01 S

Neural correlates of working memory in early-treated adult patients with Phenylketonuria

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Background/Introduction:

Phenylketonuria (PKU) is an inborn error of metabolism affecting the conversion of Phenylalanine (Phe) to Tyrosine (Tyr). Prior research suggests functional brain alterations also in early-treated patients with PKU. We aimed to investigate the fronto-parietal working memory network in early-treated adults with PKU.

Methods:

This cross-sectional study included 20 early-treated adults with PKU and 40 age, gender, and education comparable healthy controls. All participants completed a working memory task during functional magnetic resonance imaging (fMRI) to assess the fronto-parietal working memory network. Fasting blood samples were collected to obtain concurrent Phe concentrations in patients.

Results:

Mean Phe concentration was 702 µmol/l ± 203.27. Patients with PKU displayed significantly lower task accuracy ($F(1,56) = 7.541$, $p = .008$) but comparable reaction times ($F(1,56) = 0.127$, $p = .723$) in the fMRI task compared to the control group. Region-of-Interest analyses revealed that during the fMRI task, patients with PKU displayed significantly reduced activation in the left ($F(1,57) = 5.685$, $p = .020$) and right middle frontal gyrus ($F(1,57) = 6.070$, $p = .017$) and right superior frontal gyrus ($F(1,57) = 6.990$, $p = .011$).

Conclusion:

Our results demonstrate alterations in performance and neural activation, particularly in frontal regions of the working memory network in early-treated adult patients with PKU. These findings align with previous studies indicating that patients with PKU display changes in functional parameters of the brain despite early-initiated treatment.

02

The global threat of non-communicable diseases Cost and drivers for diabetes type 2 in Germany

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Background:

Since the last decade the disease pattern has significantly changed around the world. Non-communicable diseases, most commonly diabetes mellitus, have become the main threat to global health. The incidence of diabetes mellitus type 2 (DM2) is rising steadily, accounting for about two-thirds of deaths in Germany. Based on a prevalence of 9 million diabetic patients per year, DM2 constitutes a considerable medical and economic burden in Germany. However, the healthcare spending and its cost drivers are not yet sufficiently known.

Aims of the study:

The primary objective of this study was to describe healthcare resource use and cost development of DM2 treatment in Germany, focusing on most significant cost drivers and cost-saving opportunities. The secondary objective was the analysis of the impact of technical progress on diabetes care.

Methods:

A systematic literature search was conducted in PubMed and Embase. Additionally, publications of the national health authorities (Robert Koch Institute RKI), Federal Joint Committee (Gemeinsamer Bundesausschuss G-BA) and the German Diabetes Society (Deutsche Diabetes Gesellschaft DDG) were included. Following the PRISMA guidance, the review identified the study design, epidemiological approach, analytical perspective, and data collection approach in each of the included studies.

Results:

There are no reliable, calculated cost data for Germany, only estimated calculations. The few cost-of-illness studies are strongly influenced by the perspective chosen or different data sources. Direct costs are estimated at 7.4 billion €, representing 2.2% of the national healthcare balance sheet. The most used method is the incremental or excess cost approach (1.8-fold higher costs compared to individuals without type 2 diabetes). In addition to the increase in direct costs of illness, there is also an increase in indirect costs (loss of economic productivity) due to increased inability to work, disability pension claims, mortality and disability. Intangible costs - such as psychological well-being - are not considered in the existing cost-of-illness studies.
Confirmed risk factors include tobacco use, physicial inactivity and obesity. People with low social and income status have a significantly increased risk of developing DM2. The preventive measures taken so far have not yet paid off.
Confirmed risk factors and major cost drivers are demographic change with overaging, exponentially increasing obesity, political decisions on the state health insurance coverage (Leistungskatalog), increased patients´ use of medical services and costs due to available treatment options of diabetic complications (increase in average treatment costs from 4.500 € in 2013 to 4.949 € in 2015). Increasing prevalence, especially in childhood, is a major cost driver on its own (70% estimated diabetes-related cost share in 2050). The potential financial savings from medical-technological progress are eroded by increasing age and use of medical services.

Conclusion:

DM2, based on the results of this study, constitutes a considerable medical and economic burden in Germany and has serious impact on the government health expenditure. Analysis of the real and total cost of diabetes are urgently needed. To successfully combat diabetes and reduce health care expenditures, preventive efforts must be intensified. Political decisions such as the introduction of a sugar tax or an increase in tobacco tax are necessary to reverse the trend of development.

03

Exploring hyperandrogenism in PCOS by multi-omics approaches

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Background/Introduction:

Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder of women affecting about 8-10%. It is characterized by signs and symptoms of androgen excess and ovarian dysfunction. Androgen excess is seen in most PCOS women, but its pathomechanism is unclear. Studies on steroid hormone levels and corresponding enzyme activities in serum and tissue samples show that they differ significantly between PCOS and control groups, but the underlying dysregulation is unknown. Small RNAs are a class of non-coding (nc) RNAs which have been recognized as potential regulators of biological processes and thus bear the potential as biomarkers of disease pathologies. This study aimed at investigating the steroid and RNA profiles of hyperandrogenic PCOS women compared to healthy controls by multi-omics approaches in order to find specific disease characteristics as diagnostic and therapeutic targets.

Methods:

Eightyfour PCOS women and healthy controls were recruited for this study. Clinical data and biomaterials were collected. PCOS diagnosis was made by AE-PCOS 2006 criteria requiring hyperandorgenism and ovarian dysfunction for the diagnosis. Comprehensive steroid analysis of the serum samples was performed by an in-house LC-MSMS method. Only estradiol was measured by an immunoassay. Steroid enzyme activities were calculated by product/substrate ratios. For RNA seqencing, isolation of small RNAs from serum was performed with spin-column purification, and small RNA sequencing was then performed with the Illumina miSeq system.

Results:

PCOS patients (n=42) were 16 to 33 years old; healthy controls (n=42) were normal cycling and 18 to 38 years old. Steroid profiling revealed significantly higher serum androgen levels in PCOS patients as expected, while progesterone and estradiol levels were lower with PCOS. Furthermore, PCOS women had higher levels of steroid metabolites belonging to the androgen backdoor pathway and the 11-oxysteroid pathway as compared to metabolites comprised in the classic steroid pathways. Calculations of steroid enzyme activities indicated increased CYP17A1 and SRD5A1 activities for PCOS and decreased activities for HSD3B and aromatase (CYP19A1) compared to controls. Small RNA profiling of serum samples revealed that 7 miRNAs, 14 lncRNAs, 1 piRNA and 1 snoRNA were differentially expressed in the PCOS patient group.

Conclusion:

Hyperandrogenic PCOS women present with characteristic changes in the steroid metabolome, the underlying defect seems to lie outside steroid biosynthesis in a supra-regulatory system. This would maybe explain other metabolic and reproductive features of PCOS. We found differentially expressed circulating RNAs and suggest that they can give us a hint to molecular mechanisms of PCOS. By testing the specific ncRNAs on steroid hormone biosynthesis, we aim at finding novel disease markers and targets

04 S

Subclinical thyroid dysfunction and incidence of diabetes: an individual participant data analysis of prospective cohort studies

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Background/Introduction:

Thyroid dysfunction and diabetes mellitus are two of the most common endocrine diseases and they often coexist. Studies have shown that subclinical thyroid dysfunction (SCTD) is associated with adverse events, including an increased risk of cardiovascular disease (CVD) events and CVD mortality. Only a few prospective studies have assessed whether persons with subclinical thyroid dysfunction are more likely to develop diabetes and results are conflicting. We therefore aim to conduct a systematic review of the literature and an individual participant data meta-analysis (IPD) of multiple prospective cohorts to investigate the association between SCTD and incidence of type diabetes.

Methods:

We performed a systematic review of the literature from Medline, Embase, and the Cochrane Library from inception to 15th of March 2021. We included prospective cohorts with data on thyroid status at baseline and diabetes status during follow-up. We also identified additional unpublished data by contacting the Thyroid Studies Collaboration, a consortium of cohort studies that investigate the association between subclinical thyroid dysfunction and clinical outcomes. The primary outcome is incidence of diabetes at last available follow-up. Diabetes will be defined according to the American Diabetic Association criteria as either: (i) fasting blood glucose ≥ 7 mmol/l, (ii) 2-hour glucose ≥ 11.1 mmol/L after an OGTT, (iii) HbA1c (glycated hemoglobin) ≥ 6.5%, or use of blood glucose lowering medication. A two-stage IPD analysis will be conducted to compare participants with subclinical hypothyroidism or hyperthyroidism versus euthyroidism at baseline and the risk of developing diabetes at follow-up. The Newcastle-Ottawa Scale will be used to assess the quality of observational studies.

Results:

Of the 1438 studies we identified through the literature search, five studies met our inclusion criteria, of which three have accepted to be included in the current IPD analysis. We further identified 14 cohorts from the Thyroid Studies Collaboration with data on thyroid function and diabetes (we have received data from 11 cohorts and are currently waiting for data from 3 cohorts). The sample size for this IPD is expected to be around 15,000.

Conclusions:

Finding an association between SCTD and incident diabetes can have clinical significance as it can help guide physicians to screen patients with SCTD for diabetes and can lead to an earlier diagnosis of diabetes. Both SCTD and diabetes are prevalent in the general population and results from this study may pave the way for future studies which can have an important public health impact

05

Changes in complications of thyroid surgery: A retrospective analysis of medical records at the Gemeindespital Riehen 1930-1939 vs. 1970-1979.

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Background/Introduction:

At the beginning of the 20th century, iodine deficiency was prevalent and goiter was a frequent indication for thyroid surgery. The "Gemeindespital Riehen" was an established center for thyroid surgery in the 20th century. The complete standardized medical records of about 14'000 thyroidectomies performed in this institution from 1929-1979 were retrieved. The goal of this preliminary study was to analyze how the complication rate of thyroid surgery has changed over time, bearing in mind the changing incidence of goiter after the introduction of iodine supplementation in the third decade of last century in the wider population and the development of the surgical technique.

Methods:

Retrospective analysis of medical records of all patients, thyroidectomized in the two decades 1930-1939 and 1970-1979 was performed. Parameters analyzed were demographics of patients, number of thyroidectomies, thyroid weight, surgical technique, aggravating surgical conditions, surgical complications. The data was collected per year and then the mean of the respective decade was calculated.

Results:

A total of 3280 thyroidectomies were analyzed (1930-1939 n=1826, 1970-1979 n=1454). In both decades, the female to male ratio of thyroidectomized patients was not significantly different (f:m 5.9:1 vs. 4.9:1 P=0.1487). Goiter weight of resected thyroid glands decreased significantly in the second decade (1930-1939 141±99 g, 1970-1979 107±89g; P<0.0001). The dominant technique for thyroid surgery was bi-lobular subtotal thyroidectomy in 1930-1939 in 81% vs 1970-1979 in 65% of patients, P<0.0001. This technique was gradually replaced by hemi-thyroidectomy and total thyroidectomy.
Aggravating surgical conditions like intrathoracic position, intraoperative adhesions and hemorrhage decreased significantly (1930-1939 59%, 1970-1979 27%, P<0.0001). The complications rate of postoperative recurrent laryngeal nerve palsy (1930-1939 29%, 1970-1979 6%, P<0.0001) and postoperative tetanies (1930-1939 6%, 1970-1979 1%, P = 0.0001) declined significantly.

Conclusion:

This preliminary analysis of this unique historical surgical data set of an established thyroid surgical center in Switzerland document for the first time the effect of iodine supplementation on the weight of thyroid glands in association with the surgical outcome in two decades of the last century. Whether only the iodine supplementation or rather also the improved skills of the endocrine surgeons with time explain these findings, remains an open question.

06

Effectiveness of a real-life group program (DIAfit) to promote physical activity in patients with type 2 diabetes: a pragmatic cluster randomized clinical trial.

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On behalf of all the DIAfit collaborators that helped in the different centers

Background/Introduction:

Type 2 diabetes mellitus (T2DM) is a major public health issue. Physical activity is crucial to effective management of T2DM. Yet, it is unclear which structured physical activity intervention strategy for the management of T2DM is feasible and pragmatic to translate into real-life clinical settings. The aim of this study was to evaluate the effectiveness of a real-life clinical group physical activity program (DIAfit) on improving physical fitness, body composition, and cardiometabolic health in an unselected population with type 2 diabetes mellitus (T2DM). An additional aim was to compare the effects of two variants with different structured exercise frequencies on the same outcomes.

Methods:

The DIAfit program was a pragmatic cluster randomized controlled and single-blinded trial. It was conducted in all 11 clinical centres (clusters) in the French speaking part of Switzerland. A total of 185 patients with T2DM were recruited and randomized by centre to a standard program (3 sessions/week during 12 weeks) vs an alternative program (one session/week during four weeks and then two sessions/week during 16 weeks). Centers offered both programs in a random order and both programs included a total of 36 supervised sessions of combined aerobic and resistance training. The primary outcome included the change in aerobic fitness (expressed in watts). The secondary outcomes included changes in body composition, BMI, HbA1c, lower limb muscle strength, walking speed, balance, flexibility, blood pressure, and lipid profile (total, high- and low-density cholesterol, and triglycerides).

Results:

All 185 patients were included (87 in standard group and 97 in progressive group). Mean age was 59.7 ±10.2 years with a disease duration of 8.9 (7.9) years, 52% were men. There was an 11% increase in aerobic fitness after the program (12.5 Watts; 95% CI 6.76 to 18.25; $p<0.001$). Significant improvements in most physical fitness, body composition, and cardiometabolic parameters were observed at the end of the DIAfit program (improvements between 2-29%) except for lean body mass, triglycerides and cholesterol. No differences were observed between both programs, except for a larger weight reduction of -0.97kg (95% CI -0.04 to -1.91; $p=0.04$) in the standard program.

Conclusion:

Both frequency variants of the nation-wide structured DIAfit group program had beneficial effects on physical fitness, HbA1c, body composition, and blood pressure in T2DM patients and differences between programs were negligible.

07

Excessive food intake increases cortisol levels independent of body weight

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Background/Introduction:

Obesity is one of the most serious health problems of the 21st century. Chronic dysregulation of glucocorticoids causes obesity and potentially contributes to the current obesity pandemic. In lean subjects, glucocorticoids increase with food intake. The role of this food-induced cortisol peak is unknown, and whether it also occurs in obese subjects is not well described. Here, we investigate whether the cortisol response to food intake differs between lean and obese subjects.

Methods:

In an open-label study, 36 male subjects (18 lean, 18 obese) received a high-caloric breakfast (2100 kcal). Total cortisol was measured before food intake and until 180 minutes thereafter.

Results:

Total cortisol levels increased in response to food intake in lean subjects (body mass index 22.3 ±1.3 kg/m^2, age 24 ±5.3 years) from 340 ± 107 nmol/l to 475 ±124 nmol/l, and in obese subjects (BMI 35.6 ±4.70kg/m^2, age 28.4 ± 5.8 years) from 349 ±170 nmol/l to 420 ±125 nmol/l. There was no difference in cortisol increase between both groups (area under the curve lean: 60273 ±17969, obese: 55071 ±16216, p=0.4).

Conclusion:

Cortisol levels increased with excessive food intake in lean and obese subjects. To further understand the physiological role of glucocorticoids is crucial, as repetitive secretion of glucocorticoids with excessive food intake could potentially become harmful over time

08

Glucagon-stimulated copeptin measurements: a novel approach for the differential diagnosis of polyuria-polydipsia syndrome

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BACKGROUND The differential diagnosis between central diabetes insipidus and primary polydipsia ischallenging. To date the most reliable approach is copeptin measurement after hypertonic saline infusion. However, this test includes a rapid increase in plasma sodium levels often causing discomfort and demands permanent supervision. Recent research has shown that arginine infusion – known to stimulate growth hormone – is a potent stimulator of the neurohypophysis and provides a new diagnostic tool. Similar to arginine, glucagon is also known to stimulate growth hormone release.

METHODS
In this double-blind, randomized, placebo-controlled, cross-over trial we enrolled 22 (52%) healthy participants, 10 (24%) patients with central diabetes insipidus and 10 (24%) patients with primary polydipsia at the University Hospital Basel. Each participant underwent the glucagon-test i.e., subcutaneous injection of 1mg glucagon, and placebo-test i.e., subcutaneous injection of 1ml 0.9% sodium chloride on two separate days. Plasma copeptin levels were measured at baseline and 30, 60, 90, 120, 150, 180 minutes after injection. Adverse effects were monitored using a visual analogue scale (VAS) ranging from 0 i.e., no, to 10 i.e., maximum discomfort. The primary objective was to determine whether glucagon stimulates copeptin and to see whether the copeptin response differentiates between central diabetes insipidus and primary polydipsia.

RESULTS
A total of 42 participants underwent both tests. Median (IQR) age of all participants was 27 years (23; 32), 59% were female. In healthy participants, glucagon injection stimulated copeptin release with a median (IQR) increase of 7.56pmol/l (2.38; 28.03) [p-value < 0.001]. Under placebo, no notable increase in copeptin was observed, the median increase was 0.10pmol/l (-0.70;0.68). In patients with central diabetes insipidus, glucagon injection showed no notable increase after glucagon injection, with a median increase of 0.55pmol/l (0.21; 1.65), whereas there was a clear stimulation in patients with primary polydipsia with a median (IQR) increase of of 15.70pmol/l (5.99; 24.39) [p-value < 0.001]. The test was safe and well tolerated with a median (IQR) test burden according to VAS of 1.5 (1; 4) in healthy participants, 3 (1.5; 4.5) in central diabetes insipidus, and 3 (2; 4.5) in primary polydipsia. The copeptin cutoff level of more than 4.6pmol/l had a 100% sensitivity (95%CI 100-100) and 90% specificity (95%CI 70-100) to discriminate between primary polydipsia and central diabetes insipidus, with a receiveroperating characteristic area under the curve for this discrimination of 0.99 (95%CI 0.96-1.00).

CONCLUSION
In conclusion, our data provide evidence for a strong effect of glucagon on copeptin. The direct measurement of glucagon-stimulated plasma copeptin has the potential for a safe, novel, and precise test in the differential diagnosis of polyuria-polydipsia syndrome.

09

Association of CT-based sarcopenia diagnostics and clinical outcome in patients with risk of malnutrition – a secondary analysis of the EFFORT trial

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Background/Introduction:

The therapeutic and prognostic implications of CT-based diagnosis of sarcopenia remains understudied. We investigated the association of CT-based diagnosis of sarcopenia with clinical outcomes and treatment response to nutritional support in patients included in the randomized EFFORT trial.

Methods:

This is a secondary analysis of the randomized controlled, multicentre EFFORT trial, which compared the effects of individualized nutritional support with usual hospital food in medical inpatients at nutritional risk. Sarcopenia was defined according to the cut-off values proposed by Martin (3rd lumbar vertebra mean SMI of 43.0 cm2/m2 for males with BMI <25kg/m2 and 53.0 cm2/m2 for males with BMI >25kg/m2 and 41cm2/m2 for females). Primary endpoint was adverse clinical outcome within 30 days of hospital admission. We calculated multivariable regression analyses, adjusted for gender to study associations of CT findings and outcomes and used interaction terms to investigate possible effect modification regarding the nutritional support intervention.

Results:

In the 573 included patients 392 (68.4%) met the definition of sarcopenia. Compared to patients with no CT-based sarcopenia, patients with sarcopenia had an increased risk for adverse clinical outcome (adjusted OR 1.59 (95% CI 1.05-2.39), p=0.026) and increased rehospitalization rates (adjusted OR 1.86 (95% CI 1.01-3.47), p=0.048). Non-sarcopenic patients showed a significant reduction in 30-day mortality (adjusted OR 0.25 (95% CI 0.08-0.84), p=0.025) due to nutritional support, whereas sarcopenic patients did not (adjusted OR 0.95 (95% CI 0.50-1.79), p=0.87).

Conclusion:

In this cohort of malnourished medical patients, sarcopenia was an independent risk factor for adverse clinical events and risk for rehospitalization within 30 days. However, sarcopenic patients did not benefit from nutritional support as did patients without sarcopenia in terms of a mortality reduction. Further research is needed to better understand the pathophysiological context of this finding and to improve our current therapeutic approach.

10

Canagliflozin and Non-Alcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus (CaNAFLD) – A Secondary Analysis of Two Randomized Controlled Trials

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Background/Introduction:

Non-alcoholic fatty liver disease (NAFLD) is highly prevalent among patients with type 2 diabetes (T2DM), however no approved pharmacological treatment exists. While sodium glucose cotransporter 2 inhibitors (SGLT2i) have shown to decrease glycemia, blood pressure, body weight, and albuminuria in patients with T2DM, data from large randomized clinical trials on liver-related outcomes are lacking.

Methods:

This is a secondary analysis of two randomized controlled cardiovascular and renal outcome trials: CANVAS (NCT01032629) and CANVAS-R (NCT01989754). Patients with T2DM and high cardiovascular risk were randomly assigned to receive canagliflozin or placebo and were followed for a duration of up to 6 years. The primary endpoint of this study was a composite of a reduction of alanine aminotransferase (ALT) levels more than 30% or ALT normalization (decrease <30IU/L). Secondary outcomes included achievement of weight reduction of 5% or 10%, and improvement of non-invasive fibrosis scores (NAFLD fibrosis score; FIB-4 score). Data were provided by Yale Open Data Access (Project ID 2020 4409).

Results:

We included 10’135 patients with T2DM . The majority of patients was male (64.2%) with a mean age of 61.8 years and a 13.5 years mean duration of diabetes. Of those, 2781 patients (27.4%) had elevated ALT levels (>30 IU/L) at baseline. These patients had a higher body weight (94.9kg vs. 88.4kg), elevated diastolic blood pressure (79.1mmHg vs. 77.2mmHg), higher glycemic indices and lipid parameters when compared to patients with normal ALT levels. The rate of the primary outcome was achieved in 35.6% of patients receiving canagliflozin compared to 26.2% with placebo, yielding an odds ratio (OR) of 1.55 (95%CI, 1.42−1.65; p<0.001). Treatment with canagliflozin was associated with lower NAFLD fibrosis and FIB-4 scores (p<0.001). Weight reduction of more than 10% was achieved in 38.5% of patients with canagliflozin compared to 16.1% with placebo (OR 3.49; 95%CI, 2.94−4.15; p<0.001).

Conclusion:

In two large randomized controlled trials involving patients with T2DM and risk of metabolic liver disease, treatment with canagliflozin resulted in a significant improvement of liver-related outcomes when compared to placebo.

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Association of admission albumin levels with effectiveness of nutritional support in hospitalised patients at risk for malnutrition: Secondary analysis of a randomised clinical trial

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Background/Introduction:

Today, no specific blood biomarker is recommended for malnutrition screening in routine clinical care. The role of albumin, historically used as surrogate for nutritional status, is controversial because it is now known to be strongly influenced by other disease-related factors such as inflammation. We investigated the prognostic implications of admission albumin levels with regard to clinical short- and long-outcomes and response to nutritional support, taking into account the level of inflammation.

Methods:

Pre-planned, secondary analysis of the randomised controlled EFFORT trial, which included medical inpatients at nutritional risk (NRS score of ≥3 points) and randomised them to receive individualised nutritional support or standard hospital food. Based on admission albumin level, we stratified patients into „low albumin“ (<30g/L) and „high albumin“ (>30g/L) groups. Primary endpoint was all-cause 30-day mortality. We used multivariable regression analyses to investigate association between admission albumin level and clinical outcomes. Interaction terms were used to assess possible effect modification of albumin regarding the effect of nutritional intervention on mortality. We performed subgroup analyses according to inflammation status by means of CRP levels at admission (>100mg/L vs <100mg/L).

Results:

Of the 1389 patients with available albumin levels (68.5% of the initial cohort), 676 (48.7%) had „low albumin“ and 713 (51.3%) „high albumin“ levels. Overall, “low albumin” was associated with a significantly increased 30-day mortality (HR 1.62 95%CI 1.16-2.27; P 0.005) with pronounced results for patients with high inflammation (HR 2.4 95%CI 1.11-5.42; P 0.027). The effect of nutritional support on 30-day mortality was similar in patients with „low albumin“ (HR 0.68; 95%CI 0.55-1.05; P 0.084) and „high albumin“ (HR 0.70; 95%CI 0.41-1.2; P 0.196), p for interaction = 0.969. There was no significant effect modification of albumin in the subgroup analysis stratified by inflammation status.

Conclusion:

Hypoalbuminemia was linked to higher risk of death in 30 days. Individualised nutritional support did reduce the risk for short-term mortality independent of albumin serum levels as compared to standard hospital food. Hence, Albumin admission levels may be used as parameter for severity of disease, but not for the identification of patients who benefit most from nutritional support.

