20 and sniffin test) is descriptively reported.

Results:

At a median follow up of 18 months (range 3-70) three patients (2.3%) had new postoperative hyposmia. One patient only had severe impairment of sino-nasal function (SNOT-20 > 40). There was no mortality and only 1 case of permanent new neurological deficit. As of the last available follow-up, 10.7% had a worsening of pituitary function, whereas 26.0% had an improvement of endocrinological function. Gross total resection (GTR) was achieved in 72.3% of cases at the 3 months postoperative MR, with an average EOR of 98%. GTR was the surgical goal in 100/130 cases and could be achieved in 88/100 (88.0%), with an EOR of 99.2%. The operation resulted in endocrine remission in 80.5% of patients with secreting adenomas.

Conclusion:

In our hands, the chopsticks technique allows to achieve good resection results with an acceptable morbidity. This technique permits a single surgeon to perform effective endoscopic bimanual dissection through a single nostril reducing manipulation of healthy mucosa thereby minimizing nasal morbidity.

82

Multicenter external validation of the Zurich Pituitary Score for predicting surgical outcome of endoscopic pituitary surgery

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*PRESENTER (Dr. Carlo Serra)

Background/Introduction:

In transsphenoidal surgery (TSS) for pituitary adenoma (PA), gross total resection (GTR), extent of resection (EOR), and residual tumor volume (RV) are important parameters relevant to endocrinological and overall outcomes. Recently, the Zurich Pituitary Score (ZPS) has been proposed as a new quantitative pre-operative classification scheme for predicting GTR, EOR, and RV in PA surgery. We evaluate the external validity of the ZPS.

Methods:

In three reference centers for pituitary surgery, the ZPS was applied and correlated to GTR, EOR, and RV. Furthermore, its inter-rater agreement was assessed.

Results:

A total of 485 patients (256 [53%] male; Age: 53.8 +- 15.7) were included. ZPS Grades I, II, III, and IV were observed in 110 (23%), 270 (56%), 64 (13%), and 41 (8%) patients, respectively. GTR was achieved in 358 (74%) cases, with mean EOR of 87.6% +- 20.3% and RV of 1.42 +- 2.80 cm3. With increasing ZPS Grade, strongly significant decreasing trends for GTR (I: 92%, II: 77%, III: 67%, IV: 15%; $p < 0.001$) and EOR (I: 93.8%, II: 89.9%, III: 88.1%, IV: 75.4%; $p < 0.001$) were found. Similarly, RV increased steadily ([cm3] I: 0.16, II: 0.61, III: 2.01, IV: 3.84; $p < 0.001$). Inter-rater agreement was excellent, with intraclass correlation coefficients (ICCs) of 0.837 (95% CI: 0.804 to 0.865) intercarotid distance and 0.964 (95% CI: 0.956 to 0.970) for PA diameter, and Cohen’s Kappa of 0.972 (95% CI: 0.952 to 0.992) for the ZPS Grades.

Conclusion:

Application of the ZPS in three external cohorts was successful. The ZPS generalized well in terms of GTR, EOR, and RV, and demonstrated excellent inter-rater agreement, and can safely and effectively be applied as a quantitative classification of PAs with relevance to surgical outcome.
p

83

Adherence with lipid treatment guidelines in Swiss patients with diabetes mellitus - results from the Swiss Diab Study

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Background/Introduction:
The major cause of death and disability in patients with diabetes mellitus (DM) is atherosclerotic cardiovascular disease (ASCVD). Beside tight glycaemic control it is crucial to aggressively treat other cardiovascular risk factors such as dyslipidaemia to prevent ASCVD. Treatment guidelines specify strict target lipid levels to be achieved in patients with DM. The aim of this study is to evaluate the compliance of patients with DM type 1 and 2 (DM1 and DM2, respectively) with respect to the European, Swiss, American, and English lipid treatment guidelines (ESC/EAS, ALGA, ADA, and NICE, respectively).

Methods:
The Swiss Diabetes Registry (SwissDiab) is a multicenter prospective observational cohort study of patients with diabetes treated at Swiss tertiary centers. Participants attend annual standardized examinations. SwissDiab participants with DM1 and DM2 and a visit between 01.01.2018 and 30.06.2019 were included in the analysis, and compliance to the lipid treatment recommendations as defined by the 2016 ESC/EAS (LDL-target only), 2018 AGLA, 2018 ADA, and 2014 NICE lipid guidelines was assessed. The ACC/AHA ASCVD risk calculator was used to estimate 10-year risk of ASCVD. Baseline characteristics as well as lipid lowering medication were assessed stratified by diabetes type and in secondary analysis also by adherence to the respective guidelines. The prescribed statin dosages were categorized into low, medium and high intensity based on the ADA definition. Data are presented as median (IQR) unless otherwise specified.

Results:
Overall, 364 patients with DM1 and DM2 had data available in the SwissDiab database. Of these, 17 had to be excluded due to missing data. In DM1, 138 patients were included; 35% female, 15% smokers. Median (IQR) age was 47 (34, 59) years, diabetes duration 15.5 (9, 26) years, LDL-cholesterol 2.6 (2.0, 3.1) mmol/l. Lipid lowering medication was prescribed in 30% of the patients: 98% statins (2% low, 57% medium, 41% high intensity), and 13% ezetimibe. In DM2, 209 patients were included; 22% females, 19% smokers. Median age was 65 (57, 72) years, diabetes duration 15.0 (8, 21) years, LDL-cholesterol 2.2 (1.7, 2.7) mmol/l. Lipid lowering medication was prescribed in 80% of the patients: 100% statins (3% low, 46% medium, 51% high intensity), 7% ezetimibe, and 1% PCSK9 inhibitor. The proportion of patients with DM1 that met the ESC/EAS, AGLA, ADA and NICE lipid guidelines was 41%, 36%, 60% and 34%, respectively, and in DM2 32%, 31%, 48% and 72% respectively. Consistent results across all the four guidelines was observed in 38% and 49% of patients with DM1 and DM2, respectively. In the 142 patients with DM2 that did not fulfil the ESC/EAS recommendations, the median 10-year risk of ASCVD was 27% and 73% received statin therapy. Similar results were observed for the other guidelines.

Conclusion:
Based on 3 out of 4 guidelines, more than 50% of participants receive lipid treatment that does not meet recommendations, and in those with DM2 a considerate estimated 10-year risk of ASCVD was observed. Our data strongly support that lipid lowering strategies including high-dose statins and combination lipid-lowering treatment must be reinforced in Swiss patients with diabetes in order to adhere with current recommendations and provide patients with the full benefits of these therapies.

84 S

Machine Learning in Pituitary Surgery: Prediction of Surgical Outcome and Intraoperative Cerebrospinal Fluid Leaks in Transsphenoidal Surgery

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Background/Introduction:

Transsphenoidal surgery has become the standard of care for most pituitary adenomas, and is a relatively safe procedure with a high success rate. Personalized medicine has moved to the forefront of medical research in the past decade, and can potentially impact clinical practice. For example, preoperative identification of patients at high risk for subtotal resectability or intraoperative cerebrospinal fluid (CSF) leaks may allow surgeons to better inform patients on the likelihood of outcomes and complications, and create potential for prevention of complications. Recently, machine learning algorithms have demonstrated superiority to conventional statistical modeling in a range of fields for predictive analytics.

Methods:

From a prospective registry, patients who underwent endoscopic transsphenoidal surgery for pituitary adenoma were identified. Subsequently, the authors developed prediction models for gross total resection (GTR) and intraoperative CSF leaks using both advanced machine learning and conventional logistic regression algorithms.

Results:

154 patients were included. Intraoperative CSF leaks occurred in 29%, whereas GTR was achieved in 68% with a mean extent of resection of 96.8% ± 10.6%. For GTR, the neural network achieved excellent area under the curve (AUC; 0.96), accuracy (91%), sensitivity (94%), and specificity (89%) on the test set. For CSF leaks, the neural network classified 88% of patients in the test set correctly, with an AUC of 0.84. Sensitivity (83%) and specificity (89%) were high. No risk factors for CSF leaks were identified using conventional statistical methods. Both machine learning models demonstrated improved performance compared to logistic regression.

Conclusion:

Machine learning algorithms can help identify subsets of patients who are susceptible to certain adverse outcomes and events, and may enable a more personalized and targeted treatment plan. Outcomes that were previously near unpredictable, such as intraoperative CSF leaks, can be robustly predicted using machine learning techniques.

85

Sialic acid supplementation in *NANS* deficiency: An open-label, proof of concept study

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Background:
NANS deficiency presents clinically with developmental delay, intellectual disability, short stature and skeletal dysplasia. Biallelic mutations in the N-acetylneuraminic acid synthase gene cause a block in the endogenous synthesis of sialic acid and accumulation of the precursor, N-acetyl mannosamine (ManNAc). We aimed at assessing the short term metabolic fate of orally administered free sialic acid in patients with NANS deficiency and in control subjects.