12

Aldosterone and pro-atrial natriuretic peptide kinetics in response to rehydration in children with diabetic ketoacidosis

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Background/Introduction:

Diabetic ketoacidosis (DKA), a frequent complication of type 1 diabetes (T1D), is characterized by hyperosmolar hypovolemia. The response of water-regulating hormones to DKA treatment in children not well known. While arginine vasopressin (AVP) is thought to respond to changes in osmolality, aldosterone and atrial natriuretic peptide (ANP) are expected to respond to volume changes (dehydration and overhydration, respectively). The objective of this analysis was to describe the change of aldosterone and pro-ANP during rehydration therapy in children with DKA.

Methods:

An observational multi-centre study was conducted in 2015-2019, including paediatric T1D patients treated for DKA according to ISPAD guidelines. Aldosterone and pro-ANP concentrations were measured at 0-4-8-12-24-72h after start of hydration therapy. Data were log-transformed to calculate the mean (95%CI) and coefficient of variation [CV] for each time point. Expected dehydration and correction was calculated based on protocol fluid infusion rates, weight and DKA severity [mild (pH<7.3): 5%, moderate (pH 7.1-7.2): 6%, severe (pH<7.1): 8.5%]. A semi-mechanistic modelling approach was further applied to describe aldosterone kinetics as a function of a volume-dependent secretion rate (non-linear mixed effects regression).

Results:

95 pro-ANP and 92 aldosterone samples were obtained from 20 (male: 14) children (median age: 12 [IQR: 9.8-14]) with mild (n=1), moderate (n=9) or severe (n=10) DKA. Pro-ANP levels were normal and did not change significantly during the study. Mean aldosterone concentration at start of rehydration was increased (4672 pmol/L, 95%CI: 2561-8524, CV: 106%), remained elevated up to 8h (5135 pmol/L, 95%CI: 3595-7335, CV: 94%) and reached 748 pmol/L (95%CI: 514-1088, CV: 67%) at 72h. Mean time to correction of dehydration was calculated to 14.1h (mild), 16.5h (moderate) and 22.7h (severe DKA). Under the assumption of fast aldosterone degradation (expected turnover half-life <1h), semi-mechanistic modelling showed a delayed aldosterone response to rehydration (turn-over half-life in the order of 10-20h).

Conclusion:

Stable pro-ANP levels suggest adequate fluid replacement. In contrast to the immediate copeptin decline after start of treatment, the decrease in aldosterone levels was delayed and levels were still elevated at 72h, despite restored fluid balance. One possible explanation for this could be chronic upregulation of aldosterone synthase (CYP11B2) expression caused by prolonged exposure to angiotensin II and potassium in response to longstanding polyuria during DKA development.

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Experience with the use of recombinant parathyroid hormone (Natpar®) in two patients with a severe form of idiopathic hypoparathyroidism

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Background/Introduction:
Hypocalcemia due to hypoparathyroidism can be adequately treated with standard therapies consisting of calcium supplementation and calcitriol in most cases. Rarely this therapy is insufficient or proves difficult and results in relevant hypo- or hypercalcemias. On the long term an inadequately adjusted hypoparathyroidism can lead to secondary damages with calcium deposits in individual. Nephrocalcinosis and intracerebral calcifications (M. Fahr) are considered the most important ones. New therapeutic approaches include the use of recombinant parathyroid hormone (Natpar®), which has so far been approved in the USA and the EU. With Natpar®, significant reductions in calcium supplementation, calcitriol doses and calciuria can be achieved. Risk reductions regarding secondary complications are postulated. However, hard endpoint data regarding mortality or morbidity are missing so far.

Methods:
Case report

Results:
We present two cases of idiopathic hyoparathyroidism with difficult control under a conventional therapy and secondary complications (nephrocalcinosis and basal ganglia calcification). Under Natpar®, stable electrolyte values and a significant reduction in calciuria could be achieved for the first time.

Conclusion:
The use of recombinant parathyroid hormone (Natpar®) can be considered in individual cases of a "difficult-to-adjust hypoparathyroidism". However, negotiations with the health insurance companies regarding the assumption of costs, the purchase of the preparation and the change in therapy are complex.

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Interferon alpha-induced thyroid dysfunction – a case report.

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Background:

Interferons (IFN) are used in the treatment of malignant, non-malignant and chronic inflammatory diseases. Physiologically, they are produced as messenger substances by cells of the blood-forming and lymphatic system. Binding of IFN alpha to the transmembrane receptor induces activation of various signaling pathways (i.e., JAK-STAT, IRS). The therapeutic use of IFN alpha can lead to a profound disruption of thyroid function. IFN alpha induced thyroid dysfunction can be divided into two groups: autoimmune-mediated (Hashimoto-thyroiditis, Graves' disease, autoantibody-production without clinical symptoms) and non-autoimmune-mediated (direct toxic effect with destructive thyroiditis). The most common form of autoimmune-mediated IFN alpha thyroid dysfunction is Hashimoto thyroiditis whereas development of Graves' disease is uncommon. Here we present the case of a patient who developed thyrotoxicosis under treatment with IFN alpha.

Case report:

A 66-year-old patient with known IFN alpha-treated polycythemia vera was referred from the hematology clinic with newly diagnosed and severe hyperthyroidism. Of note is the fact that the patient has one son suffering from Graves' disease. Therapy with IFN alpha (Pegasys®) 45 µg/week was started in December 2019 and it was slowly dosed up to 135 µg/every 8 days. The patient complained of typical hyperthyroidism symptoms (increased sweating and nervousness, palpitations). The clinical examination found a diffuse enlarged but indolent thyroid gland and no signs of endocrine orbitopathy. Sonography detected inhomogeneous parenchyma with increased perfusion. Laboratory analysis revealed severe thyrotoxicosis with suppressed TSH and elevated fT3- and fT4-levels. Anti TSH-receptor antibodies were negative but anti-TPO-antibodies were detectable. To further elucidate the origin of hyperthyroidism 99mTc-scintigraphy was performed which demonstrated increased and diffuse uptake consistent with Graves' disease.
IFN alpha was paused and treatment with carbimazole and a betablocker was started. Clinical course was favorable with complete normalization of the thyroid function tests within several weeks, disappearance of all clinical symptoms and stabilization of the hematological parameters.

Conclusion:

The spectrum of IFN-induced thyroid dysfunction is broad and includes different forms of under-/over-function and production of thyroid-specific antibodies without clinical symptoms. Differential diagnosis is essential and thyroid scintigraphy discriminates between destructive thyroiditis and antibody-negative Graves' disease allowing correct treatment decisions. Regular thyroid function tests in patients under treatment with IFN are mandatory.

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Impact of risk factors on short and long-term maternal and neonatal outcomes in women with gestational diabetes mellitus: a prospective longitudinal cohort study

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Background:

Universal screening of gestational diabetes mellitus (GDM) in women with no factors remains controversial. This study identified the impact of GDM risk factors screening on perinatal and postpartum outcomes.

Methods:

This prospective cohort study included 780 women with GDM. GDM risk factors included previous GDM, first grade family history of type 2 diabetes, high-risk ethnicity and pre-pregnancy overweight/obesity (OW/OB). Outcomes included obstetrical, neonatal and maternal metabolic parameters during pregnancy and up to 1 year postpartum.

Results:

Out of 780 patients, 24% had no risk factors for GDM. Of these women, 40% needed medical treatment and 21-27% had glucose intolerance at 6-8 weeks and 1-year postpartum. In women with risk factors, the prevalence of postpartum glucose intolerance increased by 2.1-2.9 fold. The most important risk factors were previous GDM and pre-pregnancy OW/OB for poor perinatal outcomes, and high-risk ethnicity and pre-pregnancy OW/OB for adverse postpartum metabolic outcomes. Increasing number of risk factors were associated with worsened perinatal outcomes except for pregnancy induced hypertension, C-section delivery and neonatal hypoglycaemia.

Conclusion:

Women without risk factors had a high prevalence of adverse perinatal and postpartum outcomes, while the presence of risk factors significantly increased the risk for postpartum glucose intolerance. This calls for a risk factor-based long-term follow-up of women with GDM.

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Neuropeptide Y and its fragments are increased in pheochromocytomas and paragangliomas

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Background/Introduction:

Neuropeptide Y (NPY1-36) is a vasoconstrictor peptide co-secreted with catecholamines and is likely to be involved in the hypertensive crisis observed in patients with pheochromocytomas and paragangliomas (PPGL). NPY1-36 is degraded into multiple fragments without biological activity, with the exception of NPY3-36 that inhibits norepinephrine release. Plasma NPY assays were initially of interest since RIAs with polyclonal antibodies detected 100% patients with PPGL. However, a more specific sandwich ELISA showed an increase of NPY in only 33% and 67% of benign and malignant PPGL. We hypothesized that these discrepancies between immunoassays might be due to the specificity of antibodies used. Therefore we decided to validate a new LC-MS/MS assay for NPY and its fragments (NPYs) to evaluate the diagnostic performance of NPYs and their relationship with symptoms and tumor size.

Methods:

This multicenter study includes a total of 30 patients with PPGL (1 MEN2, 1 MAX, 2 SDHB and 2 VHL). Plasma was collected before, during (for 16 patients) and 24h after surgery for quantification of metanephrines and NPYs by LC-MS/MS. Biomarker concentrations were correlated with symptoms, tumor weight and location, and genetic background.

Results:

We found concentrations above reference intervals for NPY3-36 in 69% (20/29) and for metanephrines in 87 % (26/30) patients with PPGL. Two patients with metanephrines concentrations below the upper reference limits (URL) had increased NPY3-36 concentrations; conversely, among 8 patients with NPYs concentrations below the URL, 6 had elevated metanephrines. Tumor weight correlated with normetanephrine (NMN) and 3-methoxytyramine (MT) concentrations ($r=0.58$, $p=0.009$ and $r=0.49$, $p=0.032$) but not with NPYs concentrations. NMN and MT, but not metanephrine, correlated with NPY before and after surgery ($p<0.05$). Normetanephrine concentrations were higher in hypertensive patients ($p=0.04$). Biomarker levels were not affected by the tumor localization.

Conclusion:

NPYs concentrations measured by RIA/ELISA and MS strongly differ because of the lack of antibody specificity. Plasma free metanephrines provide better diagnostic performance than NPY for PPGL. However, the NPYs assay was useful in 2 of 30 PPGL cases with normal metanephrine concentrations.

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Biochemical follow-up of patients with Pheochromocytomas and paragangliomas (PPGL): A Swiss retrospective study

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Background/Introduction:

Patients previously affected with a PPGL or carrying a genetic mutation predisposing to a pheochromocytoma have a definite risk of relapse. Recommendations edicted by the Endocrine Society propose lifelong annual biochemical testing to assess for recurrent or metastatic disease. The aim of this study was to assess the performance of this monitoring and to determine the frequency of testing that would be optimal to detect tumor relapse.

Methods:

This retrospective study used our clinical laboratory database, established at CHUV since 2008. A total of 568 patients were monitored specifically for a risk of PPGL, including 312 cases following a pheochromocytoma and 106 a paraganglioma. Among them, 109 patients harbored a known mutation (MEN2, NF1, SDHx and VHL). Plasma metanephrines (free and total) were determined by LC-MS/MS and samples were collected at intervals varying from 6 months to one year. Biomarkers trajectories followed during 3-13 years were described using longitudinal mixed-effect modeling, contrasting patients developing a tumor or relapsing versus those remaining unaffected. The biochemical adrenergic/noradrenergic phenotype associated with the susceptibility gene mutation was included as covariate.

Results:

The 568 patients provided a total of 3355 samples, with a median of 5 per patient (IQR 1-19). Our longitudinal analysis confirmed a significant trend for increase in the plasma levels of metanephrine, normetanephrine or methoxytyramine (both free and total conjugated forms), depending on the type of familial or sporadic predisposition, over the 4-5 years preceding an occurrence or a relapse of PPGL, an outcome that occurred in 279 patients (2 or more relapses occurred in 9 patients). Conversely, the patients remaining unaffected during the follow up period, either after a PPGL (321 patients) or with a predisposing condition showed no significant biomarker changes other than biological fluctuations. Both the absolute levels and the relative increases between consecutive samples are important for predicting the risk of tumor appearance or relapse in patients at risk. Rational monitoring rules can be deduced from these observations to support clinical decisions during the biochemical follow up of these patients.

Conclusion:

Our retrospective case-control longitudinal analysis confirms that the follow up of plasma biomarkers levels is effective for the monitoring of PPGL in patients at risk, and globally supports the monitoring recommendations of the Endocrine Society.

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Two weeks of fluvastatin administration in young, healthy men results in reduced insulin sensitivity, but has no effect on brown adipose tissue activity.

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Background/Introduction:

Statins are commonly prescribed drugs for primary and secondary prevention of atherosclerotic disease that inhibit cholesterol synthesis and thereby lower cholesterol levels. However, several studies reported a significant increase in the diagnosis of diabetes mellitus with statin treatment. The molecular mechanisms behind this adverse effect are not yet fully understood. Brown adipose tissue (BAT), which plays a role in thermogenesis, has been associated with a reduced risk of insulin resistance. One of the key enzymes necessary for cholesterol synthesis is highly expressed in BAT and is inhibited by statins. The aim of this study was to investigate the effect of two weeks of fluvastatin administration in young, healthy men on insulin sensitivity and BAT.

Methods:

A prospective study was conducted in 16 young, healthy men. After screening for the presence of BAT by cold-induced thermogenesis (CIT), participants underwent glucose tolerance testing (oGTT) and assessment of BAT activity by FDG-PET/MRI. Fluvastatin 2x40mg was then administered for two weeks and oGTT and FDG-PET/MRI were repeated.

Results:

Two weeks of fluvastatin treatment led to a significant increase in glucose area under the curve (AUC) during oGTT ($p=0.02$), reduction in total cholesterol and LDL cholesterol (both $p<0.0001$). Insulin AUC ($p=0.26$), energy expenditure (EE) ($p=0.44$) and diet induced thermogenesis (DIT) ($p=0.27$) did not change significantly. A trend towards insulin resistance with lower Matsuda index after fluvastatin intake was observed ($p=0.09$). Standard uptake value (SUVmean) ($p=0.12$), Volume ($p=0.49$) and total Glycolysis ($p=0.74$) as parameters of BAT activity, did not change significantly with the intervention. Matsuda index displayed a negative correlation with the SUVmean and respiratory exchange ratio (RER) (both $R2=0.44$, $p=0.005$) at baseline, but it disappeared after fluvastatin administration ($R2=0.08$, $p=0.29$).

Conclusion:

Treatment with fluvastatin 2x40mg daily for two weeks reduced serum lipids and increased glucose AUC in young, healthy men, indicating reduced insulin sensitivity. We found no evidence that the decrease in insulin sensitivity was due to impaired BAT function.

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18F-Fluorocholine-PET combined with contrast-enhanced CT for localizing hyperfunctioning parathyroid glands in patients with hyperparathyroidism.

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Background/Introduction:

Hyperparathyroidism (HPT) is a common endocrine disorder. Definitive cure can be achieved by removal of all diseased glands. Exact preoperative localization of hyperfunctioning parathyroid tissue is critical for treatment success and prevention of extensive surgical exploration. Standard imaging modalities (i.e., ultrasound, 99mTc-sestamibi scintigraphy/SPECT/CT) bear the risk of false negative/inconclusive results. This study evaluated the diagnostic accuracy of 18F-Fluorocholine-PET in combination with contrast-enhanced CT (FCH-PET/CT) and its sensitivity in patients with primary, secondary/tertiary and familial HPT with negative and/or discordant findings in ultrasound and/or 99mTc-sestamibi scintigraphy/SPECT/CT.

Methods:

This was a retrospective, single-institution study carried out on 69 HPT patients (60 with primary HPT, 4 with secondary/tertiary HPT and 5 with familial HPT) who have undergone preoperative imaging with 18F-Fluorocholine-PET/CT, parathyroidectomy and histopathological work-up of the resected lesions. Sensitivities and positive predictive values were calculated.

Results:

Sensitivity/positive predictive value (PPV) per lesion was 87.5/98.3% for primary HPT, 75/100% for secondary/tertiary HPT and 25/66.7% for familial HPT. Sensitivity/PPV per patient was 91.5/98.2% for primary HPT, 100/100% for secondary/tertiary HPT and 50/100% for familial HPT. The follow-up rate was 97%. 58 of 60 patients with primary HPT, and 4 of 4 patients with secondary/tertiary HPT and 4 of 5 patients with familial HPT showed normal calcium and parathyroid hormone (PTH) levels after 6 months and were cured.

Conclusion:

Diagnostic accuracy of 18F-Fluorocholine-PET/CT for patients with primary HPT is excellent and the data of this study is line with previous published results. 18F-Fluorocholine-PET/CT is a valuable tool for endocrine surgeons helping to optimize the treatment success in patients with hyperparathyroidism.

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Clinical outcomes in patients with Cushing's disease after pituitary surgery: a population-based matched cohort study

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Background/Introduction:

Cushing`s disease (CD) is characterized by excess levels of cortisol with multisystem morbidity and increased mortality that is only partially reversible following treatment. Whether the risk for adverse clinical outcomes in CD patients remains elevated after pituitary surgery warrants further investigation.

Methods:

In this population-based retrospective cohort study using nationwide claims data from 2012 to 2018, patients with CD undergoing pituitary surgery were compared with propensity-score matched controls with surgery for non-functioning pituitary adenoma (NFA). The primary outcome was a composite of hospitalization for major adverse cardiovascular events (MACE), thromboembolic events, fractures, sepsis, and psychiatric disorders.

Results:

After matching, we identified 368 adult patients undergoing pituitary surgery, of those 84 with CD and 284 with NFA. After a median follow-up of 2.9 years, the event rate per 1000 person-years was 81.9 for CD and 31.6 for NFA (hazard ratio [HR] 2.38 [95% CI, 1.23 to 4.62]; rate difference, 50.2 [95% CI, 10.6 to 89.8]. The strongest driver for the between-group difference was the incidence rate of sepsis per 1000 person-years of 24.1 for CD and 5.3 for NFA (HR 5.94 [95% CI, 1.69 to 20.86]; rate difference, 18.8 [95% CI, -1.0 to 38.6]. There were no significant between-group differences in the rates of MACE (HR 2.07 [95% CI, 0.43 to 10.02]), thromboembolic events (HR 3.11 [95% CI, 0.35 to 27.43]), fractures (HR 2.54 [95% CI, 0.74 to 8.75]), and psychiatric disorders (HR 2.14 [95% CI, 0.89 to 5.10]).

Conclusion:

Patients with CD have higher risk for adverse clinical outcomes after pituitary surgery compared to patients with NFA. This emphasizes the importance of early identification and management of modifiable risk factors in the post-surgery phase.

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Perioperative fully closed-loop insulin delivery versus standard insulin therapy in adults undergoing pancreatic surgery

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Background/Introduction:

Pancreatic surgery imposes high demands on perioperative glucose management. The sudden increase in exogenous insulin requirements is further compounded by surgery-induced stress, medication, and nutritional interventions, often resulting in suboptimal glucose control. Fully closed-loop systems regulate insulin delivery autonomously based on continuous sensor glucose readings and may therefore better accommodate the complex need of this challenging patient population. We hereby report first results on the efficacy and safety of fully closed-loop insulin delivery vs. standard insulin therapy in patients undergoing pancreatic surgery.

Methods:

Patients planned for pancreatic surgery at the University Hospital Berne and expected to require insulin were randomly assigned to closed-loop (CL group) or usual (OL group) insulin therapy from hospital admission to discharge or a maximum of 30 days. The CL group was treated with CampAPS HX system, directing s.c. insulin aspart insulin based on continuous sensor glucose (Dexcom G6). The OL group was treated according to local practice and wore a blinded CGM for study outcome assessment. Glucose control was assessed from time of surgery until study completion and compared between the two groups using the Mann-Whitney U test.

Results:

Twelve patients (6 per group, 58% female, mean±SD age 69±18years, BMI 27.3±3.9kg/m2, HbA1C 7.8±2.0%) were included in this analysis. Total pancreatectomy was performed in 6 and 3 patients in the CL and OL group, respectively. The remaining patients underwent partial pancreatectomy. After surgery, the proportion of time with sensor glucose in the target range (3.9-10.0 mmol/l) was higher (85.0±5.2% vs. 44.5±28.6%, p<0.01) and the time in hyperglycemia (>10mmol/l) was lower in the CL vs. the OL group (14.8±5.2% vs. 53.7±30.7%, p=0.03). Mean glucose tended to be lower in the CL vs. OL group (8.2±0.4mmol/L vs. 11.3±3.4mmol/L, p=0.064). During surgery (duration 6±1hour), CL insulin therapy also resulted in improved glucose control during surgery, however differences in this small sample size did not reach statistical significance (mean glucose 8.1±1.1mmol/L vs. 10.1±3.1mmol/L; time in target range 73.4±21.4% vs. 57.2±41.6%; time in hyperglycemia 23.6±21.8% vs. 42.8±41.6%; all p>0.05). Both groups experienced neither severe hypoglycemia nor clinically significant hyperglycemia.

Conclusion:

Fully closed-loop insulin therapy in patients undergoing pancreatic surgery resulted in large improvements of glucose control compared to standard insulin therapy. These first findings suggest that a fully autonomous insulin delivery in complex surgical patients offers great promise to provide highly effective and safe perioperative management of glucose levels.

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Management of severe hypophosphatemia after intravenous ferric carboxymaltose in a postbariatric patient: A case report

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Background/Introduction:

Postbariatric patients are prone to iron deficiency and often treated with iron preparations. In the last years, an increasing number of case reports have been published about hypophosphatemia after intravenous (i.v.) treatment of iron deficiency. Especially ferric carboxymaltose can cause hypophosphatemia by inhibiting degradation of fibroblast growth factor 23 (FGF-23), which causes renal phosphate excretion and suppresses the 1-α-hydroxylation of vitamin D. Hypophosphatemia can be aggravated by preexisting vitamin D deficiency which is also common in postbariatric patients.

Methods:

We describe the clinical presentation, the initial and follow-up laboratory values and treatment of a patient with severe hypophosphatemia as a result of i.v. ferric carboxymaltose.

Case presentation:

A 32-year old woman presented for a regular postbariatric follow-up four years after sleeve gastrectomy. Blood had already been drawn prior to the visit showing severe hypophosphatemia (0.28 mmol/L; normal range 0.81 - 1.45 mmol/L). The values for calcium, alkaline phosphatase, creatinine, eGFR, parathyroid hormone and pH were within the reference range and 25-hydroxy vitamin D was slightly low (47 nmol/L; 50-135 nmol/L). The ratio of renal tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/ GFR) was 0.23 mmol/L (0.80–1.35 mmol/L) indicating renal phosphate wasting. FGF-23 was elevated (64.5 pg/mL; 10-50 pg/mL) and 1,25-dihydroxy vitamin D in the low reference range (66 pmol/L, 48-190 pmol/L). Further investigation revealed administration of ferric carboxymaltose 1000 mg i.v. 2.5 weeks prior to our initial laboratory evaluation. No symptoms of hypophosphatemia were identified. Supplementation of cholecalciferol was enhanced and calcitriol was initiated. Follow-up showed substantial improvement of the hypophosphatemia. After 7.5 weeks, phosphatemia had normalized and calcitriol was stopped.

Conclusion:

Ferric carboxymaltose can cause hypophosphatemia and in prolonged cases this is associated with osteomalacia including recurring pseudofractures. Therefore, we recommend optimizing vitamin D supply before i.v.-iron-supplementation and screening for hypophosphatemia, especially in patients with malabsorption if repeated doses are necessary or if symptoms occur. A detailed anamnesis and calculating TmP/ GFR are indicated to identify the cause of hypophosphatemia and measuring FGF-23 can clarify the pathophysiology. In this situation, temporary calcitriol improved phosphatemia substantially.

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Mechanisms and Clinical Course of Endoscopic Overstitch Procedure in Patients with Gastric Bypass and Late Dumping Syndrome (The MECCEO Study). Preliminary results.

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Background/Introduction:

Late dumping syndrome (LDS) is a complication following gastric-bypass surgery characterized by postprandial hypoglycemia. Enhanced secretion of insulin and incretins (GLP-1 and GIP) seems to play a major role. Mechanical factors (i.e., widening of the gastrojejunal anastomosis) leading to a more rapid passage of food bolus into the intestine may exaggerate insulin- and incretin secretion. Medical treatment options are restricted and data on these regimens is scarce. A newer minimally invasive endoscopic procedure, the transoral outlet reduction (TORe), allows narrowing of the gastrojejunostomy and is performed in patients with weight-regain after bariatric surgery. In smaller case series this intervention demonstrated some benefit in patients with LDS. However, exact data on the physiological mechanisms of this intervention and long-term follow-up is missing. We present preliminary data of a pilot study investigating the mechanisms and the follow-up in patients undergoing TORe.

Methods:

Patients with severe LDS (defined by the presence of severe hypoglycemia) are included prospectively. Investigations (continuous glucose monitoring, scintigraphic measurement of gastric emptying velocity, dynamics of insulin-/C-peptide-, incretin- and glucagon-secretion studied by mixed meal test [MMT], profiling of miRNA, changes in gut microbiota, patient reported outcomes [PRO, Arts-/Sigstad-/GIQLI-score, SF-36 questionnaire]) are carried out before and 12, 24 and 48 weeks after TORe.