Methods:
Four adult patients with molecularly confirmed NANS deficiency and four control subjects received free sialic acid supplementation (150 mg/kg/d in three doses) for 3 days. Plasma and urinary total N-acetylneuraminic acid (NeuNAc; sialic acid), free NeuNAc and ManNAc were analyzed at baseline, T+2h, T+4h and T+6h on day 1, at T2 on days 2 and 3 and at T0 on day 4. Urinary metabolites were also measured at T0, T+2h, T+4h and T+6h on days 2 and 3 using the quantitative stable-isotope dilution assisted liquid chromatography tandem mass spectrometry assay. Data were analyzed using Time x Condition mixed models.

Results:
At baseline, patients had higher ManNAc concentrations in plasma and in urine than control subjects (P<0.001). On day 1, free NeuNAc in plasma increased over time (p<0.001) in both groups, but did not affect plasma total NeuNAc and ManNAc. Urinary free and total Neu5Ac/creat. ratios increased similarly in the first 6h (P<0.01). In contrast, urinary ManNAc/creat. ratio did not change over time and remained higher in patients than controls (P<0.01). Liver enzymes, blood count, glucose and creatinine levels remained stable in both groups. No clinical adverse event was reported.

Conclusion:
Ingestion of 150 mg/kg/d free NeuNAc appeared to be safe and well tolerated in the short term. Higher plasma and urinary ManNAc concentrations in patients before and after supplementation were compatible with NANS deficiency. NeuNAc administration increased free NeuNAc levels within 6h in plasma and urine, suggesting that oral NeuNAc is rapidly absorbed and excreted. Oral NeuNAc did not affect total NeuNAc or ManNAc/creatinine concentrations. In a next step it needs to be proven that orally taken NeuNAc can be successfully delivered to the brain where it might have a potential impact on intellectual development. To proceed on a path to oral therapy with NeuNAc in NANS deficiency, pharmacokinetics of various forms of NeuNAc should to be evaluated.

86 S

Incretin response in gastric bypass surgery patients with or without extended distal pancreatectomy

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Background/Introduction:
Postprandial hyperinsulinemic hypoglycemia (pHH) is an increasingly recognized late complication of gastric bypass surgery. Relative meal-induced hyperinsulinaemia triggers hypoglycaemic events 1-3 hours postprandially, but the exact pathophysiology remains incompletely understood. Extended distal pancreatectomy (dP) has been utilized as a salvage therapy in refractory severe hypoglycaemia. The aim of this study was to contrast the glucose and gut/pancreas peptide response to an oral glucose load in pHH patients with or without extended dP.

Methods:
Three dP-pHH patients (pancreatectomy was held 6 -11 years ago) and three pHH patients, matched for sex, age and BMI were investigated. Patients underwent Roux-en Y gastric bypass surgery 3 - 16 years ago. An oral glucose tolerance test (75g g, OGTT) was performed (total duration 210 minutes) and glucose, insulin, C-peptide, glucagon, active glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) levels were measured every 30 minutes. Hormones were determined using conventional immunoassays. Comparisons were performed using incremental areas under the curve (iAUC) and peak hormone values. Results are presented as mean±standard deviation.

Results:
Postprandial glycaemia was higher in dP-PHH compared to PHH (iAUC = 1133 ± 416 mmol*min/l vs 178 ± 52 mmol*min/l). Postprandial insulin and C-peptide levels were lower in dP-pHH compared to pHH patients (mean iAUC for insulin and C-peptide: 3479 ± 2471 vs 11592 ± 6940 mU*min/l; 172697 ± 98894 vs. 335230 ± 103672 pmol*min/l). GLP-1 and GIP peaked at 30min after the oral glucose load in both groups. dP-PHH showed more than two-fold higher peak GLP-1 concentrations compared to PHH (114 ± 2 vs 50 ± 16 pmol/l). Similarly, higher peak GIP levels were observed in dp-PHH compared to PHH, but the difference was less pronounced (77 ± 51 vs 53 ± 17 pmol/l). The glucagon response in dP-pHH compared to PHH was lower (mean iAUC= 1240 ± 1087 pg*min/ml vs 6210 ± 3643 pg*min/ml).

Conclusion:
We observed elevated incretin levels (mainly GLP-1) after an oral glucose challenge in dP-PHH compared to PHH with intact pancreas. These preliminary results suggest a compensatory increase in incretin levels after reduction of pancreatic β-cell mass and support the critical role of GLP-1 in the maintenance of residual β-cell function.

87

Porphyria cutanea tarda : a novel monoallelic intronic splice variant in UROD

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Background/Introduction:

Porphyria cutanea tarda is a disorder of heme biosynthesis which manifests with blistering lesions on sun-exposed areas due to the accumulation of photosensitizing porphyrins. It occurs in sporadic and familial forms, which are clinically indistinguishable and have so far been differentiated by extra-hepatic uroporphyrinogen decarboxylase (UROD) activity. Familial PCT (fPCT) is an autosomal dominant disorder with low penetrance associated with monoallelic variant in the UROD gene. It is currently estimated to constitute about 20% of PCT cases, but since it is likely that many cases of fPCT remain genetically undiagnosed, this estimation is probably too low.

Methods:

Results:

We suspected porphyria cutanea tarda (PCT) in a 23 years old woman with skin blisters, skin fragility and hypertrichosis related to exposure to several triggering factors including iron overload. Peak fluorescence scan of porphyrins and porphyrins profile in urine and stool confirmed the diagnosis. Phlebotomies led to a striking clinical and biochemical improvement with resolution of bullous lesions and almost normalized hair growth. We identified a novel heterozygous intronic variant in UROD gene, c.21-12C>G, and shown to cause aberrant splicing in fibroblasts and thus cause truncation of the UROD protein.

Conclusion:

This case illustrates that genetic analyses have a central role in the diagnosis of PCT. Firstly, in front of a highly suggestive clinical and biochemical presentation of PCT, molecular investigations should be performed. If needed, this should include intronic sequences. Secondly, the confirmation of a variant of UROD allows genetic counselling for parents and possibly the identification of carriers of the variant who can benefit from prevention. With increasing availability of gene sequencing

88 S

Inhibition of IL-1beta improves glycaemia in a mouse model for gestational diabetes

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Background/Introduction:

Gestational diabetes mellitus (GDM) is one of the most commonpregnancy accompanying diseases, however the underlying mechanism remains unclear.

Methods:

We established a mouse model for GDM on the basis of two major risk factors, obesity and aging, and investigated the role of inflammation.

Results:

We observed increased uterus and placenta expression of IL-1β along with elevated circulating IL-1β concentrations in animals with GDM compared to normoglycemic pregnant mice. Treatment with an anti-IL-1β antibody improved glucosetolerance of GDM mouse without apparent deleterious effects for the fetus. Finally, IL-1β antagonism reduced conversion of 11-deoxycorticosterone to corticosterone, possibly explaining the metabolic improvement.

Conclusion:

We conclude that IL-1β is a causal driver of impaired glucose tolerance inGDM, possibly due to its effects on steroid synthesis.

89 S

The dual role of Interleukin-1β in non-glucose-dependent cephalic phase insulin release in health and obesity

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Background/Introduction:

The non-glucose dependent spike in insulin levels immediately following the beginning of a meal is called the cephalic or pre-absorptive phase of insulin secretion. Even though this early insulin response is of marked consequence for overall postprandial insulin release, its basic mechanisms remain largely unexplored.

Methods:

We evaluated glucose metabolism and insulin secretion of wild type as well as IL-1β whole body KO with cephalic phase experiments. Mice were either fed a standardised chow or lard-based high-fat-diet. Briefly, for cephalic phase experiments, mice were fasted overnight for 12h and either kept fasted or given access to a single food pellet. Immediately following first contact with the food pellet, blood was taken for insulin or IL-1β measurements and in some cases the mice were sacrificed for organ-excision and further processing. IL-1β mRNA expression of FACS sorted immune-cell populations was assessed ex vivo by RT-qPCR. Insulin and IL-1β protein was measured in samples using a electrochemiluminescence based assay (mesoscale).

Results:

Here, we show that both genetic and pharmacologic blockade of interleukin-1β (IL-1β) leads to a pronounced reduction in cephalic phase insulin secretion (-0.65 [95%CI= -1.137 to -0.172]). Assessing mice fed a high-fat diet, we found that the cephalic phase insulin response was abolished in obesity. In contrast, high-fat diet-fed mice pre-treated with a specific anti-IL-1β antibody once a week developed no such impairment.

Conclusion:

Here, we identify a beneficial physiologic role for IL-1β during cephalic phase insulin secretion. We therefore conclude, that dysregulation of physiologic IL-1β signalling, specifically during cephalic phase and in obesity, may contribute to the overall pathology of metabolic disease. Thus, we identify cephalic phase inflammatory signalling as a novel and potentially modifiable target in the regulation of glucose metabolism.

For your notes

For your notes