Results:

To date 5 patients were included. Preliminary data suggest lower peak values for MMT-induced glucose-, insulin-/C-peptide- and GLP-1-levels, delayed liquid and solid phase gastric emptying and improvement of PRO, including reduction of hypoglycemic events after TORe. Analysis of CGMS-data, glucagon, miRNA and microbiota is pending, and definitive data analysis of all datasets should be available in November 2021.

Conclusion:

TORe may represent a promising new treatment option in patients with severe LDS after gastric bypass surgery.

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Two pregnancies in a patient with Tyrosinemia type I under continued treatment with nitisinone

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Background/Introduction:

Tyrosinemia type I is a rare inborn error of metabolism, caused by a deficiency of the enzyme fumarylacetoacetase, leading to a block in the degradation pathway of tyrosine. As a result, upstream metabolites and toxic intermediates accumulate, that may result in severe liver damage, along with other disease manifestations. Nitisinone has revolutionized the treatment of the disease. The substance blocks a proximal enzyme of the pathway and thus prevents formation of the toxic substances, but leading to hypertyrosinemia, which needs to be controlled by low protein diet. Only few pregnancies with maternal tyrosinemia type 1 have been reported, and little is known about potential harmful effects of hypertyrosinemia on fetal development or the safety of nitisinone in pregnancy.

Methods:

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Results:

We report on a patient born in 1988 with Tyrosinemia type I known since the age of two, who became pregnant intentionally in 2018 and again 2020. Treatment with nitisinone was continued during the pregnancies. The patient made every effort to follow a strict low-protein diet, with regular intake of the tyrosine- and phenylalanine-free amino acid mixture.
She achieved a satisfactory metabolic control, but with lower tyrosine levels in the first (Median 488 µmol/l, normal < 31 µmol/l) than in the second pregnancy (562 µmol/l). Both pregnancies were without complications with normal development of the children, although they were rather small (P5, P<3) and light (P10, P25) and had a small head circumference, too (P25, P5). Both deliveries were vaginal and on term. Nitisinone was detected in the blood of the umbilical cords and the children in similar concentrations as in the mother. Minor amounts were also detectable in the breast milk. Tyrosine was similarly elevated in both newborns and decreased within two months.
During the observation period of two years, or three months, respectively, the children developed without any abnormalities.

Conclusion:

With good metabolic control and continued treatment with nitisinone, successful pregnancy with normal child development can be achieved in tyrosinemia type 1. However, continued monitoring to assess the development of children from such pregnancies in the long-term is needed.
This is a unique opportunity to compare the outcome of two pregnancies, in which almost all conditions are identical except for the level of tyrosine during pregnancy.

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Implementation of SGLT2 inhibitors in patients with type 2 diabetes mellitus and chronic kidney disease - a SwissDiab study

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Background/Introduction:

Randomized controlled trials have shown that sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduce the progression of chronic kidney disease (CKD), the risk of end-stage kidney disease, and deaths from renal causes in patients with type 2 diabetes mellitus (T2DM) and CKD. As a result, guidelines on diabetes management were updated in 2019/2020 to recommend SGLT2i for all patients with T2DM and CKD (as long as the estimated glomerular filtration rate (eGFR) is ≥30 ml/min/1.73m2). However, implementation of new treatment regimes in daily clinical practice can be slow and challenging. The objective of this study was to use the Swiss Diabetes Registry (SwissDiab) to determine how many of the patients with T2DM and CKD that are currently treated with SGLT2i. The aim was to evaluate the need to reinforce and promote clincial guidelines to ensure that patients receive the full benefit of available therapies.

Methods:

SwissDiab is a multicentre longitudinal observational study of outpatients with diabetes in tertiary care. Patients were enrolled at the tertiary diabetes care centre at the Cantonal Hospital of St. Gallen, Bern University Hospital/Inselspital and Zürich University Hospital. In this cross-sectional study, SwissDiab patients with T2DM and a study visit between 01.01.2020 – 31.03.2021 were analyzed. CKD was determined in accordance with the KDIGO definitions as reduced eGFR (<60 ml/min/1.73m2) and/or albuminuria (albumin to creatinine ratio of 3 mg/mmol or greater). Since the SwissDiab study is based on annual study visits, albuminuria was defined by a minimum duration of 12 rather than 3 months as suggested by KDIGO. The proportion of patients with CKD that were prescribed SGLT2i at the time of the study visit was determined. Data are means±sd unless otherwise specified.

Results:

There were 370 patients with T2DM and a visit between 01.01.2020-31.03.2021 available in the SwissDiab database. Clinical data needed to determine CKD was missing in 2.7% (n=10) leaving 360 patients for the analysis. Patients were 64.6±10.9 years old with a T2DM duration of 15.3±8.9 years, and 26% (n=96) were female. Overall, 48.1% (n=173) had CKD. Mean age was 68.7±9.8 years, diabetes duration 18.1±8.3 years, and 24.9% (n=43) were female. The definition of CKD was based on reduced eGFR only in 26.6% (n=46), albuminuria only in 41.6% (n=72), and both reduced eGFR and albuminuria in 31.8% (n=55). SGLT2i were prescribed to 31.8% (n=55) of the patients with CKD. Another 26.6% (n=46) were prescribed GLP-1 receptor agonists (of which four had an eGFR <30 ml/min/1.73m2), leaving 41.6% (n=72) of the patients without treatment with either renal-protective agent. Of these, 10 patients had an eGFR <30 ml/min/1.73m2 leaving 62 patients with indication for SGLT2i treatment; 33.9% (n=21) were defined by reduced eGFR only, 37.1% (n=23) by albuminuria only, and 29% (n=18) by both reduced eGFR and albuminuria.

Conclusion:

The results show an apparent divergence between the recommended standard of care in terms of renal-protection in T2DM and the implementation in daily clinical practice. Why two in five patients with CKD were not prescribed either SGLT2i or GLP-1 receptor agonist is unclear. Treatment should first and foremost consider patient-specific cirumstances but the results highlight the need to reinforce the implementation of current guidelines to ensure patients benefit from the best treatment available.

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Glycemic Improvement in 3,436 Patients With Type 1 Diabetes (T1D) using the Omnipod DASH® Insulin Management System Over the First 90 Days Of Use

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Background/Introduction:

Clinical outcomes describing real-world use of various devices by people with T1D are important to support decision-making. This retrospective study characterized patient-reported clinical outcomes of people with T1D in the United States before (baseline) and 90 days after (follow-up) initiation of the tubeless Omnipod DASH® Insulin Management System.

Methods:

The primary outcome was change in self-reported HbA1c levels from baseline to follow-up. Secondary outcomes were change in self-reported total daily dose (TDD) of insulin and frequency of hypoglycemic events (HE) per week (#/week <70 mg/dL). Outcomes were assessed overall, by prior treatment modality (MDI or CSII), and by age (<18y, ≥18y).

Results:

Patients (n=3,436) were divided into 2 age groups (<18y: n=1,020, ≥18y: n=2,416), aged 10.1±4.2y and 43.9±16.5y (mean±SD) and 48.4% and 59.7% were female, respectively. The change in HbA1c at follow-up for patients <18y was -0.8±1.9% ($p<0.0001$). Prior MDI users had a change of -0.9±2.0% ($p<0.0001$), while there was no statistically significant change for prior CSII users (-0.3±1.2%; $p>0.05$). The TDD of insulin was similar at baseline and follow-up, while the frequency of HE decreased significantly at follow-up by -1.4±2.7 episodes per week ($p<0.0001$).

For patients ≥18y, the overall change in HbA1c was -0.9±1.6% ($p<0.0001$), with a change of -1.0±1.7% ($p<0.0001$) for prior MDI users, and -0.6±1.1% ($p<0.0001$) for prior CSII users. Overall change in TDD of insulin was -12.5±30.2 U/d ($p<0.0001$). HE frequency decreased by -1.6±3.2 ($p<0.0001$) episodes per week.

Conclusion:

This large cohort of patients with T1D using the Omnipod DASH® Insulin Management System exhibited significant reductions in HbA1c and number of HE after 90 days of use across both age groups. In adults, the glycemic improvement was achieved with a concomitant reduction in the amount of insulin used.

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Glycemic Improvement in 6,034 Pediatric Patients With Type 1 Diabetes (T1D) Using Omnipod® Insulin Management Systems Over First 90 Days Of Use

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Background/Introduction:

Clinical outcomes describing real-world use of various devices by people with T1D are important to support decision-making. This retrospective study characterized patient-reported clinical outcomes in 6,034 patients aged <18 years in the United States with T1D before (baseline) and 90 days after (follow-up) the initiation of a tubeless insulin pump (Omnipod® Insulin Management System or Omnipod DASH® System).

Methods:

The primary outcome was change in self-reported HbA1c from baseline to follow-up. Secondary outcomes were change in self-reported total daily dose (TDD) of insulin and frequency of hypoglycemic events (HE) per week (#/week <70 mg/dL). Outcomes were assessed overall and stratified by prior treatment modality (MDI or CSII) and age group.

Results:

Patients were aged 11.0±3.9y (mean ± SD). The overall change in HbA1c at follow-up was -0.6±1.6% ($p<0.0001$). Overall change in TDD of insulin was -1.1±12.2 U/d ($p<0.0001$) and the HE frequency decreased significantly by -1.4±2.9 episodes per week ($p<0.0001$). Reductions in HbA1c and HE were seen regardless of prior treatment, and for most age groups . For the adolescent group (age 13-17y), the decrease in HbA1c was achieved with a 6% decrease in the total daily dose of insulin .

Conclusion:

In this large cohort of pediatric patients with T1D, initiation of a tubeless insulin pump was associated with significant reductions in HbA1c and number of HE after 90 days of use compared to prior MDI and CSII treatments and across age groups.

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Efficacy of GLP-1 analogues for the treatment of secondary weight gain following bariatric surgery: an observational study.

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Background/Introduction:

Although bariatric surgery is currently the most efficacious treatment for severe obesity and its associated comorbidities, secondary (postoperative) weight gain may occur in up to 20% of the cases and significantly reduce the long-term benefits of the procedure. GLP-1 receptor analogues (GLP-1ra) can reduce hyperglycaemia and cause significant weight loss and have been approved for the treatment of both type 2 diabetes mellitus and obesity, but their role in the treatment of patients with secondary weight gain after bariatric surgery remains to be established.
Our objective with the present study was to investigate the effect on weight of GLP-1ra in patients with secondary weight gain after bariatric surgery.

Methods:

Retrospective observational study in a single outpatient bariatric centre in St. Gallen, Switzerland in adults fulfilling the above-mentioned inclusion criteria. Data are presented as median with interquartile range in brackets, if not indicated otherwise, and nonparametric statistics were used. A p-value <0.05 was considered significant.

Results:

44 patients (82% females), with a preoperative weight of 114.2kg (109.8-124.6) and BMI of 43.5kg/m² (39.1-47.7), were included. Following bariatric surgery (Roux-en-Y gastric bypass 77%, vertical sleeve gastrectomy 9%, other procedures 14%), a weight loss of 32.7kg (27.7-42.5), BMI loss of 12.7kg/m² (10.2-15.4), equivalent to a 28.5% (25.0-32.8) reduction of preoperative weight, occurred to a nadir weight and BMI of 82.6kg (74.0-96.2) and 30.2kg/m² (27.7-34.2), respectively.
Eventually, a secondary weight gain of 11.7kg (7.9-16.7), BMI gain of 4.4kg/m² (2.9-6.1) ensued, tantamount to 13.8% (8.3-18.5) of nadir weight. Thus, 71.0 months (41.0-97.3) postoperatively, a GLP-1ra therapy (liraglutide 1.8/3.0mg once daily, n=2/27; semaglutide 1.0mg once weekly, n=15) was initiated. At baseline, the weight was 94.7kg (86.7-105.9), BMI 34.2kg/m² (32.0-40.4), age 50.0 years (44-60.3) and 25% (12-38) of the patients had type 2 diabetes mellitus.
After 6 months GLP-1ra therapy, the patients had lost 7.0kg (3.3-10.7; p<0.0001) with a BMI loss of 2.64kg/m² (1.2-3.7; p<0.0001), corresponding to a loss of 67.3% (30.1-88.3) of the secondary weight gain. The most common adverse events were gastrointestinal and mild.

Conclusion:

In patients with secondary weight gain following bariatric surgery, approximately two thirds of the regained weight can be lost safely with a GLP-1ra therapy, thus providing clinicians with a new therapeutic option for this not uncommon scenario.

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Nutrition literacy in normal-weight and obese Swiss populations using an anonymized online survey

Author/Address of institution:

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Background/Introduction:

Nutrition literacy, defined as the skills necessary to obtain, understand and process nutrition information, plays an important role in daily dietary choices. As the burden of diet-related disorders such as obesity is increasing worldwide, insights into people's nutrition literacy will unravel important gaps that may be addressed using targeted interventions. The aim of the online survey was to assess nutrition literacy in normal-weight and obese populations in Switzerland.

Methods:

Participants completed an anonymized online survey (disseminated in clinical (University Hospital Bern, Swiss Nutrition and Dieticians Societies) and non-clinical (internet, social media) environments in Switzerland with the help of flyers) containing sociodemographic and time-limited multiple-choice questions related to nutrition facts of packaged and non-packaged food items displayed using images. Comparative questions (n=6) with packaged food assessed qualitative attributes (content of sugar, dietary fibres, protein, fat, salt and energy density). Rating scale questions with non-packaged foods (n=8, randomly selected out of 70) assessed energy content (displaying a scale of calorie options). BMI was used to stratify participants into normal-weight (BMI 18.5-24.9 kg/m2) and obese (BMI ≥30 kg/m2) groups. Results are reported as percentage of correct answers for each question set. Between-group comparisons were performed using two-sided t-tests. Data are reported as mean or percentage.

Results:

Between October 2020 and February 2021, 507 individuals (79.1% female, mean age: 37.9 years) of whom 464 were normal-weight (BMI: 21.8 kg/m2) and 43 obese (BMI: 35.1 kg/m2), completed the survey. Individuals with obesity were older (46.0 vs. 37.1 years) and had a lower educational level compared to normal-weight individuals (48.8% vs. 88.8% high school, university/tertiary or higher vocational education). Mean percentage of correct answers for qualitative nutritional attributes of packaged food was <50% in both groups and turned out to be lower in obese vs. normal-weight subjects (37.9% vs. 45.4%, p=0.01). Mean percentage of correct answers for energy content of non-packaged food were <50% in both groups, with a trend towards lower performance in obese vs. normal-weight subjects (34.3% vs. 28.9%, p=0.06). Mean absolute relative error in energy estimation of non-packaged food was comparable between groups (18.0% vs. 17.7% in obese and normal-weight, respectively, p=0.71).

Conclusion:

Findings suggest substantial qualitative and quantitative nutrition literacy gaps in obese and normal-weight adults. This corroborates the need for valid education and decision support systems in the field.

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Hyperinsulinemic hypoglycemia in transthyretin-related familial amyloid polyneuropathy: successful therapy with a somatostatin analogue

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Background/Introduction:
Hyperinsulinemic hypoglycemia (HH) is defined by low blood glucose levels in individuals without diabetes due to inappropriate insulin secretion from pancreatic β-cells. The latter is excessive relative to the concurrent blood glucose level, thereby resulting in hypoglycemia. HH can occur in the neonatal and childhood period (congenital hyperinsulinism), as well as in adults, due to a broad spectrum of etiologic mechanisms. Somatostatin is a peptide hormone released by the pancreatic delta cells in the pancreas, with pleotropic effects, including inhibition of insulin release and reduction of gastrointestinal motility.

Methods:
A 72-year old woman without diabetes, known for late-onset Val30Met hereditary transthyretin amyloidosis (hATTR), presented with a history of repeated postprandial hypoglycemic events occurring 3-5 times per week and requiring administration of intramuscular glucagon once or twice per month. hATTR is a rare disease, predominantly caused by mutations of the transthyretin (TTR) gene, whose symptoms are related to TTR amyloid deposits in peripheral nerves, heart and sometimes kidney, eyes or meninges. In the current situation the patient had severe axonal sensory-motor polyneuropathy, autonomic symptoms including orthostatic hypotension, gastroparesis, diarrhea and neurogenic bladder and heart failure with preserved ejection fraction. She was treated with patisiran, a small interfering RNA that targets the TTR messenger RNA, thereby reducing the expression of wild-type and mutant protein.

Results:
Continuous glucose monitoring (CGM) during 7 days revealed postprandial hypoglycemic events that correlated with capillary glucose levels. Extensive biochemical and radiological testing excluded etiologies such as insulinoma, adrenal insufficiency, neuroendocrine tumors, insulin secretagogues, exogenous insulin, alcohol consumption, hepatic or renal failure. A 75 g oral glucose tolerance test (OGTT) showed overt hypoglycemia at 90 min (in mmol/l: t0 4.7; t30 8.4; t60 3.5; t90 2.7; t120 3.6; t180 6.9) with excessive insulin secretion (in mU/l: t0 9.5; t30 328.0; t60 44.6; t90 15.3; t120 7.0, t180 25.9). We eventually diagnosed a postprandial HH associated with hATTR. Diet and monitoring with CGM with alarms only partially decreased the frequency and intensity of the hypoglycemic events. Acarbose, diazoxide and empagliflozin did not have a positive impact. Because the patient experienced recurrent diarrhea concomitant with the hypoglycemic episodes, we treated her, due to an intolerance of loperamide, with a short-acting somatostatin analogue administered three times daily. This led to the disappearance of low blood sugar level s and diarrhea, prompting therapy with an ultra-long-acting somatostatin analog (Sandostatine LAR). The subsequent evolution with 3 injections during 3 months showed a marked decrease in both frequency and intensity of hypoglycemic events. A subsequent 75 g-OGTT showed an impressive decrease in insulin response (in mU/l: t0 7.9; t30 9.4; t60 43.0, t120 34.4; t180 11.4), and an absence of hypoglycemia (in mmol/l: t0 5.1; t30 6.7; t60 10.5; t120 10.7; t180 6.3).

Conclusion:
HH is an established but rare complication of hATTR. It is presumably underestimated due to the complex clinical presentation of affected individuals. The HH episodes may be severe and impair quality of life. In refractory hATTR-associated HH, the administration of long-acting somatostatin analogues may be an alternative therapeutic modality that reduces the inappropriate insulin secretion.

Broad range of phenotypes in an international cohort of 75 DSD individuals with SF 1/NR5A1 variants

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Background/Introduction:

Steroidogenic Factor 1 (NR5A1/SF-1) is essential for the development and function of human sex and steroid organs. Variants of SF-1 lead to a broad spectrum of phenotypes including adrenal insufficiency and differences of sex development (DSD), but data on the whole picture of phenotypes in individuals with SF-1 variants are currently lacking. We aim to investigate the phenotype of individuals with SF-1 variants in a large international cohort.

Methods:

Individuals with known SF-1 variants were 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 excluded 46,XX individuals with disorders of androgen excess or disorders of Müllerian development, and 46,XY individuals with Leydig cell defects or Persistent Müllerian Duct Syndrome. We identified the individuals through the international I-DSD network. Eighteen collaborators entered comprehensive phenotyping data according to the Human Phenotype Ontology project in a RedCap database.

Results:

By May 2021, 75 individuals with SF-1 variants participated. They were born between 1964-2018 and had their last follow up between 2009-2021. Forty-eight percent of individuals were assigned as boys and girls, respectively (both 36/75). Only 1% was assigned as “other” (1/75) and 3% had unknown sex assignment (2/75). SF-1-variants were mainly identified by single gene analyses (59%, 44/75), followed by gene panels (25%, 19/75), Next Generation Sequencing (15%, 11/75) and Comparative Genomic Hybridization Array (1%, 1/75). Apart from DSD, more than half of SF-1 individuals (56%, 42/75) had at least one organ abnormality, and 18% (14/75) had two or more. One fifth (15/75) of SF-1 individuals had disturbancies of the endocrine system, 18% (14/75) of the urinary system, 9% (7/75) had abnormalities of skeleton or limbs, 8% (6/75) of the blood system, 8% (6/75) of the central nervous system, 8% (6/75) of the abdominal sytem, 5% (4/75) of head or neck, 4% (3/75) of the immune system, 4% (3/75) of the musculature, 2% (2/75) of the integument, and 4% (3/75) had separate abnormalities, each with the adrenal, metabolism, or peripheral nervous system. Four percent (3/75) of SF-1 individuals had psychosocial problems.

Conclusion:

More than half of individuals with SF-1 variants had multiple organ abnormalities, with a broad spectrum of phenotypes. Systematic phenotyping together with more comprehensive gene profiling will allow to find patterns in patients with SF-1 variants and to identify likely disease-causing variants in additional genes that might impact the phenotype. Genotype-phenotype patterns will help to evaluate the individual risk for adverse health outcomes and to improve long-term care of these patients.

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Title:

Thymic Rebound Syndrome after Cushing's Syndrome

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Case Report:

We describe the case of a 39-year-old woman with rapidly progressive Cushing's syndrome. Hormonal investigations revealed ACTH-dependent hypercortisolism (ACTH approx. 2.5-fold and 24h-cortisoluria approx. 5-fold of the upper reference range). With unremarkable MRI Sella a search for an ectopic source was done by [18F]FDG-PET/CT. This revealed a 15 mm mass in the right lobe of the lung, which was surgically removed by segmental resection. Histology showed a G1 neuroendocrine tumor with immunohistochemical positivity for ACTH. In the follow-up scan after 11 months, there was no sign of recurrence of the neuroendocrine tumor, but a thymic mass, which was previously nonexistent.

Comment:

The response of the thymus to glucocorticoids is known since 1960. In a diagnostic way, Caffey et al. used exogenous glucocorticoids to represent the children’s heart silhouette free of overlays. Rebound thymic hyperplasia is a phenomenon that occurs in up to 40 % after termination of stressful conditions (surgery, chemotherapy, trauma, bone marrow transplantation) and abrupt normalization of hypercortisolism. Many cases go undetected as thoracic CT scans are not done routinely after correcting hypercortisolism. High cortisol levels are thought to lead to thymic depletion, which is followed by rebound thymic hyperplasia when hypercortisolism normalizes. Radiographically, thymic hyperplasia typically presents as a diffuse enlargement, a fine mixture of lymphoid tissue and fat, with smooth contour, normal vessels and maintained triangular shape. In contrast, thymic neoplasia usually presents with a nodular contour and frequently contains necrotic or calcified foci. If in doubt, a minimally invasive fine needle aspiration can assist in differentiating between benign and malignant. Specific follow-up is usually not necessary for thymic hyperplasia. If performed, resolution is usually seen within 5 years.

Conclusion:

Thymic rebound syndrome may be a common, benign and transient phenomon after resolution of Cushing's syndrome and be considered as a potential pitfall in reading images in patients after glucocorticoid excess.

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Non-invasive hypoglycemia detection for drivers with diabetes: A machine learning approach using driving and gaze behavior data

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Background/Introduction:

Hypoglycemia is one of the most dangerous acute complications of diabetes mellitus and is associated with an increased risk of driving mishaps. Current approaches to detect hypoglycemia are limited by invasiveness, availability, costs, and technical restrictions. Based on changes in driving and gaze behavior in hypoglycemia, we aimed at developing machine learning (ML) models that detect hypoglycemia in drivers with diabetes.

Methods:

We included active drivers with well-controlled type 1 diabetes (T1D), aged 21-50 years. We recorded in-vehicle driving (CAN) and eye tracker (ET) data during controlled euglycemia (EU) and hypoglycemia (<3.0 mmol/L, HYPO) using a driving simulator and an eye tracker. Venous blood glucose (BG) served as the gold standard. Using CAN and ET data, we built machine learning (ML) models that predict the probability of the driver being in hypoglycemia. To expand applicability of our approach to different generations of vehicles, we present three ML models: first, the combined model CAN+ET, representing the contemporary car with integrated eye tracker. Second, since contemporary cars are not generally equipped with ET, we tested the CAN model when restricted to driving data. Third, anticipating that autonomous driving will be available in the future, which limits the role of CAN data, we conversely, evaluated a model solely based on ET.

Results:

The study encompassed 18 participants with T1D (HbA1c 7.1±0.6 %, age 32.2±7.1 years, 12 male) and preserved hypoglycemia awareness (Clarke Score 0.6±0.7 [range 0–2]). Mean BG was 5.85±0.63 mmol/L in EU and 2.37±0.23 mmol/L during HYPO. The model CAN+ET achieved an AUROC of 0.87±0.10, sensitivity of 0.87±0.14, and specificity of 0.79±0.18 in detecting hypoglycemia (<3.0 mmol/L) during driving. Using CAN or ET data exclusively, resulted in an AUROC of 0.79±0.13 and 0.80±0.16, respectively.

Conclusion:

We propose an accurate ML-based approach to non-invasively detect hypoglycemia while driving, which is applicable to contemporary cars and anticipates future developments in automotive technology.

Similar driving behavior despite differences in symptom perception and hormonal counter-regulation during hypoglycemia in adults with type 1 diabetes compared to adults with postbariatric hypoglycemia

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Background/Introduction:

Hypoglycemia is a frequent and potentially dangerous acute complication of diabetes. Increasingly, hypoglycemia is also recognized as a relevant complication of bariatric surgery (i.e. postbariatric hypoglycemia, PBH). Here, we compared counter-regulatory response during hypoglycemia in people with type 1 diabetes (T1D) and PBH. In addition, we assessed whether differences occurred regarding individual symptom perception. Finally, we investigated, whether the impact on a complex daily activity (driving) was different according to the type of hypoglycemia.

Methods:

We included 18 adults with T1D (age 32±7y, 12 male, HbA1c 7.1±0.6%) and 11 with PBH after gastric bypass (age 37±15y, 2 male, HbA1c 5.2±0.3%). Hypoglycemia was induced by intravenous insulin in T1D and by ingestion of 75g glucose in PBH. Counterregulatory hormones (glucagon, catecholamines, cortisol and growth hormone [GH]) were measured at baseline (BASE) and in hypoglycemia (HYPO). Symptoms (sweating, palpitation, tremor, incoordination, drowsiness) were rated on a 7-point scale (1=absent, 7=extreme) in HYPO. Driving was performed in a simulator at BASE and in HYPO. Seven driving features reflecting traffic violations and unsteady driving were integrated in a Bayesian hierarchical regression model to quantify change in driving behavior from BASE to HYPO as z-score. A similar Bayesian approach was used for counterregulatory hormones. Change in driving features and hormones is presented as mean[95% credible intervals]. Glucose and symptom scores were compared with non-parametric tests.

Results:

Blood glucose in T1D and PBH was 5.9±0.6 vs 4.8±0.3mmol/L ($p<0.001$) at BASE and 2.4±0.2 vs 3.0±0.6 mmol/L ($p=0.002$) at HYPO. Conterregulatory hormones significantly increased in HYPO compared to BASE in T1D, whilst in PBH only norepinephrine showed a significant increase (T1D 0.4[0.2;0.6]; PBH 0.3[0.01;0.6]nmol/L). Individuals with T1D reported a higher symptom score in HYPO compared to PBH (14±7 vs 7±4, $p=0.001$). When driving, both groups showed more safety margin violations (T1D 0.4[0.1;0.7]; PBH 0.4[0.1;0.6]) in HYPO compared to BASE. A similar tendency was observed for speed violations (T1D 0.3[0.0;0.6]; PBH 0.2[0.0;0.5]). Gas pedal acceleration was significantly higher in HYPO in PBH (0.3 [0.1;0.5]), while the difference was smaller and non-significant in T1D (0.2[-0.1;0.5]).

Conclusion:

Despite significant differences in hormonal counter-regulation and symptom perception between well-controlled individuals with T1D and age-matched individuals with PBH, the impact of hypoglycemia on driving behavior was comparable between the two populations.

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Higher doses of dulaglutide induce weight loss in patients with type 2 diabetes (T2D) regardless of baseline BMI: post hoc analysis of AWARD-11

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Background/Introduction:

The AWARD-11 trial demonstrated that dulaglutide (DU) 3 mg and 4.5 mg once weekly improved glycated hemoglobin (A1C) and bodyweight (BW), compared to DU 1.5 mg once weekly, in patients with T2D inadequately controlled with metformin monotherapy. The aim of this post hoc analysis was to assess the effect of DU on BW in clinically relevant baseline body mass index (BMI) categories as defined by clinical practice guidelines.

Methods:

Eligible patients had screening A1C 7.5 – 11% and BMI ≥ 25 kg/m2. Patients (N=1842) were randomized to DU 1.5 mg, DU 3 mg, or DU 4.5 mg. Total treatment period was 52 weeks with primary efficacy endpoint at 36 weeks. Baseline BMI (kg/m2) was categorized as overweight (<30), obesity Class I (30 - <35), Class II (35 - <40) or Class III (≥40). Mixed model for repeated measures was used within the BMI subgroups for assessing change in BW.

Results:

At 36 weeks, mean absolute reduction in BW within each DU dose group increased by baseline BMI category, whereas mean percentage weight loss was similar regardless of BMI category in DU 3 mg and 4.5 mg groups. Treatment-by-BMI subgroup interaction was not significant for either change or % change in BW (p = 0.905 and 0.473, respectively). The pattern of common adverse events was similar across BMI subgroups.

Conclusion:

Treatment with DU 3 mg and 4.5 mg induces weight loss across a range of clinically relevant BMI categories in patients with T2D.

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Once Weekly Basal Insulin Fc (BIF) is Safe and Efficacious in Patients with Type 2 Diabetes Mellitus (T2DM) Previously Treated with Basal Insulin

Author/Address of institution:

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Background/Introduction:

Basal insulin Fc (BIF; LY3209590) is a novel, once-weekly, long-acting IgG Fc-fusion protein that is being assessed for the treatment of diabetes mellitus. The presented study evaluated the safety and efficacy of BIF compared to insulin degludec (IDeg) over 32 weeks (wks) in patients with T2DM previously treated with oral antidiabetic drugs and a basal insulin.

Methods:

The study design included 2 different dosing algorithms for BIF (BIF-A1 and BIF-A2) with two different fasting glucose (FG) targets of ≤7.8 mmol/L (140 mg/dL) (BIF-A1) and ≤6.7 mmol/L (120 mg/dL) (BIF-A2). IDeg was titrated to a FG target of ≤5.6 mmol/L (100mg/dL) using a modified Riddle treat-to-target algorithm.

Results:

Study participants (N=399) were randomized in a 1:1:1 ratio to 1 of 3 parallel treatment-groups. Average age of participants was 60.2 years, baseline (BL) HbA1c was 65.2 mmol/mol (8.1%) and duration of diabetes 14.7 years. No statistically significant differences in demographics or BL characteristics across 3 treatment-groups. Both BIF groups achieved non-inferiority (non-inferiority margin = 0.4%) for primary endpoint of HbA1c change from BL to wk 32 with mean±SE reduction for BIF-A1, BIF-A2 and IDeg of 0.6±0.1%, 0.6±0.1% and 0.7±0.1%, respectively. In line with the different fasting serum glucose (FSG) targets, IDeg achieved greater FSG lowering from BL vs BIF arms. Both BIF dosing-groups showed significantly fewer hypoglycaemic events vs IDeg (all documented events as well as nocturnal events) when assessing events ≤3.9 mmol/L (70 mg/dL). Hypoglycemic events <3.0 mmol/L (54 mg/dL-all documented events as well as nocturnal events) were not significantly different between the 3 dosing-groups. Two severe hypoglycemic events were reported in BIF-A2. The reported treatment-emergent adverse events (AEs) and serious AEs were balanced across the 3 treatment-groups. Both BIF groups had statistically significantly smaller increase in body weight compared to IDeg from BL to wk 32.

Conclusion:

Weekly BIF (either dosing algorithm), was noninferior to IDeg for change in HbA1c after 32 wks with lower rate of documented and nocturnal hypoglycemia ≤3.9mmol/L (70mg/dL) and less weight gain. No safety signals detected. While higher FG targets were chosen in this first Phase 2 study with BIF, the safety and tolerability results allow assessment of lower target glucose ranges in future trials. Results support continued development of BIF as a once-weekly insulin treatment of diabetes mellitus.

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Efficacy and Safety of Tirzepatide, a Dual GIP/GLP-1 Receptor Agonist, Compared to Insulin Degludec in Patients with Type 2 Diabetes (SURPASS-3)

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Background/Introduction:

Tirzepatide (TZP) is a novel dual GIP/GLP-1 receptor agonist under development for the treatment of type 2 diabetes (T2D). The efficacy and safety of TZP vs titrated insulin degludec (IDeg) were assessed in insulin-naive patients with T2D inadequately controlled on metformin with/without SGLT-2i.

Methods:

In this open-label, 52-week, Phase 3 study, 1444 patients with T2D were randomised (1:1:1:1) to once-weekly TZP (5, 10, 15 mg) or once-daily IDeg (mean baseline [BL] age, 57.4 years; T2D duration, 8.4 years; HbA1c, 8.17%; BMI, 33.5 kg/m2; 32% on SGLT-2i). The primary efficacy endpoint was mean change in HbA1c from BL to Week 52. Secondary efficacy endpoints included mean change in fasting serum glucose (FSG) and body weight (BW) and proportion of subjects achieving HbA1c and BW goals. Safety data included all data through safety follow-up from the mITT population.

Results:

TZP 5, 10, and 15 mg were superior to IDeg in mean change from BL in HbA1c at Week 52. LSM treatment difference values vs IDeg (95% CI) were -0.59% [-0.73, -0.45], -0.86% [-1.00, -0.72], and -1.04% [-1.17, -0.90], respectively ($p<0.001$ all doses). All TZP doses were also superior to IDeg in the proportion of subjects achieving HbA1c <7.0% at Week 52. Among patients taking TZP, 25.8–48.4% achieved HbA1c <5.7% vs 5.4% with IDeg. FSG was significantly reduced ($p<0.001$) from BL to Week 52 in all treatment arms and to a similar extent with TZP 10 and 15 mg vs IDeg. All TZP doses decreased BW from BL to Week 52 while IDeg increased BW. Significantly larger proportion of patients ($p<0.001$) achieved BW loss goals in all TZP arms vs IDeg. The most common AEs in TZP-treated patients were mild to moderate gastrointestinal events. Higher incidence of nausea (11.5–23.7%), diarrhoea (15.4–16.7%), decreased appetite (6.1–12.0%), and vomiting (5.9–10.0%) was reported in patients treated with TZP vs IDeg (1.7%, 3.9%, 0.6%, and 1.1%, respectively). Hypoglycaemia incidence (<3.0 mmol/L [54 mg/dL] or severe) was lower in all TZP arms (1.11–2.23%) vs IDeg (7.26%). One patient in the TZP 15 mg group had one episode of severe hypoglycaemia while receiving 2.5 mg at Day 28.

Conclusion:

In patients with T2D, TZP demonstrated clinically meaningful reductions in HbA1c and BW that were significantly greater vs titrated IDeg at Week 52. TZP was associated with lower incidence of hypoglycaemia.

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The Impact of Glycemic Variability on the Relationship Between Hypoglycemia and HbA1c

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Background/Introduction:

Continuous glucose monitoring (CGM) guidelines suggest a target glycemic variability, as measured by coefficient of variation (CV) ≤36%, to mitigate hypoglycemia in people with type 1 diabetes (T1D). However, they provide no context to hemoglobin A1c (HbA1c) values. The aim of this study was to evaluate the relationship between CV, hypoglycemia, and HbA1c among adults with T1D.

Methods:

A retrospective sample of adults (≥18 years) with T1D from the Barbara Davis Center for Diabetes who had available ambulatory glucose profiles and laboratory-measured HbA1c were analyzed at the patient-visit level between 2014 and 2020. Negative binomial regression of aggregated data over 7 days was used to estimate the number of level-2 (<3 mmol/L [54 mg/dL]) hypoglycemic events at cross-sections of HbA1c and CV for a maximum of 2 weeks, after adjusting for time of CGM use.

Results:

Among 466 adults with T1D (mean age=37 years) at 1,648 visits, percentage of CGM use was 91%. We observed wide variation in level 2 hypoglycemic events across CV and HbA1c categories. The highest mean estimated number of events was 3.5 (95% CI 2.4, 4.6) per week, found in patients with CV >36%, HbA1c <6.5%.

Conclusion:

Glycemic variability (CV) provides meaningful insights about level 2 hypoglycemia that should be used in combination with HbA1c and other factors to inform clinical decision making to help mitigate risk for possible hypoglycemia.

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Screening for hepatic fibrosis using Fibrosis-4 Index (FIB-4 Index) in subjects with type 2 diabetes

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Background/Introduction:

Screening for diabetic complications (i.e., retinopathy, nephropathy) is part of the annual check-up in diabetic patients. Non-alcoholic fatty (NAFLD) liver disease is a frequent comorbidity, especially in subjects with type 2 diabetes (T2DM). In this context it can be interpreted as a diabetes-related end-organ damage. However, in clinical practice there is lack of screening guidelines/procedures regarding NAFLD/hepatic fibrosis in these persons.
The FIB-4 score is a simple, non-invasive serologic scoring system using 4 parameters (age, ALAT, ASAT, platelets) allowing an estimation of hepatic fibrosis grade. A score ≥1.3 indicates possible fibrosis and further investigations are indicated whereas a score ≥3.25 is a strong predictor of advanced fibrosis. This study investigated the use of the FIB-4 index as a screening tool in patients with T2DM.

Methods:

This is a retrospective analysis of data from subjects with T2DM treated at a our outpatient clinic between October and December 2020. Data are presented as mean und standard deviation. A linear regression model with FIB-4 score as response variable and BMI, diabetes duration, basal insulin dose, use of SGLT 2-inhibitors (SGLT 2-i), GLP1-receptor agonist (GLP1-RA), metformin and statin therapy as predictor variables has been carried out. Furthermore, best subset selection has been applied to the linear regression model in order to detect the most influential predictor variables.

Results:

342 patients with T2DM were treated in our outpatient clinic from October to December 2020. In 119 patients, a blood sample was taken with determination of ALAT, ASAT and blood count as part of the annual check-up; these were included in the analysis. 67% of them were men, 33% were women. The mean age was 61.3 (±11.8) years. Mean diabetes duration was 11.49 (±8.6) years and BMI was 31.05 (±5.5) kg/m2. 70.6% of the subjects were treated with insulin,18.5% with SGLT2-I, 37.8% with GLP-1-RA, 55.5% with Metformin and 60.5% with statins.
51 (42.9%) subjects had a FIB-4-score ≥1.3 and 4 (3.4%) had a FIB-4-score ≥3.25.
Linear regression analysis showed that the predictor variable statin therapy had a significant ($p<0.05$) effect on the response variable FIB-4 score. Subjects treated with statins had a significantly lower FIB-4-score. Whereas the other variables (BMI, diabetes duration and type of glucose lowering therapy) didn't show a significant effect.

Conclusion:

The FIB-4 score is frequently elevated in patients with T2DM and thus screening for NAFLD/liver fibrosis should be given importance as part of the annual examination as well as a dedicated hepatologic work-up in persons at risk. In addition, lack of statin therapy is associated with an increased FIB-4 score. This finding is consistent with current studies on the treatment of NASH. Longitudinal studies and larger datasets are needed to support the conclusions.

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Impact of different *NR5A1* variants on the phenotype of DSD patients

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Background/Introduction:

Variations in the *NR5A1* gene, also known as steroidogenic factor 1 (SF1) are amongst the most frequently identified causes of 46,XY and 46,XX disorders/differences of sex development (DSD), and are associated with a broad gonadal and reproductive phenotype. The pathogenic effect of *NR5A1* variants has been widely shown in clinical association studies, however mechanistic proof through *in vitro* studies remain inconclusive and a dominant negative effect for heterozygous variants has not been found. In our SF1next study, we aim to investigate the impact of different *NR5A1* variants on the phenotype of patients in a large international DSD cohort.

Methods:

By May 2021, we have collected genetic information from 75 individuals with disorders of 46,XX or 46,XY gonadal development, disorders of androgen synthesis/action or non-specific disorders of undervirilization, and a genetically defined *NR5A1* variant. Gene variants were identified by single gene analysis, next generation sequencing and/or comparative genomic hybridization array. Variant classification was performed according to ACMG (American College of Medical Genetics and Genomics) guidelines.

Results:

Most individuals (70/75, 93%) had a 46,XY and 5/75 (7%) had 46,XX karyotype. Phenotypes ranged from complete gonadal dysgenesis to undervirilized males in 46,XY individuals, and in 46,XX from ovotesticular DSD to ovarian insufficiency. All but 3 individuals were heterozygous for a *NR5A1* gene variant, and healthy carriers were identified in 70% of the relatives with the same genetic variant (n=40), whereas 30% had a DSD phenotype themselves. We found total of 56 different *NR5A1* variants throughout the whole gene, mostly in the DNA-binding domain (23/56, 41%) and ligand-binding domain of the protein (20/56, 36%). Variants were mostly missense (36/56, 64%), small indels (11/56, 20%) and nonsense (5/56, 9%), although there were also few intronic variants, deletions of exons, and one complete gene deletion. We classified 29/56 (52%) variants as pathogenic, 18/56 (32%) as likely pathogenic and 6/56 (11%) as variants of unknown significance. The remaining three were polymorphisms, categorized as likely benign. So far, we could not identify any clear genotype-phenotype association.

Conclusion:

The presence of heterozygous *NR5A1* variants cannot explain the complex phenotypic variability in our DSD cohort, as individuals with the same *NR5A1* variant present with different clinical characteristics, even within the same family. More than half of *NR5A1* variants were disease-causing and were located in critical functional domains of the SF1 protein. In-depth gene profiling will allow us to identify additional variants or disease modifiers that might explain the broad range of phenotype.

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Short-Term, High-dose Glucocorticoid Treatment does not Reduce Brown Adipose Tissue Activity in Healthy Human Adults - The GlucoBAT-Study

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Background/Introduction:

Brown adipose tissue (BAT) differs significantly from white adipose tissue as it can actively dissipate chemical energy as heat. Active human BAT expends energy and is associated with reduced obesity and improved insulin sensitivity. In contrast, treatment with glucocorticoids leads to weight gain and insulin resistance. Data from in vitro and rodent studies indicate that glucocorticoids inhibit BAT differentiation and activity. The influence of glucocorticoids on human BAT is still contended. Therefore, we investigated the metabolic and functional changes triggered in human BAT after short-term, high dose prednisone exposure.

Methods:

Sixteen healthy male volunteers took part in a double-blind, placebo-controlled, cross-over trial. Participants took 40 mg of prednisone daily or placebo, respectively, over the period of one week. After a washout-period of six weeks the treatment was switched to the other study arm. Metabolic activity of BAT was assessed at the end of each treatment period. In order to activate BAT we used a controlled mild cold exposure of two hours duration. Metabolic activity of BAT was determined by 18-F-FDG-PET/CT. Energy expenditure (EE) during warm and cold exposure was measured by indirect calorimetry. Cold induced thermogenesis (CIT) was defined as the difference in EE between cold and warm temperature. Additionally, we determined the fat fraction of BAT by MRI.

Results:

Sixteen healthy male volunteers took part in a double-blind, placebo-controlled, cross-over trial. Participants took 40 mg of prednisone daily or placebo, respectively, over the period of one week. After a washout-period of six weeks the treatment was switched to the other study arm. Metabolic activity of BAT was assessed at the end of each treatment period. In order to activate BAT we used a controlled mild cold exposure of two hours duration. Metabolic activity of BAT was determined by 18-F-FDG-PET/CT. Energy expenditure (EE) during warm and cold exposure was measured by indirect calorimetry. Cold induced thermogenesis (CIT) was defined as the difference in EE between cold and warm temperature. Additionally, we determined the fat fraction of BAT by MRI.

Conclusion:

Prednisone treatment increased the absolute EE during warm and cold conditions. However, the cold induced increase in EE and the activity of BAT were unchanged. This is contrary to the pre-clinical results in rodents and suggests species-specific mechanisms in BAT regulation.Short-term high-dose exposure to glucocorticoids did not alter BAT activity in healthy human volunteers.

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Transgender care at the University Children's Hospital Bern: experience over the past 7 years

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Background/Introduction:

Gender-dysphoria describes an incongruence between biological sex and gender identity. This occurs typically in people identifying as transgender. Prevalence of transgender in children and adolescents in Switzerland is unknown, but the number of (pediatric) individuals referred to specialized clinics increased considerably in the last decade worldwide, maybe due to better social acceptance and destigmatization of the condition. People with gender-dysphoria often suffer from psychological discomfort and have increased risk of depression, autolesionism, drug abuse and suicide. Therefore, these persons need multidisciplinary care, especially if identified during childhood and adolescence. In first place, expert mental health care professionals elaborate on their needs. Then, other medical specialists provide additional support including hormonal therapy and/or surgical interventions.

Methods:

We reviewed the medical files of patients referred to our specialized center with a suspected diagnosis of transgender (2014-2021) for the following items: age and pubertal stage at referral, history (e.g. age of start of feeling gender incongruent), physical anomalies overall and genital specifically; psychiatric comorbidities; provided treatments, their effects and side effects as well as conformity to current guidelines; number of regrets.

Results:

Over the past 7 years, 57 children and adolescents were referred to our multidisciplinary team and were identified as gender-dysphoric, with an increase in recent years. Of these, 41 (71.9%) had a diagnosis of transgender, with 30 (73.2%) trans males and one (2.4%) non-binary. Two individuals (6.1%) were found with anatomical anomalies due to a difference in sex development and were excluded from further analysis. Of the 41 transgender individuals, 29 (70.7%) received a hormonal therapy. Of this group, psychiatric comorbidities were diagnosed in 15 (51.7%). The average age at first presentation was 13.2 yrs; at average age 15.5 yrs GnRH agonist therapy was started, and at avarage age 16 yrs they received gender-affirming therapy. Two people (6.9%) experienced side effects of the therapy. Four individuals (13.8%) underwent surgical therapy. Two people (6.9%) had second regrets, none of them after surgical interventions.

Conclusion:

Since 2014, we observed in our clinic like worldwide an increase of transgender children and adolescents, who seek specialized care. We provide multidisciplinary services under mandatory guidance of psychological support. In line with current international guidelines, hormonal treatments was offered and claimed by 70%. In our cohort of 29 transgender, two individuals had regrets during first step of hormonal therapy with a GnRH agonist and suffered from no (obvious) persistent damage. The percentage of regrets in our cohort was higher (6.9%) than in the literature (1-2%), but this might be due to the small number of our cohort.

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The changes of thyroid surgery over 6 decades: A retrospective analysis of medical records at the Gemeindespital Riehen from 1929-1979

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Background/Introduction:

In the 20th century, iodine deficiency was prevalent and a frequent indication for thyroid surgery. An archive with the complete historical standardized medical records of about 14'000 thyroidectomies performed at the "Gemeindespital Riehen" from 1929-1989 exists to this day. The goal of this study is to analyze how indication and technique of thyroid surgery have changed over the century, bearing in mind the changing incidence of iodine deficiency after the introduction of iodine supplementation in the wider population.

Methods:

Retrospective analysis of medical records (number of thyroidectomies/year, gender, age, thyroid weight, number of intrathoracic goiters, histology, surgical technique) of all patients thyroidectomized in the following years 1929/1939/1949/1959/1969/1979 was performed. Results are mean±SD.

Results:

A total of 1233 thyroidectomies were analyzed (1929 n=114, 1939 n=240, 1949 n=283, 1959 n=294, 1969 n=180, 1979 n=122). Between 1929 and 1979 female to male ratio of thyroidectomized patients remained high (overall f:m 4.8:1). Goiter size assessed by weight of resected thyroid (1929 160±197g, 1939 136±95g, 1949 107±81, 1959 110±89g, 1969 103±79g, 1979 82±64g; $P<0.0001$), as well as the number of intrathoracic goiters (1929 51%, 1939 42%, 1949 33%, 1959 17%, 1969 17%, 1979 3%; $P<0.0001$) decreased significantly over six decades.
The dominant technique for thyroid surgery was bilobular subtotal thyroidectomy, (1929 81%, 1939 97%, 1949 86%, 1959 92%, 1969 81%, 1979 58%, $P<0.0001$) that was gradually replaced by hemithyroidectomy and total thyroidectomy. Histological diagnosis changed significantly with a predominance of diffuse or multinodular goiters from 1929-1969 ranging from 94-96% and an increase of adenomas and carcinomas (62%) in 1979 ($P<0.0001$).

Conclusion:

This preliminary analysis of this unique historical medical dataset of about 14'000 thyroidectomies documented over decades in a standardized way, provides important insights how the introduction of iodine supplement decreased the average size of goiter and how histology and surgical techniques changed over time.

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Combination of two rare endocrinopathies related to a diffuse large B cell lymphoma (DLBCL): a case report

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Background/Introduction:

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL) accounting for approximately 25 % of NHL cases. The reported prevalence of hypercalcemia in NHL ranges between 7 to 34 %. The aetiology of hypercalcemia in NHL is heterogenous but has most often been attributed to extrarenal production of 1,25-Dihydroxy-Vitamin D (calcitriol), or less frequently, secretion of parathyroid hormone-related protein (PTHrP). The extrarenal calcitriol source remains uncertain but has been postulated to originate from infiltrative macrophages and can be treated with corticosteroids. Adrenal metastases in patients with malignancy and adrenal lymphoma manifestation are common, probably due to a rich sinusoidal supply of the adrenal glands. Involvement of the adrenal glands in patients with NHL occurs in around 4 %. However, the prevalence of adrenal insufficiency (AI) in patients with bilateral metastases or lymphoma manifestation is low (3 – 8 %) with lymphoma being the cause of AI in about 10 % of the cases (lung cancer 35 %, colorectal cancer 20 %, breast cancer 15 %).

Methods:

We describe the clinical presentation, imaging, laboratory findings and short-term follow-up of a patient with DLBCL presenting with hypercalcemia and primary AI due to bilateral adrenal manifestation.

Results:

A 74-year old woman with a newly diagnosed multifocal relapse of a DLBCL was hospitalised because of deteriorated general state, fatigue and anorexia. Laboratory evaluation showed a severe hypercalcemia (3.72 mmol/l). Furthermore, a reduced iPTH (6.4 pg/ml [ref 15 - 65 pg/ml]) and a markedly elevated 1,25-Dihydroxy-Vitamin D (346 pmol/l [ref 48 – 190 pmol/l]) were found, corroborating an increased calcitriol production by the lymphoma as the underlying cause for the malignant hypercalcemia. As immediate treatment, hydration was established with a subsequent administration of methylprednisolone. After normalisation of the calcium level with improvement of the clinical situation, short-term methylprednisolone treatment was stopped. This was followed by adynamia, even though calcium was normalised. Due to the suggestive symptoms, fasting cortisol was measured revealing a pathologically low value of 59 nmol/l. The subsequent ACTH stimulation test confirmed the adrenal insufficiency ($cortisol_{max}$ 117 nmol/l). The clearly elevated ACTH (723 ng/l) accompanied by increased renin values (65 ng/l [ref < 20 ng/l]) with inadequately low aldosterone (53 pmol/l) indicated a primary adrenal insufficiency. The PET-CT scan showed extensive bilateral adrenal manifestation as the cause of the adrenal insufficiency. Hydrocortisone substitution was initiated, leading to an immediate improvement in the health state of the patient.

Conclusion:

NHL may present with various neoplastic and paraneoplastic endocrinopathies. Typical manifestations encompass hypercalcemia, and less frequently adrenal involvement with primary AI. Here we present the rare case of the synchronous occurrence of both of these conditions with delayed diagnosis of AI due to the corticosteroid treatment of the hypercalcemia.

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Prevalence of admission hyponatremia in diabetic patients treated with and without an SGLT2-inhibitor - a cross-sectional study

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Background/Introduction:

Hyponatremia is the most common electrolyte disturbance in hospitalized patients and often reflects a free water excess resulting from a disbalance between water intake and excretion. Sodium/glucose co-transporter 2 (SGLT2) inhibitors mediate their glucose-lowering effect through increased glucosuria, leading to osmotic diuresis and therefore to an increase in water excretion. In a prospective randomized controlled trial in patients with the syndrome of inappropriate antidiuresis (SIAD), we showed that empagliflozin increased plasma sodium concentration more effectively in combination with fluid restriction compared to fluid restriction alone. We hypothesized that long-term therapy with SLGT2 inhibitors reduces the prevalence of hyponatremia in hospitalized patients.

Methods:

In this retrospective analysis, we extracted data from adult patients with type 2 diabetes, hospitalized at the University Hospital Basel between 2015 and 2020, who had an available plasma sodium measurement in the first 24 hours following admission. Patients with an SGLT2 inhibitor on admission were matched 1:1 according to age (+/- 5 years), gender, diagnosis of heart failure and ICD-10-GM chapter of principal diagnosis at discharge, to patients without an SGLT2 inhibitor on admission. We computed hyponatremia prevalence on admission as the first plasma sodium measurement in the 24 hours following admission. The statistical analysis was performed once with the raw plasma sodium values and once with plasma sodium values corrected for glucose. The primary outcome was the prevalence of hyponatremia in the first 24 hours following admission in patients with type 2 diabetes with an SGLT2 inhibitor compared to patients without an SGLT2 inhibitor.

Results:

We analyzed 1008 diabetic patients treated with and 1008 diabetic patients without an SGLT2 inhibitor on admission. Hyponatremia prevalence on admission was 16.4% in the treated group, and 15.2% in the matched control group (p=0.5015), i.e. the risk for hyponatremia did not differ (OR 1.09; 95%-CI 0.85-1.40; p=0.5015). There was no difference in the median [IQR] plasma sodium concentration between both groups (treated: 138 mmol/L [136-141], controls: 138 mmol/L [136-140]; 95%-CI: -7.87-4.5; p=0.269). Plasma glucose was available for 821 (81.5%) treated patients and 774 (76.8%) matched controls. Glucose-corrected hyponatremia prevalence on admission was 9.9% in the treated group, and 7.2% in the matched control group (p=0.1812), i.e. the risk for hyponatremia did not differ (OR 1.29; 95%-CI 0.97-2.04; p=0.07346). There was no difference in the median [IQR] corrected plasma sodium concentration between both groups (treated: 140 mmol/L [138-142], controls: 140 mmol/L [138-142]; 95%-CI: -0.000032-0.000054; p=0.4228).

Conclusion:

Based on these retrospective findings SGLT2 inhibitors do not prevent from hyponatremia development. Prospective randomized data suggest their efficacy at a higher dosage in overt SIAD, but their efficacy in other hyponatremia subtypes remains to be demonstrated.

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Canakinumab in patients with COVID-19 and Type 2 Diabetes, the CanCovDia Trial

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Background/Introduction:

Patients with a metabolic syndrome have a particularly bad outcome if infected with SARS-CoV2. This may be explained by an over-activation of the IL-1β System. Indeed, metabolic stress (increased glucose and lipid levels) induces NLRP3-mediated IL-1beta secretion. SARS-CoV2 also activates NLRP3. We hypothesized that Canakinumab (Ilaris®, Novartis), an antibody inhibiting IL-1β, improves outcome of hospitalized overweight patients with type 2 diabetes affected by COVID-19.

Methods:

In this randomized, placebo-controlled, double-blind trial 116 overweight or obese patients with type 2 diabetes hospitalized for COVID-19 in 7 different hospitals across Switzerland were treated with Canakinumab (450 to 750 mg depending on bodyweight) or placebo additionally to standard of care at the discretion of the site clinicians. Patients were enrolled between October 2020 and May 2021. Eligible patients were randomly assigned (1:1) in block sizes of 2 and 4 through an electronic data record system without stratification. The primary outcome was the unmatched win ratio determined by the ordered components: longer survival time, longer ventilation-free time, longer ICU-free time, shorter hospitalization time within 4 weeks after treatment with canakinumab compared to placebo.

Results:

The last study visit (90 days after randomization) for the last patient is planned around the 12th of August 2021. We expect to present the first results at the conference.

Conclusion:

Will depend on the results.

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Persistent gynecomastia and hypospadia in an adolescent - think twice

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Background/Introduction:

A 15-year old boy presented with gynecomastia. Surgical correction of a penoscrotal hypospadia and urethral reconstruction was performed in infancy. First pubertal signs were observed at the age of 11.5 years. His past medical and family history was otherwise uneventful with normal development. The patient's height (+1.26 SDS) and body mass index (+ 0.55 SDS) were within normal range and within familial target height. At present, penile length was 6 cm (< -2.5 SDS), Tanner stage P5 G4 and testicular volume 12 ml. His gynecomastia has persisted for more than three years at Tanner stage B3.

Methods:

Blood values for testosterone, dihydrotestosterone, androstendione, LH, FSH, beta-HCG, estradiol and estron were measured. Steroid profile was determined in urine collected for 24 hours. Genetic sequencing of the androgen-receptor (AR) gene was done. DNA- and PCR-sequence analysis included all exon and intron regions of the AR gene.

Results:

Laboratory analysis revealed initially normal values for beta-HCG (<0.5 U/l; N <5), estradiol (<18.4 pmol/l; N <56), dihydrotestosterone (1.35 nmol/l; N 1-10) and FSH (4.5 U/l; N 1.26-7.4). Estron was elevated (99 pmol/l; N <48). Testosterone (27.4 nmol/l; N 2.5-5.3), androstendione (3.2 nmol/l; N 0.7-1.8) and LH (10.9 U/l; N 0.81-8.96) were repeatedly above the normal range for age. Testosterone/DHT ratio 21 (N <8.5) was increased. The 24 h-urine steroid profile showed no defect in steroid hormone biosynthesis and 5-alpha reductase deficiency was excluded. The androgen sensitivity index (product of testosterone and LH) was elevated with (298.7; N <138) . Partial androgen sensitivity syndrome (PAIS) was suspected and genetic sequencing analysis of the AR gene performed. Two known pathogenic variants c.1174C>T (p.Pro392Ser) in exon 1 and c.2270A>G (p.Asn757Ser) in exon 5 were found confirming the diagnosis of PAIS in our patient.

Conclusion:

Variable phenotypes of PAIS were reported for the AR variant p.Pro392Ser. The cause of this phenotype variability is unknown. Previously, an association of p.Pro392Ser with isolated gynecomastia was described . We hypothesize that the additional p.Asn757Ser variant is responsible for the more severe presentation in our patient.

Alterations in cortical grey matter volume in adults with early-treated phenylketonuria

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Background/Introduction:

Despite strict dietary adherence, the gold-standard treatment of phenylketonuria (PKU) seems unable to prevent damages to the white matter of the brain. However, only few studies investigated the impact of PKU on brain grey matter (GM) with results mostly showing GM volume decreases in parietal brain regions. We therefore aimed to investigate cortical GM volume in adults with PKU and their relationship to concurrent metabolic parameters and cognitive functions shown to be prone to alterations in PKU.

Methods:

Twenty-one adult patients with early-treated PKU and 49 healthy controls of comparable age, sex, and education were included. Structural T1-weighted magnetic resonance images were acquired and analysed with FreeSurfer. Subsequently, performance in general intelligence, attention, and working memory was assessed. In patients only, concurrent plasma phenylalanine and tyrosine levels were measured.

Results:

Patients showed significant decreases in cortical volume of frontal and parietal brain regions. Within the parietal lobes, GM volume of the superior parietal lobe was most decreased compared to controls (left: $F(1,66)=5.04$, $p=.028$, right: $F(1,66)=6.59$, $p=.013$). Within the frontal lobes, the lateral orbitofrontal cortex showed most pronounced volume reductions (left: $F(1,66)=8.49$, $p=.005$; right: $F(1,66)=7.64$, $p=.007$). Neither cognitive performance nor phenylalanine and tyrosine levels correlated with frontal and parietal GM volume.

Conclusion:

As indicated by recent findings, we located GM volume decreases in the parietal lobe of adults with PKU. Notably, we also found frontal brain regions to be affected by the disease. GM volume reductions might be more widespread than originally anticipated, but neither related to concurrent metabolic parameters nor cognitive performance.

Audit of Extending Rapid On-Site Evaluation to all Thyroid Fine Needle Aspirations

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Background/Introduction:

Most studies have shown that rapid on-site evaluation (ROSE) of thyroid fine needle aspirations (FNAs) can significantly reduce the rate of nondiagnostic Bethesda category I results. However, there is insufficient data on whether ROSE is also able to reduce the rate of Bethesda categories III and V. In particular, it is unclear whether ROSE is able to improve the quality of the smears. Before April 2019, physicians at the Inselspital Bern included ROSE only for repeated FNAs. Since April 2019, the Interdisciplinary Thyroid Clinic of the Inselspital Bern provides ROSE as a standard of care for all thyroid FNAs. We aimed to assess the influence of this change in practice on the clarity of cytological diagnosis and specimen quality.

Methods:

We conducted a retrospective study including 5030 FNA of thyroid nodules taken between January 2015 and December 2020. Cytology specimens were categorized according to the Bethesda classification. In addition, we separately analyzed if nondiagnostic Bethesda I results were due to too low cellularity or due to artifacts. Furthermore, we differentiated Bethesda III and Bethesda V results into cellular without artifacts, sparsely cellular or artifacts. Artifacts were defined as heavy bloodstaining or preparation artifacts that impaired evaluation. We hypothesized that ROSE reduces the rate of Bethesda categories I, III, and V and, in turn, increases benign and malignant cytological diagnoses (Bethesda category II and VI, respectively). We assume that this is due higher rates of satisfactory cellularity on the one hand, and due to a decrease in artifacts on the other.

Results:

3726 aspirates were taken without ROSE and 1304 were taken with ROSE. FNAs with ROSE not only showed a significant lower nondiagnostic Bethesda I rate, but also a significant reduction of Bethesda III category. Combined, they decreased the need for a repeated FNA by a factor of 9.3 (non-ROSE 39.9 % *vs*. ROSE 4.3 %). With ROSE, Bethesda III and V results were less likely to be sparsely cellular compared to without ROSE. Moreover, ROSE was also associated with a significantly 8.3 times lower rate of artifacts obstructing Bethesda I, III, and V cytologies (non-ROSE 2.5 % *vs*. ROSE 0.3 %). The better diagnostic conclusiveness with ROSE not only resulted in an increase in benign Bethesda II results (non-ROSE 51.1 % *vs*. ROSE 86.5 %), but also doubled the rate of malignant Bethesda VI cytologies (non-ROSE 2.6 % *vs*. ROSE 5.1 %).

Conclusion:

ROSE was able to generate more diagnostically conclusive FNAs and can be seen as a valuable addition to FNAs of thyroid nodules. We therefore recommend the implementation of ROSE as standard of care, especially in institutions where less than 90 % of specimens are categorized as either benign (Bethesda II) or malignant (Bethesda VI).

Cognition and metabolic parameters in early-treated adult patients with phenylketonuria

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Background/Introduction:

A low-protein diet is currently the best available treatment for patients with phenylketonuria (PKU). However, rigid adherence to this diet cannot prevent subtle cognitive impairments. We aimed to investigate the cognitive performance in adult patients with early-treated PKU and its relationship to concurrent phenylalanine (Phe) and tyrosine (Tyr) levels as well as Phe:Tyr ratio.

Methods:

Twenty-one adult patients with early-treated PKU and 50 healthy controls of comparable age, sex, and education were included. All participants underwent a neuropsychological assessment including IQ, working memory, cognitive flexibility, divided attention, sustained attention, and alertness. On the same day, blood Phe and Tyr levels were assessed in patients after an overnight fast.

Results:

Patients displayed lower IQ ($z=-2.68$, $p=.007$) and lower accuracy in the working memory task ($F(1,68)=13.60$, $p=.0004$) as well as worse sustained attention ($F(1,68)=13.82$, $p=.0004$) compared to controls. In patients, none of the cognitive measures correlated with concurrent Phe levels or Phe:Tyr ratio. Fluctuations in reaction times during the alertness task, however, were negatively correlated with Tyr levels ($r=.-59$, $p=.006$).

Conclusion:

Our findings add to a growing body of literature on abnormalities in attention and executive functioning in adult patients with early-treated PKU. Interestingly, concurrent Phe levels and Phe:Tyr ratio were not related to cognitive performance, whereas Tyr levels negatively correlated with alertness. Overall, the present results support the shift away from concurrent Phe levels towards other metabolic parameters such as Tyr or lifetime blood Phe levels as predictor for cognitive performance.

Systematic evaluation of transition to a hybrid closed-loop system - individuals with poorer glycemic control benefit the most

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Background/Introduction:

The goal of the present analysis was two-fold: First, to systematically assess and compare glycemic control before and after transition to the hybrid closed-loop system (HCL) MiniMed 670G (Medtronic) in patients treated at our tertiary referral center. Second, to examine whether prior HbA1c has an influence on glycemic outcomes after switch to HCL treatment.

Methods:

We retrospectively screened all 65 adult patients changing to HCL between 11/2018 and 03/2020 at our center within a structured training program. Patients were included in the analysis, if (1) a 30-day CGM period with at least 50% sensor use before and after transition was available, with the “after period” being in-between 1.5 and 9 months after change, and (2) with a corresponding HbA1c value for both periods. We collected diabetes history and HbA1c values from medical records. CGM data were analyzed with the open-source Glyculator-2 script. Variables prior and post switch were compared using paired t-test. Based on the HbA1c value before transition, patients were divided in two groups (>7% and ≤7%) and between-group changes in glucose control compared using unpaired t-test. Association between prior HbA1c values and CGM metrics were further assessed using a linear regression. Results are presented as mean±SD.

Results:

Forty patients (39 T1DM, 1 pancreatogenic DM; 28 male; age 38.9±14.1y) were included. Insulin therapy before transition was performed with CSII in 38, and MDI in 2 patients. Mean sensor use before and after transition was 79.1±14.5% and 82.8±14.2% (p=0.024), respectively. Mean time spent in HCL automatic mode was 74.0±27.6%. CGM data prior and post switch to HCL showed an increase of time in range (TIR, 60.3±19.9% vs 70.0±12.8%, p=0.000), decreasing time above range (TAR, 36.6±21.1% vs 27.3±13.6%, p=0.000), mean glucose (9.4±2.1mmol/l vs 8.6±1.1mmol/l, p=0.001) and coefficient of variation (CV, 36.4±5.8% vs 33.4±5.3%, p=0.001), whereas time below range did not differ (TBR, 3.2±2.9% vs 2.7±3.0%, p=0.216).
Patients with baseline HbA1c >7.0% (n=20) showed greater improvements after transition to HCL compared to those with HbA1c ≤7.0% (n=20) with regard to TIR (+16.1±12.5% vs +3.5±6.7%, p<0.001), TAR (-15.4±12.1% vs -3.2±7.0%, p<0.001) and mean glucose (-1.6±1.5mmol/l vs -0.1±0.6mmol/l, p<0.001). No differences were found for TBR (-0.7±2.7%, vs -0.3±2.3%, p=0.673) and CV (-2.7±6.1% vs -3.3±3.7%, p=0.712). Linear regression revealed a 6.5% increase of TIR for every 1% increase in HbA1c prior to transition (p<0.001).

Conclusion:

Overall, transition to the HCL system resulted in a significant improvement in glucose control without increasing the risk of hypoglycemia. Patients with moderate to poor glycemic control before switch (HbA1c >7%) benefited more from HCL therapy than well-controlled patients (HbA1c ≤7.0%) with regard to TIR and TAR, whereas well controlled individuals profited mainly from reduced glycemic variability.

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Precision medicine in diabetes: A non-invasive prenatal diagnostic test for the determination of fetal glucokinase mutations

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Background/Introduction:

Diabetes caused by mutations in the glucokinase gene, *GCK,* is the most common form of monogenic diabetes. *GCK* diabetes represents the cause of gestational diabetes in 1% to 2% of affected women. The fetal *GCK* genotype impacts on treatment recommendations, which differ from other causes of gestational diabetes. Non-affected fetuses are prone to excessive weight gain due to the hyperglycemic maternal environment and exposed to the risk of macrosomia and related complications. By contrast, an affected fetus will present with a normal weight gain, because of a higher threshold to elicit adequate insulin secretion. Maternal insulin treatment is thus only recommended to prevent or in the presence of fetal signs for macrosomia, but this may not always be reliable. So, the aim of our study was to develop a monogenic non-invasive prenatal diagnostic (NIPD-M) test to determine fetal genotype.

Methods:

Here we apply "relative haplotype dosage" (RHDO) analysis to non-invasive prenatal diagnostic (NIPD) of *GCK* mutations at distinct time points during pregnancy. The method relies on allelic imbalance caused by small amounts of fetal circulating cell-free DNA (ccfDNA) in maternal ccfDNA. The allelic balance is 50:50 in a heterozygous mother carrying a heterozygous fetus, but becomes skewed if the fetus is homozygous wild-type. The low abundance of circulating DNA makes it difficult to achieve significance by testing only the mutation, therefore RHDO queries adjacent single nucleotide polymorphisms (SNPs) to increase statistical power.

Results:

The analyses were performed at different timepoints, to test several fetal DNA fractions (FF), as they increase in maternal plasma with the advancement of pregnancy. In three pregnancies of two families with known maternal *GCK* mutations, we unambiguously determined the fetal genotype already at 12 weeks of gestation, confirmed by cord blood analysis.

Conclusion:

We provide proof of feasibility for NIPD-M in *GCK* diabetes. This new test can now be used in a diagnostic manner in pregnancies, to introduce precision treatment of maternal diabetes during pregnancy avoiding serious side effects, such as a reduction in birth weight of affected fetuses or severe maternal hypoglycemia (present in 23%). The proposed technique can be applied to diagnose any *GCK* mutation or deletion and can be adapted for other monogenic diabetes genes, but needs access to DNA from a sibling.

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Use and Perception of Telemedicine in People with Type 1 Diabetes during the COVID-19 Pandemic: A One-Year Follow-Up

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Background/Introduction:

In the spring of 2020, our research group circulated a worldwide survey with the aim of gathering information on the use and perception of telemedicine in people living with type 1 diabetes (T1D) at the start of the COVID-19 pandemic. The data suggested that a large number of respondents had rapidly adopted telemedicine, as in-person visits were not possible, and that this was perceived positively by many. Here, we conducted a 1-year follow-up to investigate changes in opinions and experiences to telemedicine over the last year of the pandemic, and to explore the respondents' expectations for the future of telemedicine.

Methods:

An anonymous questionnaire was widely distributed via social media (Twitter, Facebook and Instagram) between 9th and 15th May 2021 using an open-access web-based platform (SurveyMonkey.com). The survey was identical to that used in the original study, covering questions relating to the use and perception of telemedicine, diabetes treatment and control, and medical supplies during the COVID-19 pandemic. The questionnaire was available in English, Spanish, German, French and Italian. Data were analysed descriptively and results were stratified according to age, sex and HbA1c.

Results:

There were 531 survey responses from 40 countries (54% in Europe, North America 36%, South America 2%, and 2% from Africa and Asia). A large percentage of respondents (67%) reported meeting with their healthcare provider remotely since the beginning of the pandemic, with a further 4%, who have not yet had a remote appointment, planning to have a remote appointment in the future. Remote appointments were most frequently undertaken via telephone (50%) and video call (45%). Eighty-three percent of respondents found remote appointments to be somewhat-to-extremely useful. Forty-five percent of respondents were likely to consider remote appointments instead of in-person appointments in the future, whereas 37% indicated they would not. The majority of respondents (84%) reported no issues in their access to diabetes supplies and medication over the past year.

Conclusion:

This study suggests that telemedicine in the form of remote appointments was widely adopted by people living with T1D due to the COVID-19 pandemic. Almost half of the survey respondents stated a willingness to continue with remote appointments beyond the pandemic. However, the large proportion of respondents stating a preference for in-person diabetes care, suggests the use of telemedicine should be considered on an individual basis.

Feasibility and Usability of a Novel Home-Based Exergame Prototype

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Background/Introduction:

Due to a number of exercise barriers as well as the COVID-19 pandemic, there is a greater need and desire for alternative exercise options to help combat rising levels of physical inactivity. Exergames, games controlled by active (whole) body movements, have been suggested as potentially attractive and effective training tools. One exergame that demonstrably fulfils this is the ExerCube (by Sphery Ltd), a physically immersive and adaptive functional fitness game originally developed for use in gyms. The development of a home-based version of the ExerCube would increase accessibility to the system, reduce major barriers to exercise and provide an attractive solution to improve cardio-metabolic health. The present study aimed to evaluate the usability and feasibility of the early stage prototype of the newly developed fitness exergame.

Methods:

This project consisted of two visits in which 15 healthy, young participants (age: 25 ± 3 yrs) completed four 5-minute exergame sessions. In each session, the system provided a different level of feedback to the participant (light, vibration and/or sound feedback). After the second visit, participants completed several questionnaires, including; the system usability scale (SUS), physical activity enjoyment scale (PACES), flow short scale (FSS), immersive experience questionnaire (IEQ) and rated their perceived exertion (RPE) both physically and cognitively (adapted scale ranging from 1-10). Participants also answered questions regarding the feedback system and completed a semi-structured interview.

Results:

Usability of the exergame was acceptable, with a SUS score of 70.5 ± 11.6. Questionnaires revealed medium to high values for training experience (FSS: 5.3 ± 1.4; PACES: 5.3 ± 1.4; IEQ: 145.2 ± 23.7). Furthermore, participants perceived their exertion during training as moderate (RPE physical: 4.8 ± 1.6; RPE cognitive: 3.9 ± 1.5). The interviews revealed that the majority of participants liked the combination of vibration and sound feedback the best. Participants enjoyed the distinct perceptibility, processing and integration in the exergame setting of this feedback variation, as well as its supportive and motivating effect. The light feedback was less perceived by participants but was still classified as potentially helpful. The sound feedback variation was noticed clearly, but requires further development. In addition, the participants enjoyed the training experience, describing it as motivating, interactive, immersive, something new, fun, interesting, self-explanatory as well as physically and cognitively challenging. Sixty-seven percent of participants could imagine exercising at home and continuing to play the exergame in the future.

Conclusion:

The home-based fitness exergame prototype demonstrated a high level of usability and feasibility for a young, healthy population. Promising avenues emerged for future design iterations of the home-based fitness exergame prototype.

Effects of Interleukin-1 Receptor Antagonism on Hyperandrogenemia in Women With Polycystic Ovary Syndrome

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Background/Introduction:

Polycystic Ovary Syndrome (PCOS) is the most prevalent endocrine disorder in women of reproductive age. The main components are hyperandrogenemia and oligo-/amenorrhea. The pathophysiology of PCOS is not fully understood which is why no causal treatment options are available. A multitude of observational studies demonstrated elevated C-reactive protein (CRP) levels in patients with PCOS compared with weight-matched controls. CRP is a sensitive marker for the proinflammatory cytokine Interleukin-(IL)-1. IL-1 stimulated ovarian androgen production and impaired gonadotropin signaling and fertility in experimental studies. In clinical studies, therapeutic IL-1 blockade had beneficial effects on cardiometabolic health. The aim of this study was to investigate whether IL-1 blockade ameliorates hyperandrogenemia in patients with PCOS.

Methods:

This is a prospective, interventional, single-arm, proof-of-concept trial. Seventeen patients with PCOS and C-reactive protein (CRP) levels ≥1 mg/l were treated with 100 mg of the IL-1 receptor antagonist anakinra daily for 28 days. The primary endpoint was change in serum androstenedione levels on day 7 of treatment, assessed with liquid chromatography-tandem mass spectrometry. Secondary endpoints included changes in serum androgen concentrations, pituitary-gonadal axis hormones, and clinical parameters on treatment days 7, 14, 21, 28, and one week after end of treatment.

Results:

Treatment with anakinra reduced CRP levels on days 7, 21, and 28 ($p<0.001$). It increased serum androstenedione levels by a median (IQR) of 0.6 (0.2, 1.7) nmol/l to day 7 ($p=0.008$). Serum testosterone as well as dihydrotestosterone levels increased from baseline to day 7 (both: $p=0.03$). Estradiol levels were increased during the first three weeks of treatment ($p=0.02$), which was followed by a menstrual bleeding in five patients of which three were previously oligo-/amenorrheic. There was no overall change in gonadotropins or other clinical parameters.

Conclusion:

We conclude that chronic low-grade inflammation is regulated by IL-1 in PCOS as evidenced by a reduction of circulating CRP levels upon anakinra. Short-term IL-1 blockade increased steroidogenesis which resulted in the induction of an ovulatory cycle in 5 women. This data is reassuring to conduct a next randomized placebo-controlled long-term trial with menstrual cyclicity as primary endpoint.

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Hyperammonemia is an underdiagnosed prognostic complication in neuroendocrine neoplasm patients with liver metastases

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Background:

Neuroendocrine neoplasms (NEN) are rare usually slow-progressing tumors, often presenting with extensive liver metastases. Hyperammonemia due to insufficient hepatic clearance has been described in NEN cases, however no systematic evaluation of risk factors and outcomes of NEN-associated hyperammonemia exists so far.

Method:

Case report and retrospective review of NEN patients developing hyperammonemia from the years 2000-2020 at the Erasmus Medical Center in Rotterdam, the Netherlands.

Results:

44 NEN patients with documented hyperammonemia were identified. All patients had liver metastases with 30% (n=13) showing signs of portal hypertension. Patients who developed hepatic encephalopathy had higher median ammonia levels, but there was no association between the severity of hyperammonemia and liver tumor burden or presence of liver insufficiency.
84% (n=37) of patients died during follow-up. Hyperbilirubinemia, hypoalbuminemia, elevated INR, presence of liver insufficiency, hepatic encephalopathy and ascites were associated with worse outcome. Their role as independent risk factors for mortality was confirmed using the Child-Pugh score as a summary factor ($p<0.001$).
Patients with hyperammonemia had a shorter median overall survival (95% CI) of 56 months (38-73) compared to 131 months (81-180, $p=0.014$) of a control stage IV NEN cohort without hyperammonemia.

Conclusion:

Hyperammonemia comprises an under-recognized complication of NEN liver metastases and is associated with worse outcome. Child-Pugh scoring could be helpful in selecting patients for whom ammonia levels should be measured.

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Specific glucagon quantification in post-bariatric hypoglycaemia patients and controls using liquid chromatography tandem mass spectrometry and analytical comparison with a reference immunoassay

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Background/Introduction:

Glucagon is a peptide hormone which is crucially involved in the counter-regulation to hypoglyceamia. Thus, reliable quantification of glucagon is required to decipher its potential pathophysiological role in dysglycaemic disorders. However, its concentrations in the low picomolar range, proteolytic processing and the presence of several glucagon-like sequences in other gut peptide hormones impose high demands on sensitivity and specificity of analytical methods. Consequently, existing work of glucagon measured with unspecific assays has led to considerable debate and controversy. Recently, a presumably high-specificity glucagon ELISA has been developed which ideally should match the gold-standard method of liquid-chromatography tandem mass spectrometry (LC-MS/MS). Here, we describe an LC-MS/MS assay to evaluate the glucagon response to induced postprandial hypoglycaemia and compare its performance with the Mercodia ELISA.

Methods:

We have optimized a fast solid phase extraction (SPE) combined with LC-MS/MS analysis for glucagon quantification. For method comparison, glucagon ELISA (Mercodia,10-1271-01) including an additional washing step, was used. Samples were collected in 4 subjects (2 post-gastric bypass patients and 2 controls) fasting, 90min following glucose intake (15g) and after 10min of induced hypoglycaemia (2.5mM).

Results:

LC-MS/MS method LLOQ was established at 2pM (CV<20%). Whereas glucagon levels in both post-gastric-bypass and healthy subjects were comparable during fasting and in the postabsorptive state (4.4 vs 6.1pM and 3.3 vs. 4.0pM), concentrations during hypoglycaemia differed remarkably. At identical glucose levels of 2.5pM, glucagon values in post-gastric patients were 4-times lower than those in matched healthy controls (7.6 vs 27 pM) suggesting potent glucagon-inhibitory mechanisms in post-gastric bypass patients. Measurements by the ELISA from Mercodia provided concordant results. The high degree of agreement between both methodologies was evidenced by Deming regression analysis with a slope of >0.9 and a Spearman's correlation coefficient of >0.95.

Conclusion:

This highly optimized and rapid LC-MS/MS method provides an accurate and specific quantification of dysregulated glucagon responses and achieves results comparable to the best available commercial immunoassays currently employed with an additional wash.

Autoimmunity and Cancer: when goiter turns into lymphoma

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Background/Introduction:

Primary thyroid lymphoma (PTL) is a rare neoplasm comprising of 1-5% of thyroid malignancies and 1-7% of all extra nodal lymphomas. Even if not common, some factors, such as autoimmune diseases, can increase the relative risk. One of these autoimmune diseases is Hashimoto's thyroiditis, the main cause of primary hypothyroidism, especially in geographic areas with low iodine intake (prevalence 5-15 % in women and 1-5 % in men).
Epidemiological studies confirm an etiologically important role of Hashimoto's thyroiditis in the development of thyroid lymphoma: it significantly increases the relative risk, even though lymphoma is present in only 0.5% of cases.

Methods:

Case report

Results:

We report a case of a 44-year-old woman, who presented to the emergency room with neck swelling and an important dysphagia. The blood test showed high TSH levels (39.6 mU/L), low fT3 and fT4 level and the presence of TG and TPO antibodies. Thyroid ultrasound detected a large nodule in the right lobe with characteristics of malignancy (ill-defined margin, irregular shape and heterogeneity). FNA biopsy of the nodule was negative for malignant cells but was described as lymphocytic thyroiditis. The patient was diagnosed with Hashimoto's thyroiditis and started the thyroid hormone replacement therapy.
Six months later, the patient presented a further enlargement of the gland and worsening of dysphagia and surgeons decided for a total thyroidectomy. Histopathology report diagnosed a diffuse large B-cell lymphoma (DLBCL), GCB subtype, with lymphocytic thyroiditis. Whole Body PET/CT detected a lymphoproliferative disease with a high metabolic rate in multiple localizations in the gastric and supra- and infra-diaphragmatic nodal area. Gastroscopy with biopsy confirmed the DLBCL metastases in the gastrointestinal area.
In the five following months the patient received 6 cycles of R-ACOD immunochemotherapy and a consolidation radiotherapy. After that, PET/CT showed a complete metabolic response.
Therefore, after five months there was a progression of the disease with perforation of jejunal loop; the patient underwent a surgical resection of the segment and the histological report confirmed DLBCL, so she started other cycles of chemotherapy according to the R-GDP scheme. Unfortunately, the therapy increased the fragility of the intestinal loops and after just one cycle she suffered a second intestinal perforation, this time of ileal loop which was surgical repaired.

Conclusion:

This case underlines how common conditions can predispose to rare diseases with severe complications. In this type of patients, it is important to ensure serious follow-up and to keep clinical suspicion high as new signs and symptoms arise. Further studies are needed to understand the pathophysiology of lymphomas in autoimmune diseases, since several studies highline the incidence of B-cell lymphomas, not only in Hashimoto thyroiditis, but also in other autoimmune diseases such as Sjögren syndrome and rheumatoid arthritis.

Critical Analysis of the Value of Bilateral Inferior Petrosal Sinus Sampling

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Background/Introduction:

Previous studies have shown inconsistent results about the usefulnes of bilateral inferior petrosal sinus sampling (BIPSS) in the evaluation of ACTH-dependent Cushing's syndrome. Even if the examination per se can relatively reliably differentiate between central and ectopic ACTH overproduction, this does not necessarily translate in a helpful influence in the individual patient.

Methods:

Retrospective chart review of all patient found to have undergone BIPSS at the Inselspital, Bern University Hospital, between 1996 and 2019 (and 1 patient 1989). The primary question was how often BIPSS positively influenced the further therapeutic procedure. In addition, lateralization predicted by BIPSS was compared to histology of pituitary exploration.

Results:

BIPSS was carried out in 49 patients, age mean±SD 45±13 years. The rate of successfully performed samplings was 88 % (n=43). 6 % (n=3) of unsuccessful examinations were due to complications and the remaining 6 % (n=3) were based on technical difficulties.
Of the 49 patients examined, there was a successful therapeutic consequence through BIPSS in 8 % (n=4) of patients, while 22 % (n=11) showed doubtful value of the examination. For the remaining 69 % (n=34) no helpful influence on the clinical approach could be established.
After pituitary exploration in 45 of the 49 patients, a correct BIPSS-result concerning lateralization of the tumor could be verified histologically in 40 % (n=18) of patients. Other 29 % (n=13) showed a doubtfully correct or unknown BIPSS-lateralization in comparison with histology, while in the remaining 31 % (n=14) the lateralization predicted by BIPSS was incorrect.

Conclusion:

BIPSS was only rarely associated with a helpful impact on the clinical approach in ACTH-dependent Cushing’s syndrome. Further, BIPSS showed dissatisfying accuracy in terms of lateralization when compared to the histology results after pituitary exploration. A better diagnostic method is clearly needed to help the affected patients.

Attitudes and Expectations of Patients on Home Parenteral Nutrition Towards eHealth

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Background/Introduction:

eHealth denotes the use of electronic tools in healthcare to improve processes and connect patients and health care personnel. We are developing an eHealth platform for home parenteral nutrition (HPN) patients, including video consultations, instructions (e.g. for patient education), and interaction with patient support groups. In addition, this platform will serve as a central repository for treatment- and care-related data for patients and medical staff. For the creation and implementation of such an eHealth platform, we need to know the attitudes and expectations of HPN patients towards eHealth.

Methods:

We conducted an anonymous survey on the attitudes and expectations of HPN patients towards eHealth. We interacted with patients in person or by phone. The questionnaire consisted of 18 questions on HPN care, familiarity and experience with digital devices, attitudes and expectations towards video consultations and other components of the intended platform.

Results:

We included 25 HPN patients (60% females) looked after by two different HPN centers. Mean (SD) age was 55 (14) years and median (range) duration of HPN was 305 (29-4528) days. A majority of participants (n=21, 84%) reported using a smartphone, tablet or computer and 16 (64%) rated their digital skills as proficient. Almost half of the participants (n=11, 44%) found it cumbersome to go to the hospital for follow-up visits and 19 (76%) were open to video follow-up visits. Easy operation of the platform was important to 16 participants (64%). The following proposed components of the platform were most frequently rated as important: Videoconferencing with physicians (n=20, 80%) and dieticians (n=19, 76%), checklists for PN, catheter and pump handling, data collection and storage, and data protection (n=20, 80%). Participants most frequently rated the collection and storage of the following data as important: Weight (n=24, 96%), infusion plan and administration detals (n=23, 92%), medication plan and intake (n=22, 88%), laboratory parameters (n=21, 84%), blood pressure, catheter photos, pain, nausea, other test results (n=20, 80%), stool frequency and consistency, and reports from different hospitals/practices (n=19, 76%).

Conclusion:

HPN patients are open towards an eHealth platform for care support, including video follow-up visits. This is especially useful in a pandemic. Important criteria for the design of the eHealth platform were identified and confirmed by HPN patients. We plan a validation study to evaluate the benefits of follow-up visits via videoconferencing versus in person usual care in those patients.

Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

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Background/Introduction:

Various nutritional therapies have been proposed in rheumatoid arthritis, particularly diets rich in ω-3 fatty acids, which may reduce eicosanoids. Our primary objective was to investigate the effect of anti-inflammatory diets (Mediterranean, vegetarian, vegan, ketogenic) on pain.

Methods:

The primary outcome was visual analogue scale (VAS) pain score. Secondary outcomes were C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), health assessment questionnaire (HAQ), tender joint count (TJC), swollen joint count (SJC), weight, and body mass index (BMI). We searched MEDLINE via OVID and Embase via Elsevier for studies published from database inception to 10 May 2021. We included studies on the effect of these diets on pain in adults with rheumatoid arthritis and excluded studies with non-whole diet interventions. Two authors independently assessed studies for inclusion, extracted study data, and assessed the risk of bias with the RoB 2 and the ROBINS-I tool. We performed a meta-analysis with all included randomized controlled trials (RCTs) using RevMan 5. We used mean differences or standardized mean differences and the inverse variance method of pooling using a random-effects model.

Results:

The search retrieved 85 unique publications, of which we included 11 in the systematic review and 6 in the meta-analysis. No study investigated the effect of a ketogenic diet. Studies in the meta-analysis included mostly female patients (92%) with a mean age between 47 and 58 years. Compared with patients on their ordinary diets, patients on anti-inflammatory diets had significantly lower VAS pain scores (-9.32, 95% CI -15.07 to -3.56; p=0.002; 6 RCTs, 271 participants), improved HAQ (-0.22, 95% CI -0.40 to -0.03; p=0.02; 3 RCTs; 147 participants), lower SJC (-0.60, 95% CI -1.08 to -0.11; p=0.02; 4 RCTs; 214 participants), and greater weight loss (-3.84, 95% CI -5.80 to -1.88; p<0.001; 5 RCTs; 233 participants). There were no significant differences in CRP, ESR, TJC and BMI. All studies were rated to have a high risk of bias overall because of the impossibility of blinding the received intervention. Consequently, the transparent assessment and grading of the quality of evidence by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach resulted in very low or low certainty for all outcomes.

Conclusion:

The decreased subjective pain rating of patients on anti-inflammatory diets compared with patients on ordinary diets was clinically relevant. Vegetarian, vegan, and Mediterranean diets might be beneficial for some rheumatoid arthritis patients. However, due to lack of blinding, effects on the patient-reported outcome pain might be biased.

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Insulin deficient diabetes mellitus with unexpected cause

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Background/Introduction:

Pancreatic neuroendocrine tumours (PanNETs) can be associated with diabetes mellitus. The relationship goes both ways. Diabetes appears to be a risk factor for the development of any type of pancreatic tumor including PanNET and PanNET can lead to diabetes mellitus by different potential mechanisms (destruction of beta-cells, production of antagonists of insulin (glucagon, somatostatin) peripheral insulin resistance by paraneoplastic diabetogenic factors.

Methods:

Case Report
A 36-year old Caucasian male was referred by his family doctor because of new onset diabetes. due to his young age, his low BMI (23.4kg/m2), the positive diabetes-specific autoantibody screening (anti-GAD 64.4 IE/ml, n<10; anti-pancreatic islet cell antibodies titre 1:320 (n 1<1:10), anti-IA2 and anti-ZnT8 both negative) we established the diagnosis of type 1 diabetes and started a functional insulin therapy. We interpreted the persistently low insulin requirement (about 0.28U/kg body weight) even after several months in the context of the low-carbohydrate diet, excellent adherence, and prolonged honeymoon period. Within a year, weight loss of more than 5% body weight in 3 months and watery diarrhoea occurred. Further investigations revealed a non-functioning hepatic metastasized neuroendocrine tumor of the pancreas (PanNET), G2 with relevant atrophy of the corpus and pancreatic tail. Prompt removal of the primary tumor followed by somatostatin analogue therapy followed.

Results:

Discussion
Different potential mechanisms might induce diabetes mellitus. Tumor progression may cause direct destruction of pancreatic tissue or possibly trigger an immune response.
In retrospect, a strong case for the tumor as the cause of the diabetes can be made. The concomitant positive anti-GAD and anti-pancreatic islet cell antibodies are rather unspecific for the establishment of the diagnosis of type 1 diabetes and might have become positive due to local destruction of pancreatic tissue without a more specific immune response. The large tumor with relevant pancreatic destruction could have been in place a year earlier, since PanNET do not grow particularly fast. Persistently low meal insulin requirement (15 U/d) and especially low basal insulin need (5 U/d) are not common in type 1 diabetes one year after diagnosis due to a limited residual beta-cell function. Interestingly, clues for exocrine pancreatic insufficiency were lacking for quite some time.
Despite increasing incidence of PanNET, the incidence of these tumors is much lower than the one of diabetes. Accordingly, it is generally not recommended to exclude or search for a pancreatic tumor in case of a newly diagnosed diabetes mellitus.

Conclusion:

Further investigations of the relationship between PanNET and diabetes are desirable. Specifically, there is a lack of information for the cause of diabetes (mechanisms for insulin deficiency and resistance). A consensus for screening NET in patients with newly diagnosed diabetes and red flags (diarrhoea, persistently low insulin requirement, weight loss) is lacking.

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Primary hyperparathyroidism and familial hypocalciuric hypercalcemia: role of biochemical and genetic testing for the diagnosis

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Background/Introduction:

Familial hypocalciuric hypercalcemia (FHH) is a rare genetic disorder. Due to the benign nature of FHH, it is important to differentiate this disorder from primary hyperparathyroidism (PHPT) to avoid unnecessary parathyroidectomy.
The accurate diagnosis of FHH is difficult because of an overlap in biochemical markers with PHPT. Current guidelines recommend genetic testing in all patients with urine calcium-to-creatinine ratio (UCCR) <1%. If the UCCR is <2% the need for genetic testing should be considered. It is suggested that the likelihood of FHH is around 95% if the UCCR is below 1%. In everyday practice, many clinicians substitute the gold-standard 24-hour urine collection to determine the UCCR for a 2nd void urine sample or a random urine sample although the diagnostic reliability of this has not been formally tested.

Methods:

This is a single centre cross-sectional study including all patients attending the division of Endocrinology and Diabetes at the Kantonsspital St.Gallen being considered with PHPT. The aim is to include 200-250 patient. All patients were asked to provide a 2nd void urine probe, a random urine sample and 24-hour urine collection. The 24-hour urine collection was sampled twice, on two separate days, and the average was used for analysis. All patients with UCCR <2% based on the first 24-hour urine collection were sent for genetic testing. The study was approved by the cantonal ethics committee of East Switzerland and all participating patients provided written informed consent. The McNemar test for paired nominal data was used to determine significant differences in the diagnostic power of 2nd void and randome urine sample vs 24-hour urine collection.

Results:

The current results are based on interim analysis of the first 25 patients. Of these, nine patients had an UCCR <2% and underwent genetic testing. Five of these had an UCCR below 1%. None of the nine patients carried a FHH mutation.
With an UCCR cut-off of <2% for genetic evaluation, both the 2nd void and random urine sample were as sensitive as the 24-hour urine collection, but indicated an additional nine and four patients for genetic evaluation, respectively.
With an UCCR cut-off of <1%, no difference in the diagnostic results was observed between the 2nd void urine sample and the 24-hour urine collection. With the random urine sample, both the sensitivity and specificity was worse as compared to the 24-hour urine collection. One patient would have failed to be indicated, and two additional patients would have been indicated for genetic testing as compared to the gold-standard method.
Comparing the results of the two 24-hour urine collections, intra-individual differences were observed in five and three out of 23 patients with an UCCR cut-off of <2% and <1%, respectively.

Conclusion:

The preliminary results suggest that the cut-off for routine genetic testing could be lowered from an UCCR of <2% to <1% without failure to detect cases of FHH. With the lower UCCR cut-off, a 2nd void urine sample tend to be as reliable as the 24-hour urine collection in screening patients for genetic testing which would simplify the procedure.
Even with a cut-off of UCCR <1%, additional predictive biomarkers are needed to further minimize unnecessary genetic testing in the future.

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Confirmation of sensitization to isobornyl ester of acrylic acid (IBOA) in three type 1 diabetes patients using the flash glucose monitoring system FreeStyle Libre®

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Background/Introduction:

The FreeStyle® Libre system (Abbott) is widely used in patients with diabetes mellitus and owns potential to improve glycemic control. However, skin reactions have been reported early after market launch and differentiation between the more frequent irritant dermatitis versus allergic contact dermatitis is challenging. As the latter usually requires an avoidance of the allergen, the confirmation of an allergic sensitization is intended. Isobornyl acrylate (IBOA) has been identified as the major allergen responsible for allergic skin reactions related to FreeStyle® Libre sensors. Difficulties in obtaining information on chemicals by the manufacturer has hampered the allergologic work-up in several previous studies. Nevertheless, chemical analysis indicated the sensor itself as the source of IBOA, and not the commonly suspected adhesive.

Methods:

We report three patients (52y woman, 60y and 32y man) with diabetes mellitus type 1 from our outpatient diabetes clinic.They had not been using other glucose sensors or insulin infusion sets at present nor before. All had applied a FreeStyle® Libre 1 sensor on the upper arm for a period of at least half a year (7 months, 1.5 and 2 years), before skin reactions corresponding to the contact area occurred. The rather late onset of dermatitis favored an allergic skin reaction and indicated primary sensitization to a sensor component, instead of a preexisting allergy to acrylates. An itching and burning sensation was reported by all three patients, whereas skin lesions ranged from redness, eruptions to vesiculation and blistering. We performed an epicutaneous testing on the upper back with baseline series and an additional inhouse prepared patch with isobornyl acrylate at a concentration of 0.1%.

Results:

All patients (n=3) reacted positively to the patch tested with IBOA, therefore a sensitization to isobornyl acrylate could be confirmed. As a strong reaction (+++) already developed after 48 hours in one patient, the epicutaneous testing was stopped early in that case. After 72 hours the two other patients also presented with a strong (+++) or relevant (++) reaction.

Conclusion:

Diabetologists must be aware of a contact allergy to isobornyl acrylate related to sensors of the flash glucose monitoring system. Recently, a new generation of the FreeStyle® Libre sensor was implemented with a change in the manufacturing process. According to the manufacturer, elimination of IBOA was achieved. Nevertheless, allergic contact dermatitis still develops, pointing to a cross-reactivity or to other acrylates as possible new culprit allergens, and so further studies are necessary.

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Correlation of urine steroid metabolites between spot samples and 24 hour urine specimens in children with congenital adrenal hyperplasia

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Background/Introduction:

Steroid profiling in children with congenital adrenal hyperplasia (CAH) is used to monitor the balance between androgen and cortisol metabolites and to decide on the optimal glucocorticoid dosage. Twenty-four hour collection is the gold standard for measurement of steroid metabolites in urine, because steroid production follows a circadian rhythm and is influenced by short-term stress and steroid drugs. For some children, e.g. those who were diapers, it is not feasible to collect urine over 24h non-invasively, and urine spot steroid assessments might still be an alternative in CAH.- We aimed to investigate whether steroid metabolites in 24h urine collections correlate with those determined in urine spot samples in children with CAH.

Methods:

We collected 24h urine and urine spots from children and adolescents with CAH due to 21-hydroxylase deficiency and analysed 40 steroid metabolites using GC-MS (see Table). To assess the strength of correlations between 24h and spot urine metabolites, we calculated Kendall's tau-beta separate for morning and non-morning urine. We set the level to $\alpha=0.005$ to account for multiple testing.

Results:

Thirty patients provided both 24h collections and spot urine samples (n=20 morning, n=10 non-morning). Out of the 40 metabolites, there was a strong correlation between 24h and morning spot urine for 17 metabolites, and between 24h and non-morning spot urine for 9 metabolites ($tau>0.45$, $p<0.005$). Specifically, correlations were noted for progesterones, corticosterones, tetrahydroaldosterone, androgens, estriol, tetrahydro-11-deoxycortisol, but not for the cortisol metabolites.

Conclusion:

Urinary steroid profiling in children with CAH revealed correlations between 24h urine specimens and spot urines. Spot urine might suffice to recognize the specific pattern of 21-hydroxylase deficiency for diagnostics (e.g. through marker metabolites 11-oxo-pregnanetriol, TH-11-deoxycortisol). Whether a spot urine can inform about metabolic control of treatment in CAH needs to be further tested in a larger number of specimens.

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Kinetics of FT4 serum concentrations in infants with congenital hypothyroidism during follow-up differ in the three severity groups

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Background/Introduction:

The goal of congenital hypothyroidism (CH) treatment is rapid normalization and maintenance of TSH and FT4 in the reference range. Recommended starting dose of levothyroxine (LT4) ranges from 10-15 mcg/kg/d at birth. Hyperthyroxinemia can be accepted in the context of normal TSH. LT4 should only be reduced in case of symptoms or repeatedly increased FT4. The aim of this study was to quantify duration and maximum peak of FT4 levels outside the reference range for each CH severity group.

Methods:

Retrospective longitudinal multi-center study. For specifying periods of hyperthyroxinemia in each CH severity group, pharmacometric simulation of FT4 kinetics based on a recently developed mathematical pharmacokinetics (PK) model characterizing FT4 dynamics in infants with CH was performed. CH severity groups were based on FT4 at diagnosis (severe <5 nmol/l, moderate 5-10 nmol/l, mild >10 nmol/l). Data are median [IQR].

Results:

Longitudinal data of 56 CH-patients (71% females) diagnosed at postnatal day 7 [6,9] with 236 FT4 and 232 TSH measurements were included. Patients suffered from severe (n=25), moderate (n=16) and mild (n=15) CH. LT4 starting dose differed between severity groups (severe, moderate. and mild CH was 10 [8,14], 9 [7,13], and 7 [4,9] mcg/kg/d, respectively). Duration of hyperthyroxinemia were 63 [47,89], 135 [60,159], and 134 [82,152] days after start of therapy. Peak fold over FT4 reference range were 1.5 [1.3,1.8], 1.6 [1.3,1.9], and 1.4 [1,1.5]. Median starting doses for each severity group were lower than recommended by 2021 guidelines. Pharmacometric simulation of an average patient showed peak FT4 levels above target range at day 24, 24, and 27 for severe, moderate and mild CH, respectively. Hyperthyroxinemic time periods for an average patient were significantly shorter for severe vs. moderate (P 0.02) or mild CH (P 0.02) despite comparable number of consultations in the first 6 months (severe 4 [3,5], moderate 3.5 [2.5,4.5], mild CH 4 [2.5,5.5]) and no differences between severe and moderate CH in TSH at diagnosis nor starting dose.

Conclusion:

While fold of peak FT4 levels above target range were similar for all three severity groups, moderate and mild CH patients were significantly longer hyperthyroxinemic. From a pharmacological point of view, severity-based dosing during follow-up might be helpful to reduce duration of FT4 levels above reference range. Prospective data are necessary to confirm these preliminary findings

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Knowledge about Diabetic Ketoacidosis – Preliminary data of a patient-centered Questionnaire

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Background/Introduction:

Diabetic ketoacidosis (DKA) is a severe complication of diabetes mellitus with potentially life-threatening course. Sodium glucose linked transporter 2-inhibitors (SGLT2-inhibitors) have beneficial effects on cardiovascular and renal outcomes and may be increasingly used also in patients with type 1 diabetes mellitus (T1DM). Of these, sotagliflozine and dapagliflozine were approved by the European Medicine Agency (EMA) for T1DM in 2019. However, in T1DM patients risk for DKA is 5-fold increased under treatment with SGLT2-inhibitors. So far, data on patient knowledge about DKA in German-speaking countries is rare. We aim to gather data about T1DM patients' knowledge in terms of DKA.

Methods:

We developed a completely anonymous questionnaire together with two T1DM patients and a diabetes counselor covering general knowledge about DKA, as well as baseline health and social characteristics. Completion of the questionnaire takes about 10-15 minutes following an outpatient appointment and is completely voluntary. We aim to include about 500 patients in several centers throughout German-speaking Switzerland.

Results:

First data of 97 patients at the Cantonal Hospital Olten revealed that 27% of the patients were not familiar with DKA. The overall knowledge about DKA was rated 3.95 (SD 3.07) from 0 (no idea) to 10 (best knowledge) by patients, whereas physicians in charge estimated patients' knowledge higher (mean 6.02, SD 2.37). About 40% were not able to name one symptom and 43% did not know possible causes of DKA spontaneously. Having multiple answers to choose, thirst (75%), polyuria (64%), sleepiness (56%) and nausea/vomiting (46%) were among the most frequently picked answers. As causes for DKA, 63 % stated missed insulin injection and 48% illness. Only 20% did test for ketone bodies at all, even though the majority of patients (73%) stated to have test kits at home. About 38% of all patients felt secure in treating DKA with 75% wanting more information about the condition.

Conclusion:

Our preliminary data shows that patient knowledge about DKA is insufficient, especially symptoms and causes are not well known. It does not correlate with the time since last diabetes counseling or duration of the disease. However, most patients want to know more about DKA, making it a good point to start from in the attempt to reduce DKA prevalence. A possible option would be to implement DKA on a regular basis in diabetes counseling and especially prior to starting SGLT2-inhibitors in T1DM patients.

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Endocrine and metabolic counterregulation to postprandial hypoglycemia in patients with postprandial hypoglycemia after gastric bypass compared to non-affected surgical and non-surgical controls

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Background/Introduction:

Postprandial hypoglycemia after bariatric surgery (PBH) is an increasingly recognized complication of gastric bypass (GB). Whilst insulin excess is an established pathophysiological feature, the role of counterregulation remains unexplored. We assessed endocrine and metabolic counterregulation to postprandial hypoglycemia in PBH patients compared to surgical and non-surgical controls.

Methods:

Four matched groups consisting of PBH patients, GB, sleeve gastrectomy (SG) and non-surgical controls (CON) ingested 15g glucose (labeled with U-13C glucose) 100min after initiation of a primed continuous 6,6-2H glucose infusion. Using a continuous insulin and controller-guided variable dextrose infusion, glycemia was clamped to reach 2.5mM levels 150-170min after glucose intake. Primary outcome was the glucagon response to hypoglycemia calculated as mean concentration from 150-170min. Further outcomes included levels of catecholamines, cortisol, growth hormone (GH), pancreatic polypeptide (PP) and endogenous glucose production (EGP) during hypoglycemia. Hormones were measured by immunoassays or liquid chromatography-tandem mass spectrometry. Isotopic glucose enrichments were quantified by gas chromatography coupled to isotope mass spectrometry and glucose fluxes were calculated using the Steele's nonsteady-state equation. Comparisons were performed using non-parametric tests.

Results:

Thirty-two adults (8 per group) were included (42.9±12.8yrs, 4male, BMI 28.2±4.3kg/m2). Mean time since surgery was 6.0±3.9yrs. Blood glucose in 150-170min was 2.6±0.2mM across all groups. Glucagon was significantly lower in all surgical groups (PBH:10.4[5.5;16.6]pM, $p<0.01$, GB:13.8[11.1;17.0]pM, $p=0.03$ and SG:11.0[4.2;17.3]pM, $p<0.01$) compared to CON (24.1[17.2; 26.4]pM). Likewise, PP was significantly lower in the PBH (6.9[2.5;23.8]pM, $p<0.01$) and GB (19.3 [1.6;36.9]pM, $p=0.04$) groups compared to CON (163.4[85.7;312.4]pM). Adrenaline was also lower in the PBH and GB groups, but differed significantly only between the PBH and CON (1.4 [0.9;2.8] vs 3.3[3.0;5.7]nM, $p=0.04$). Cortisol was lower in the surgical groups, with a significant difference between the GB and CON (388[335;452] vs 476[408;506]nM, $p=0.03$). No significant differences were found for GH and noradrenaline. EGP was lower during hypoglycemia in the surgical groups, with a significant difference between SG and CON (0.3[-0.6;0.7] vs 1.4[1.1;2.1]mg/kg/min, $p=0.02$).

Conclusion:

Bariatric surgery lowers counterregulatory hormones and EGP during postprandial hypoglycemia when compared to matched CON. Glucagon, adrenaline and PP were lower in surgical groups vs CON, whilst no differences were found for noradrenaline and GH. Overall, PBH showed lowest counterregulation, but overlapping responses with surgical controls limit sufficient discrimination.

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Swiss prospective cohort study of children with diabetes mellitus during COVID-19 pandemic: deterioration of metabolic control in adolescents duringschool closure

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Background/Introduction:

The COVID-19 pandemic led to regional lockdowns and restrictions associated with changes in lifestyle and quality of life (QoL) thus potentially burdening metabolic control in diabetes mellitus (DM). We examined the impact of pandemic restrictions on QoL and somatic and metabolic parameter.

Methods:

This monocentric prospective longitudinal cohort study included children attending the outpatient diabetes clinic at a tertiary children's hospital between April 2020 to April 2021. In addition to SARS-CoV-2 antibodies and symptoms, BMI-SDS (Body Mass Index-Standard deviation score, adjusted for age and sex), HbA1c, mean blood glucose (MG), variability (%CV), Time in Range (TIR), health-related QoL (HrQoL) through Kidscreen-10 (Tscores >50 represent a better, <50 a poorer QoL than the reference population) were assessed at 2-3-monthly scheduled visits. Parameters were assigned to the following pandemic phases: 1: 16.03.20 – 10.05.20 Lockdown with closed schools; 2: 11.05.20 – 18.10.20 no restrictions; 3: 19.10.20 – 21.12.20 Slowdown e.g. with assembly restrictions; 4: 22.12.20 – 28.02.21 Lockdown, but open schools. For statistical analysis, we applied mixed-model-analyses

Results:

We assessed 54 children with Type1DM and two with MODY, 53.4% male and median age of 12 years (range 1 – 19). Median HbA1c during phase 1 was 7.5% (range 6.2 – 11.0%). BMI-SDS, HbA1c, MG, %CV and TIR did not significantly change during all 4 phases. During lockdown phase 1, HbA1c (p=0.003) and %CV (p=0.05) were significantly correlated with increasing age. The HbA1c decrease from phase 1 to 2 was greater the older the patients were (p=0.029). The patients showed significantly similarly decreased HrQoL mean scores in phases with high restrictions:1, 3-4, or after back to school in Pase 2 46.7 (32.2 - 65.2), but normal T-scores during the rest phase 2 (50.7, 32.4 - 83.6).

Conclusion:

The children with DM participating in this study showed a satisfying metabolic control, stable through all phases of the pandemic, despite a tendency to impaired HrQoL during higher restrictions. Nevertheless, in adolescents, metabolic control was transiently compromised during school closure. Consistent with prior studies, children with DM can activate sufficient resources for their diabetes management even during the COVID-19 pandemic, if they have a regular (school) routine and medical care.

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Cardiovascular effectiveness of gastric bypass versus sleeve gastrectomy: a population-based matched cohort study

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Background/Introduction:

Gastric bypass and sleeve gastrectomy result in weight loss and improved cardiometabolic health. Whether cardiovascular effectiveness differs according to the modality of bariatric surgery is unclear.

Methods:

In a population-based retrospective cohort study we used nationwide claims data from 2012 to 2018. Gastric bypass patients were 1:1 propensity-score matched with patients who had a sleeve gastrectomy. The primary outcome was the incidence of a major adverse cardiovascular event (MACE), defined as non-fatal myocardial infarction, stroke, or hospitalization for cardiac arrest or heart failure. Secondary outcomes encompassed each single MACE component and other clinical endpoints.

Results:

During a median observation time of 2.9 years, the MACE rate per 1000 person-years was 3.6 in the gastric bypass group and 3.9 in the sleeve gastrectomy group (hazard ratio [HR] 0.95 [95% CI, 0.69 to 1.33], rate difference, -0.27 [95% CI, -1.53 to 0.98]. There were no significant between-group differences in the rates of single MACE components. However, in the gastric bypass group there were higher rates of in-hospital mortality (0.4% vs. 0.1%; RR 3.12 [95% CI 1.41 to 6.92]), long-term postsurgical complications requiring a reintervention (6.7% vs. 0.9%; HR 6.7 [95% CI 5.06 to 8.86]), and all-cause 30-day readmission (5.2% vs. 3.3%; RR 1.38 [95% CI 1.17 to 1.63]). Escalation surgery was less frequently performed among gastric bypass patients (4.4% vs. 5.3%; HR 0.75 [95% CI 0.63 to 0.88]).

Conclusion:

Gastric bypass surgery was associated with a similar risk of MACE in direct comparison with sleeve gastrectomy as performed in clinical routine.

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Propylthiouracil-associated hepatopathy in a patient with Graves' disease and medullary carcinoma

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Background/Introduction:
Propylthiouracil (PTU) is a thionamide drug used to treat hyperthyroidism. Carbimazole (CMZ) and its precursor methimazole (MMI) are considered first-line drugs, but PTU continues to be used during the first trimester of pregnancy and in selected patients. Although rare, serious liver injury and acute liver failure do occur under therapy with PTU, in particular in children. Therefore, the United States Food and Drug Administration (FDA) has added a black box warning to the label for PTU in 2010.

Case Report:
A 68-year-old female patient reported involuntary weight loss in December 2020. Biochemical testing revealed a suppressed TSH, an elevated FT4 of 28.4 pmol/l (9-26) and a FT3 of 7.1 pmol/l (3-6.8), confirming hyperthyroidism. Therapy with CMZ was initiated but then stopped because of an exanthema and gastrointestinal side effects. At initial evaluation in our clinic in February 2021, ultrasound examination showed a thyroid of normal size but increased vascularity, and a suspicious nodule in the right lobe (EU-TIRADS 5). The TSH- receptor antibodies (TSAb) were slightly elevated (3.1 IU/L, norm <1.8) and consistent with Graves' disease (GD). Because of the adverse effects observed on CMZ, therapy with PTU (50 mg/day) was initiated. A fine needle aspiration of the suspicious nodule performed in March 2021 led to diagnosis of medullary thyroid cancer (MTC). Her serum calcitonin was >2000 ng/l (<6.4), and her CEA 18.8 µg/l (<3.5). Cross-sectional imaging with computerized tomography (CT) showed bilateral cervical lymphadenopathy but no distant metastases. Total thyroidectomy with cervical neck dissection was planned because of the MTC and for definitive treatment of GD.
Yet, in early April 2021, the patient presented with fever of 39°, icterus, and an erythematous rash. Laboratory studies showed normal thyroid function tests, anemia (hemoglobin 99 g/l), elevated transaminases (ASAT 120 U/l (5- 34), ALAT 182 U/l (0-55), a total bilirubin of 94 µmol/l (3.4-20.5), very high ferritin levels of 10'481 µg/l (5-204), and a LDH of 461 U/l (125-220. The patient was hospitalized with suspected PTU-associated hepatopathy. PTU was stopped and therapy with cholestyramine and potassium perchlorate was initiated. The following day, her liver function tests deteriorated (ALAT 806 U/l (0-55), □GT 6'67 U/l (9-36), and direct bilirubin 55 µmol/l (0-8.6)).
Because of the suspicion of PTU-associated hepatopathy, methylprednisolone (500 mg i.v. per day) was administered for 4 days. Sodium perchlorate was discontinued because of its potential bone marrow toxicity. Subsequently, the transaminases and the ferritin decreased rapidly, and the patient was discharged 8 days after admission. The patient underwent total thyroidectomy, central and bilateral neck dissection 3 weeks later. The final pathology confirmed MTC with 17/32 positive lymph nodes (pTx1N1bM0, Stage IVA) and alterations consistent with GD. The immediate postoperative calcitonin was 395.9 ng/l (<6.4).

Conclusion:
Hepatotoxicity is a potential adverse effect of thionamides. Most commonly, it consists in a cholestatic pattern, but hepatocellular damage can occur. In particular, therapy with PTU can cause fulminant hepatic necrosis that can be fatal or need liver transplantation. In patients with clinically apparent liver disease or transaminases >3 times the upper limit of normal, immediate discontinuation of antithyroid therapy is essential. Further management depends on the resolution of the liver injury and may require prompt multidisciplinary management if liver function worsens. In patients with major adverse events on MMI/CMZ, a change to PTU requires caution and careful monitoring.

Essential oil metabolites can regulate adrenal Androgen production.

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Background/Introduction:

Endocrine disrupting chemicals (EDCs) can effect steroid metabolism in the body. Previous clinical case reports have shown that essential oils like lavender oil and tea tree oil may act as potential EDCs and are linked to prepubertal gynecomastia in boys. In addition to this, cases of premature thelarche in girls have also been reported due to regular exposure to lavender based fragrance commonly used in hispanic communities. These studies suggest the role of essential oils in steroid metabolism in humans. We have screened a range of essential oil metabolites for effects on androgen production using Dehydroepiandrosterone (DHEA) production by CYP17A1, as it is the key step in the production of androgens.

Methods:

For preliminary screening, human adrenal NCI H295R cells were treated with 10 µM of test compounds for 24 hours. The test compounds had been extracted and purified from natural resources and are found as major components in essential oils. For CYP17A1 activity, the conversion of radiolabelled substrate, 17-Hydroxy-pregnenolone to DHEA was determined using tritiated water release assay.

Results:

Out of about 50 test compounds, eucalyptol, dihydro-beta-Ionone & (-)-alpha-pinene showed 20 to 40 percent inhibition of DHEA production. Rest of the compounds showed either no or low inhibition. Some compounds were also tested for effects on CYP19A1 (aromatase) activity where upto 30 percent inhibition was observed.

Conclusion:

Eucalyptol, dihydro-beta-Ionone, (-)-alpha-pinene were extracted from eucalyptus, rose and pine resin respectively. Essential oils are often used in various beauty and hygiene products as they have few known side-effects. However, prolonged exposure to these products may result in steroid imbalance. Due to their anti-androgenic activity, they may be studied further as chemical leads for the treatment of hyperandrogenic disorders such as prostate cancer and poly cystic ovary syndrome.

Colonization by the common mouse protozoa *Tritrichomonas* modulates gut innate immunity and impacts glucose tolerance

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Background/Introduction:

The commensal protozoa, *Tritrichomonads*, are unicellular, tri-flagellated and highly motile organisms of 5 – 10 µm in size. Although screened for in mouse colony health surveillance programs, their presence is considered as nonpathogenic. However, in recent years, several studies have indicated a role of *Tritrichomonads* in the exacerbation of gut inflammation in mice. As we previously found that gut inflammation is a feature in metabolic disease and associated with impaired glycemic control, we aimed to assess whether colonization with *Tritrichomonas spp.* impacts on gut immunity and glucose metabolism.

Research Design and Method:

Tritrichomonas spp. were isolated from ceca of colonized mice and orally gavaged into C57BL/6N male mice. The metabolic phenotype was monitored by glucose and insulin tolerance tests on a monthly basis. Colonization was confirmed by visual inspection under a light microscope and qPCR of cecum content. Colon and distal small intestine were assessed by flow cytometry to characterize the immune cells of innate and adaptive immunity. Systemic inflammation was analyzed through the levels of pro-inflammatory cytokine expression in blood sera.

Results:

Preliminary results showed that colonization of wild-type C57BL/6N mice with *Tritrichomonas* spp. resulted in slightly worsened glucose tolerance. Colonization led to a change in the distribution of colon macrophages with an increase in inflammatory populations. In addition, the immunological populations of CD4+ T-cells and ILC3 were decreased, with the latter being primarily involved in the maintenance of intestinal mucosal homeostasis. Systemic inflammation was absent as indicated by similar levels of circulating pro-inflammatory cytokines, which may indicate localized gut inflammation associated with *Tritrichomonas* spp. colonization.

Conclusion:

We found that despite being considered non-pathogenic, colonization of wildtype mice with *Tritichomonas spp.* modulates the immunological landscape of the gastrointestinal tract, which might be a confounding factor in many immunological and metabolic studies. This shift towards an inflammatory tone of the gut was associated with impaired glucose tolerance and an increase in inflammatory colon macrophages. It is therefore crucial to routinely screen rodents for the presence of this protist prior to their utilization in experimental models of metabolism and gut immunity. Modulation of the inflammatory tone of the gut can lead to metabolic consequences which could be pharmacologically targeted to improve glycemic control.

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Human Islet Amyloid Polypeptide Expression Combined with PC1/3 Deficiency Induces Frank Diabetes in Mice

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Background/Introduction:

Individuals with prediabetes have a high risk to develop diabetes but the mechanism of this progression is not well understood. In prediabetes, beta cells show reduced expression of PC1/3, an endoprotease involved in processing (und thus activation) of insulin as well as islet amyloid polypeptide, the major constituent of islet amyloid deposits. The aggregation of islet amyloid is associated with beta-cell toxicity and reduction in beta-cell mass.

Methods:

To test whether reduced processing of either insulin or islet amyloid polypeptide induces diabetes in a prediabetes setting, we produced mice with inducible beta cell-specific PC1/3 deficiency that additionally express human islet amyloid polypeptide, the latter to enable them to develop amyloid deposits.

Results:

Knocking out PC1/3 or expressing human islet amyloid polypeptide by itself did not alter in vivo glucose metabolism. However, combining the two models induced severe hyperglycemia (>16.7mM glucose) at around 25 weeks of age. Pancreatic islets from these mice were inflamed, functionally impaired and their architecture was abnormal, similar to histological observations in pancreata from human patients with type 2 Diabetes. These changes were associated with the deposition of islet amyloid, a known feature of human diabetes pathology.

Conclusion:

Our data suggest that the development and deposition of islet amyloid is an important trigger that causes prediabetic beta cells to fail and and thereby induces Type 2 Diabetes. Since islet amyloid deposition is a known activator of the NLRP3 inflammasome which activates the master cytokine IL-1beta, we will next investigate whether blocking inflammation prevents the development of hyperglycemia in this mouse model of prediabetes.

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Cholesterol deprivation drives DHEA production in human adrenals

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Background/Introduction:

Adrenarche is the first event in human postnatal sexual maturation. It corresponds to the development and expansion of a new zone of the adrenal cortex, which is referred to as *'zona Reticularis*' (zR). The zR produces androgens, including 11-hydroxyandrostenedione and DHEA/-S, which are converted in the periphery to bioactive hormones and lead to typical signs, such as the appearance of axillary and pubic hair and the maturation of apocrine glands, responsible for the adult-type body odor. Premature adrenarche is associated with androgen-related disorders in the adult, including polycystic ovary syndrome, hirsutism, and insulin resistance. Despite the implication of adrenarche in the homeostasis of androgens, the physiological mechanisms that lead to the timely development of the zR remain unknown.

Methods:

We profiled the transcriptional activity of adrenal zones and compared the zR with the neighboring *zona Fasciculata*, using laser capture microdissection of human tissue followed by real-time quantitative PCR. We found that the zR is characterized by a transcriptional signature typical of cholesterol deprivation. We then explored the molecular mechanisms downstream cholesterol deprivation in a cell model of human adrenal using gene manipulation, transcript quantification and liquid chromatography/tandem mass spectrometry.

Results:

Our data indicate that the zR in human adrenals displays a profile typical of cholesterol deprivation, characterized by high expression of enzymes involved in *de novo* cholesterol synthesis and cholesterol uptake, and low expression of the cholesterol exporter ABCG1. When we modeled this in a human cell line, we found that cholesterol deprivation results in decreased expression of the steroidogenic enzyme *HSD3B2*, which leads in increased DHEA production. Of note, both *HSD3B2* suppression and DHEA biosynthesis are stereotypical features of human zR. Transcriptome profiling of cells deprived of cholesterol indicated POU3F2 as a candidate transcription factor for the regulation of *HSD3B2,* and subsequent stimulation of DHEA production. Cell-based reporter assay confirmed that POU3F2 binds to the promoter of *HSD3B2* and triggers gene transcription.

Conclusion:

Altogether, our results reveal a novel signaling pathway initiated by cholesterol deprivation that explains, at least in part, the onset of zR and adrenarche in humans. Our findings represent a landmark in the understanding of adrenarche and sexual maturation in humans, and open new avenues of research on disruption of androgen homeostasis.

Loss of protein stability and function caused by a single point mutation (P228L) in the Cytochrome P450 Oxidoreductase.

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Background/Introduction:

Cytochrome P450 oxidoreductase (POR) is the obligatory redox partner of steroid and drug metabolizing cytochrome P450s located in the endoplasmic reticulum. Mutations in POR cause a broad range of disorders like congenital adrenal hyperplasia. Genome sequencing studies have revealed the existence of a POR missense variant P228L which was linked with reduced function of some P450 enzymes. We aimed to expand the enzymatic studies of POR variant P228L for its role in human metabolism.

Methods:

We expressed human wild type and the P228L variant form in bacteria. We purified the proteins by Immobilized Metal Affinity Chromatography. Subsequently, we tested the stability of the proteins using fast proteolysis. Furthermore, we performed Kinetics assays of POR activities using small molecules as substrates. At last, POR (WT or P228L) were mixed with purified cytochrome P450 proteins and activities of cytochrome P450 proteins were assayed.

Results:

The single point mutation P228L has the features of affecting the stability of the protein showing a lower melting point comparing to the WT. In the kinetics studies, the rates of the reactions with P228L were considerably lower than the WT but the Km did not show substantial changes. We observed a decrease in the enzymatic activities of CYP3A5 and CYP2C9 of more than 40% with P228L form of POR comparing to WT.

Conclusion:

A single change in the amino acid sequence can affect the protein stability and cause a severe reduction in POR activity. Molecular characterization of POR mutations is crucial to have a better understanding of the impact on the functionality of its redox Partners.

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IL-18 binding protein (IL-18BP) deficiency alters gut microbiota composition and exacerbates both type 1 and type 2 inflammation in liver during nutritional stress

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Background: Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic hepatic disease worldwide. NAFLD can progress to hepatic inflammation [nonalcoholic steatohepatitis (NASH)] and to fibrosis. Interleukin-18 (IL-18) is a prototypic pro-inflammatory cytokine, the activity of which is regulated by IL-18 binding protein (IL-18BP), a secreted protein that binds to IL-18 to prevent its signaling, thus acting as a natural inhibitor. Our goal is to delineate the role of the IL-18/IL-18BP balance in hepatic metabolism and the gut-liver axis, in particular during nutritional stress inducing NAFLD/NASH.

Methods: Wild-type (WT) or IL-18BP$^{-/-}$ C57BL/6J mice aged 2 months were fed with 1) regular chow diet; 2) high fat diet (HFD) for 10 weeks (60 kcal% from fat); 3) methionine- and choline-deficient (MCD) diet for 8 weeks; or 4) atherogenic (ATH) diet for 14 weeks (1.25% cholesterol/0.5% cholate). Gene expression was assessed by RT-quantitative PCR using a LightCycler Detection System (Roche Diagnostics). Gut microbiota composition was determined by metataxonomics, based on bacterial 16S rRNA gene sequencing and analysis using various bioinformatics tools (Trimmomatic/PEAR/USEARCH/MOTHUR). Immunohistochemistry was performed using classical protocols and images were taken using Axio Scan.Z1.

Results: We previously showed that on HFD, MCD and ATH diet, circulating levels of transaminases (reflecting hepatocyte damage), as well as gene expression of classic pro-inflammatory markers, were exacerbated in the liver of IL-18BP$^{-/-}$ compared to WT mice. Surprisingly, we now show that diet-induced over-inflammation observed in the liver of IL-18BP$^{-/-}$ mice concerns not only type 1 (IFN-γ driven) immunity, but also type 2 immune response (as reflected by an upregulation of IL-5, IL-10, IL-13 expression). Concomitant elevation in type 1 and type 2 immune responses could respectively explain increased hepatocyte damage and fibrosis observed in IL-18BP$^{-/-}$ mice. In the principal coordinates analysis, overall gut microbiota clustering pattern suggested an interaction between diet and genotype. Analysis of microbiota composition at the family level revealed consistently increased proportion of Enterobacteriaceae in IL-18BP$^{-/-}$ compared to WT mice, regardless of the diet.

Conclusion: Derepression of IL-18 signaling, through genetic deletion of its negative regulator IL-18BP, induces gut microbiota dysbiosis and an exacerbated upregulation of both type1/2 immunity in the liver during nutritional stress. Elucidation of underlying mechanisms, especially concerning the role of gut enrichment in Enterobacteriaceae on liver inflammation could lead to therapeutic perspectives in NAFLD/NASH.

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CSF1R inhibition by PLX5622 has a tissue-specific effect on glucose homeostasis in lean mice

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Background:

The colony stimulating factor 1 (CSF1) has a pivotal role in promoting proliferation, differentiation and survival of macrophages. Macrophages are known to impact on glucose homeostasis with both beneficial and deleterious effects. The aim of our study was to assess tissue-specific effects of CSF1R-inhibition by PLX5622 on immune cells and glucose homeostasis in lean mice.

Research Design and Method:

Male C57B6/N mice were treated with the CSF1R inhibitor PLX5622 mixed into standard diet (1200ppm) for either 3 weeks or 4-5 months. Immune cells were assessed by flow cytometry and glucose metabolism by glucose tolerance tests (GTT), hyperinsulinemic euglycemic clamps and *ex vivo* glucose stimulated insulin secretion (GSIS). Beta-cell mass was determined by histology.

Results:

Treatment with PLX5622 resulted in depletion of tissue resident macrophages in the brain, lung, colon, adipose tissue, peritoneum and pancreas. Depletion of macrophages was accompanied by an increase in eosinophils and innate lymphoid cells type 2 and elevated IL-6 in the blood, while triglycerides and cholesterol were reduced. These changes resulted in improved insulin sensitivity in peripheral tissues as shown by hyperinsulinemic euglycemic clamps. However, insulin secretion was reduced, leading to glucose intolerance at the late time points during GTT. Beta-cell mass and identity were unaltered, but *ex vivo* GSIS reduced in PLX5622-treated mice. This functional insulin secretory defect was partially restored by retinoic acid, indicating a potential role of macrophage-derived retinoic acid in insulin secretion.

Conclusion:

These data indicate that CSF1R-inhibition in lean mice has beneficial metabolic effects in peripheral insulin-sensitive tissues, while insulin secretion in islets of Langerhans is impaired. A better understanding on the differential effects of specific tissue resident macrophages on glucose homeostasis is crucial for the development of targeted immune-modulatory treatments in metabolic disease.

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Nasopharyngeal swab testing for COVID-19 in patients diagnosed with Subacute thyroiditis

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Background/Introduction:

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has the potential to cause multi-organ effects including endocrine disorders. The impact of COVID-19 on the thyroid gland has been described, but several aspects have to be clarified. The aim of the present study was to investigate the possible clinical link between subacute thyroiditis (SAT) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Because a potential association between SAT and covid disease has been described, we chose only patients with SAT during the COVID-19 pandemic and testing for SARS-CoV-2 with swab.

Methods:

Among 25 SAT observed during the period from March 2020 to July 2021, 11 patients undergone swab were enrolled. The presence of typical clinical presentation of SARS-CoV-2, positivity with swab diagnostic tests for SARS-CoV-2, and contact with other individuals proven to be positive for SARS-CoV-2 were searched.

Results:

Ten patients with swab testing were negative and only one patient had positive swab. Cough, dyspnea and headache were rarely reported. No patient had diagnosis of pneumonia. Six patients had moderate to severe fatigue after SAT. One patient experienced loss of smell and taste, and had persistent fatigue over the following five months. At contact tracing evaluation, only one patient had a contact with people who were diagnosed with SARS-CoV-2.

Conclusion:

Patients diagnosed with SAT during COVID-19 pandemic rarely experienced positivity of swab for SARS-CoV-2.

Lung Exposure to Diesel Exhaust Particles Leads to Atherosclerosis Progression Possibly via Changes in Pulmonary Immune Cells

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Background:

Accumulating evidence has demonstrated a close association between levels of air pollution and increased risks for pulmonary and cardiovascular diseases. The aim of this study was to investigate the impact of pulmonary exposure to air pollution particles on cardiovascular and metabolic diseases in two atherosclerosis-prone mouse models, and to elucidate a potential role of lung immune cells in mediating the disease processes.

Methods:

Lung exposure was achieved via intratracheal instillation of diesel exhaust particles (DEP) dissolved in PBS (60µg/week). LDLR-/-Apobec1-/- mice were treated for 34 weeks maintained on standard chow, while ApoE-/- mice for 16 weeks on a high fat diet (HFD). Pulmonary immune cells were analyzed by flow cytometry. Aortas were processed for histological analysis and glucose metabolism was assessed via monthly glucose tolerance tests.

Results:

HFD-fed ApoE-/- mice showed enlarged aortic plaques upon DEP exposure with no changes in plaque vulnerability. This was accompanied by impaired glucose tolerance, insulin resistance and increased TNF-a in the plasma. Lung tissue showed a significant increase in immune cells, particularly in the adaptive immunity with increased B cells and T cells. In addition, dendritic cells (DC) and macrophages were markedly decreased. Chowfed LDLR-/-Apobec1-/- mice, on the other hand, showed no changes in the abovementioned atherosclerotic and metabolic parameters upon DEP exposure. However, the lung tissue showed a slight increase in lymphocytes, specifically T cells, while DCs and alveolar macrophages remained comparable to the control group.

Conclusion:

Our data suggest that pulmonary exposure to DEP leads to atherosclerosis progression and impairs glucose metabolism in HFD-fed ApoE-/- mice, potentially mediated via pulmonary inflammation. Additionally, the absence of plaque development and metabolic impairment in LDLR-/-Apobec1-/- mice kept on standard chow highlights a potential synergistic effect between HFD-induced inflammation and air pollution exposure.

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Regular SSB Consumption Increased Fasting FGF21 Levels in Healthy Lean Men

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Background/Introduction:

Human fibroblast growth factor 21 (FGF21) is primarily produced and secreted by the liver as a hepatokine. It is a metabolic regulator with multiple effects. It regulates simple sugar intake and sweet taste preference, thermogenesis in adipose tissue as well as energy expenditure and has beneficial effects on glucose and lipid metabolism. Serum FGF21 levels are elevated in subjects with metabolic syndrome, NAFLD and coronary artery/heart disease. It is hypothesized that a state of FGF21 resistance exists under these conditions. However, factors that favor FGF21 resistance as well as the underlying mechanisms in FGF21 target tissues (e.g. liver, muscle, adipose tissue and the brain) are unknown.
This study aimed to investigate the effect of sugar sweetened beverage (SSB) intake on FGF21 serum levels in healthy lean men discriminating the effects of glucose, fructose and the disaccharide sucrose.

Methods:

Serum FGF21 levels were measured by ELISA in 83 subjects recruited from our previous randomized controlled trial on SSB consumption. During 7 weeks subjects had to consume daily fructose- (N=22), sucrose- (N=19) or glucose- (N=21) sweetened beverages (80g sugar/day) or to abstain from SSB consumption (control, N= 21).

Results:

The fasting FGF21 concentrations were significantly increased after the 7-week SSB intervention in all SSB groups compared with baseline (medians with IQR in pg/ml at week 7 vs baseline: Glucose 71.3 (80.6) vs 51.4 (27.0), p=0.022; Fructose 52.0 (76.2) vs 45.6 (69.8), p=0.033; sucrose 58.6 (70.8) vs 31.6 (38.6), p=0.002, Wilcoxon-Test). In contrast, FGF21 concentrations did not change in the control group (61.3 (56.7) pg/ml (week 7) vs 49.3 (62.3) pg/ml (baseline), p=0.473). The effects exerted by the glucose, fructose and sucrose sweetened beverages were strong (r >0.40). Analysis of dietary intake showed a compensatory reduction of sugar intake from fruits by SSB consumption (i.e. fructose and sucrose group).

Conclusion:

The increased FGF21 levels induced by regular SSB consumption in lean men may represent an adaptive metabolic response to limit simple sugar intake to maintain energy balance, glucose homeostasis and to prevent hepatic toxicity by excessive CHO consumption. Intriguingly, glucose-, fructose- and sucrose-sweetened beverages similarly increased fasting FGF21 levels. In the long-term, sustained increased FGF21 levels may reduce the physiologic response to FGF21 favoring a state of FGF21 resistance.

The influence of maternal intuitive eating and depression during pregnancy on early postpartum infant anthropometry in women with gestational diabetes mellitus

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Background/Introduction:

Gestational diabetes (GDM) is associated with higher risk of neonatal obesity. Yet, the contributing maternal behavioural and psychological mechanisms associated with this obesity risk are understudied in pregnancy. Women with GDM have a three-fold higher risk of depression and in the general population; depression is associated with lower intuitive eating (IE) behaviours and increased gestational weight gain. IE and depression may also influence higher anthropometric outcomes in infants. This study aimed to: 1) investigate the association between intuitive eating and symptoms of depression at the first GDM visit 2) determine if maternal IE at first GDM visit is associated with infant anthropometric outcomes at birth and at 6-8 weeks postpartum 3) investigate if the presence of maternal depression moderated the association between maternal IE and infant anthropometric outcomes.

Methods:

Data for this study came from a randomized intervention trial (MySweetheart trial: NCT02890693) which consisted of 211 women diagnosed with GDM between 24 and 32 weeks of gestation. Maternal IE was measured at the first GDM visit, using two subscales of the Intuitive Eating Scale–2: eating for physical rather than emotional reasons (EPR) and reliance on hunger and satiety cues (RHSC). Symptoms of depression were measured at the same time with the Edinburgh Postnatal Depression Scale (EPDS) and scores ≥ 11 indicated clinical depression. Infant anthropometric outcomes consisted of weight z-scores at birth, and at 6-8 weeks postpartum of; BMI z-scores and the sum of four skinfolds (biceps, triceps, subscapular, iliac).

Results:

The proportion of clinical depression scores was 27% at the first GDM visit. Maternal depression was negatively correlated with EPR (r=-0.239, p= 0.01) and close to negatively correlated with RHSC (r=-0.139, p=0.061). In the total sample, maternal IE was not associated with infant anthropometry (p= NS). Maternal depression moderated the association between RHSC and infant BMI-z-scores at 6-8 weeks postpartum (p for interaction=0.037), but not for the other measures. Specifically, lower maternal RHSC scores was related to higher infant BMI z-scores in women without depression (B=-7.597, p=0.021), but not in women with depression.

Conclusion:

This study demonstrated an inverse association between maternal depression and eating for emotional reasons. Overall, IE did not influence infant anthropometry. In women without depression, decreased reliance on hunger and satiety cues could lead to higher infant BMI. In women with clinical depression, the association between maternal IE and infant anthropometry is probably overdriven by other variables.

Profound changes in the intestinal immune cell landscape upon 1 week of high-fat diet in mice

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Background:

We previously found that pro-inflammatory colonic macrophages are increased in mice fed a high-fat diet (HFD), concurrent with glucose intolerance. This increase in pro-inflammatory intestinal macrophages was also observed in obese subjects. Pharmacological or genetic depletion of macrophages improved glycemic control, highlighting a potential causal role of innate mucosal immune cells in regulating glucose homeostasis. To better understand the crosstalk between different immune cell compartments in the gut, the aim of the current study was to characterize all innate and adaptive immune cell populations upon one week of HFD or standard diet by flow cytometry profiling.

Methods:

Male C57BL/6N mice were fed either HFD or standard diet for one week. Immune cells of the colon were isolated and characterized by flow cytometry. The metabolic state was assessed by glucose tolerance tests (GTT) after 6 days on the diet.

Results:

Mice fed HFD for one week showed a significantly impaired GTT and a shift towards the inflammatory macrophage subpopulation “P2”. Furthermore, immune lymphoid cells (ILC) type 1 and neutrophils were significantly increased, while natural killer cells, ILC 3 and CD4 T cells were significantly decreased upon HFD. Additionally, we found distinct changes in the dendritic cell (DC) population, as characterized by reduced CD11b+CD103+ DC and increased CD11b+ DC subpopulations.

Conclusion:

One week of HFD results in profound changes in the immune cell landscape of the gut. An integrated view of interrelated immune cell populations in response to environmental factors such as HFD might help us to better understand the disease process of obesity-related comorbidities such as glucose dysregulation.

Relationship of preoperative psychiatric profile to short and long-term weight loss after bariatric surgery

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Background/Introduction:

Bariatric surgery has proven to be an effective therapy for patients with severe obesity. However, it ensures neither adequate weight loss after intervention nor long-term weight stability. Inconsistent results have been reported regarding the relationship between psychological predictors and postoperative weight outcome and this may be explained by the fact that factors influencing initial weight loss may differ from those influencing weight regain. In the present study, we aimed to determine whether preoperative anxiety, depression, eating and alcohol use disorders assessed by psychometric tests were associated with preoperative BMI and both early (1 year) and long-term (5 years) weight loss after Roux-en-Y gastric bypass. The secondary outcome was the exploration of a preoperative psychiatric profile to predict weight outcome.

Methods:

This is a single-center retrospective cohort including 236 patients who underwent Roux-en-Y gastric bypass between 2013 and 2019. The assessed psychiatric variables were depression, anxiety, eating disorders and alcohol consumption obtained through validated, specific psychometric tests (BDI-II, STAIS-S/T, BITE, AUDIT-C) prior to surgery. Results of the psychometric evaluation were analyzed as categorial variables. Follow-up weight loss was obtained yearly until up to 5 years after surgery. A multiple regression analysis of pre-operative BMI was conducted to assess its association with the pre-operative psychiatric profile. A linear longitudinal mixed model was built to study the impact of the pre-operative psychiatric profile on excess BMI loss (EBMIL) after surgery.The most and least favorable psychiatric profiles were deduced form the longitudinal model in terms of EBMIL at 1 year and in terms of subsequent evolution.

Results:

No significant association was found between any of the included psychiatric variables and pre-operative BMI, nor with EBMIL at 1 year. Regarding EBMIL evolution until year 5, the only significant association was for patients with a preoperative unusual eating pattern who regained weight faster than those with a normal eating pattern (each year -2.53%, ± 1.27, p 0.049). There was a significant difference for EBMIL at 1 year between the most and least favourable psychiatric profiles (p 0.02) but theses profiles showed no predictive value for subsequent weight evolution.

Conclusion:

Preoperative psychiatric profiles assessing anxiety, depression and alcohol use disorder obtained by psychometric instruments has a weak predictive power on short term and long term weight evolution after surgery. Patient with unusual eating patterns from the BITE questionnaire might benefit from close monitoring to improve their long-term weight loss outcome. Further studies are needed to identify preoperative factors of weight outcome after bariatric surgery.

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Postpartum cardiovascular and metabolic health in women with early gestational diabetes mellitus; a cohort study

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Background/Introduction:

Early diagnosis and treatment of gestational diabetes mellitus (GDM), especially in high-risk women could reduce adverse obstetric and neonatal outcomes. However, data on postpartum cardiometabolic and mental health are needed. We investigated and compared these outcomes in women with early (eGDM) and classical (cGDM) GDM.

Methods:

This prospective cohort included 1185 women with cGDM and 76 eGDM women with GDM-risk factors (BMI, family history of diabetes, history of GDM, ethnicity). eGDM was diagnosed <20 weeks of gestational age (GA) using the ADA prediabetes criteria and underwent lifestyle adaptations. eGDM women presenting after 2018 (n=46) were re-tested for cGDM at 24-28 weeks GA. Data on obstetric, neonatal, mental, metabolic and cardiovascular health outcomes were assessed during pregnancy and at 6-8 weeks postpartum.

Results:

Ninety percent of eGDM women treated early and retested had confirmed cGDM. Although eGDM women represented a high-risk group, adverse obstetric and neonatal outcomes were not increased compared to cGDM except for LGA (p=0.02). Mental health outcomes during pregnancy and postpartum did not differ between groups. Although eGDM women gained less weight during pregnancy (p=0.03), they had a more atherogenic lipid profile in the postpartum (≤0.001). The postpartum prevalence of metabolic syndrome based on waist circumference/BMI was increased by 2-fold (46-62% vs 23-34%), prediabetes by 3-fold (47.5% vs 15.3%) and diabetes by 7-fold (11.9% vs 1.6%) in eGDM. These differences remained unchanged after adjusting for all GDM-risk factors.

Conclusion:

A pre-existing underlying risk-profile associated with eGDM could explain these increased cardiometabolic risks.

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Decreasing severity of obesity from early to late adolescence associates with longitudinal metabolomic changes implicated in lower cardiometabolic disease risk

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Background/Introduction:

Obesity in childhood is associated with metabolic dysfunction, adverse subclinical cardiovascular phenotypes and adult cardiovascular disease (CVD). Longitudinal studies of youth with obesity investigating changes in severity of obesity with metabolomic profiles are sparse. We investigated associations between (i) baseline body mass index (BMI) and follow-up metabolomic profiles; (ii) change in BMI with follow-up metabolomic profiles; and (iii) change in BMI with change in metabolomic profiles (mean interval 5.5 years).

Methods:

Participants (n=98, 52% males) were recruited from the Childhood Overweight Biorepository of Australia (COBRA) study. At baseline and follow-up, BMI and the %>95th BMI-centile (percentage above the age-, and sex-specific 95th BMI-centile) indicate severity of obesity, and nuclear magnetic resonance spectroscopy profiling of 72 metabolites/ratios, log-transformed and scaled to standard deviations (SD), was performed in fasting serum. Fully adjusted linear regression analyses were performed.

Results:

Mean (SD) age and %>95th BMI-centile were 10.3 (SD 3.5) years and 134.6% (19.0) at baseline, 15.8 (3.7) years and 130.7% (26.2) at follow-up. Change in BMI over time, but not baseline BMI, was associated with metabolites at follow-up. Each unit (kg/m2) decrease in sex- and age-adjusted BMI was associated with change (SD; 95%CI; p-value) in metabolites of: alanine (-0.07;-0.11 to -0.04;p<0.001), phenylalanine (-0.07;-0.10 to -0.04;p<0.001), tyrosine (-0.07;-0.10 to -0.04;p<0.001), glycoprotein acetyls (-0.06;-0.09 to -0.04;p<0.001), degree of fatty acid unsaturation (0.06;0.02 to 0.10;p=0.003), monounsaturated fatty acids (-0.04;-0.07 to -0.01;p=0.004), ratio of ApoB/ApoA1 (-0.05;-0.07 to -0.02;p=0.001), VLDL-cholesterol (-0.04;-0.06 to -0.01;p=0.01), HDL-cholesterol (0.05;0.08 to 0.1;p=0.01), pyruvate (-0.08;-0.11 to -0.04;p<0.001), acetoacetate (0.07;0.02 to 0.11;p=0.005), and 3-hydroxybuturate (0.07;0.02 to 0.11;p=0.01). Results using the %>95th BMI-centile were largely consistent with age-, and sex-adjusted BMI measures.

Conclusion:

In children and adolescents with obesity, decreasing the severity of obesity was associated with changes in metabolomic profiles consistent with lower cardiovascular and metabolic disease risk in adults.

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Long-term effect of bariatric surgery on body composition in post-menopausal women

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Background/Introduction:

Bariatric surgery (BS) induces sustained loss of body fat mass (FM) with an inevitable loss of lean mass (LM). In contrast, menopause leads to deleterious changes in body composition (BC) related to estrogen deficiency including LM loss and increases in total and visceral adipose tissue (VAT). This study aims to assess BC in post-menopausal women after RYGB (Roux-en-Y gastric bypass) and compares their profile with age and BMI matched controls.

Methods:

Cross-sectional case-control study of 41 post-menopausal women aged ≥50 years who underwent RYGB at least 2 yrs prior to the study. Control population consists of 41 age and BMI-matched post-menopausal women. 2/41 BS patients and 8/41 controls were on hormone replacement therapy. Both groups had a DEXA scan to evaluate BC and a blood test to assess lipids and glucose metabolism markers.

Results:

Mean age was 58.4[SD=6.2] vs 59.4[SD=3.2] yrs (p=0.4) and mean BMI was 29.6[SD=4.9] vs 31.1[SD=5.6] kg/m2 (p=0.2) in BS patients vs controls, respectively. RYGB was performed a median of 90 months prior to DEXA. Total weight loss was 28.5%[SD=10] and excess weight loss was 67.5%[SD=29.2]. Compared controls, BS patients showed higher LM percentage (57.7%[SD=8%] vs 52.5%[SD=5%], p=0.001) and reduced FM percentage (39.4%[SD=8.4%] vs 45.9%[SD=5.4%] p<0.01) associated with lower VAT (751[SD=496] vs 1295[SD=688] gr, p<0.01), and android fat (44.6%[SD=7.5%] vs 48.21%[SD=4.9%]). Post-BS women showed a better lipid profile compared to controls (total cholesterol 4.8[SD=0.9] vs 5.5[SD=0.94] mmol/l, p<0.001; LDL 2.4[SD=0.8] vs 3.4[SD=0.8] mmol/l p<0.001; HDL 1.9[SD=0.4] vs 1.6[SD=0.4] mmol/l p=0.008). Glucose markers were not different.

Conclusion:

These findings appear promising for long-term evolution of body composition in postmenopausal women after bariatric surgery including LM preservation and FM reduction.

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Weight-loss on Liraglutide in a real-life Swiss obese cohort

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Background/Introduction:

We aim to investigate the clinical effectiveness of liraglutide treatment in combination with diet counselling in a real-world setting of an academic obesity center in Switzerland with reimbursement of liraglutide by the Swiss National Health Insurance Service.

Methods:

This is a prospective observational cohort of 42 patients. Biological and clinical data were collected at baseline and 4 months after initiation of liraglutide. Exclusion criteria were diabetes, previous treatment with liraglutide, history of bariatric surgery. Liraglutide dose was increased by 0.6mg every week to reach a dose of 3mg. Dietary intervention was provided before and during treatment to allow a daily energy deficit of 500 kcal/day. All patients were encouraged to exercise for 150 minutes/week. Primary outcome was the prevalence of weight loss at 4 months (≥ 5% and ≥ 10%).

Results:

Baseline BMI was 40.9(SD=5.8) kg/m2, mean age was 43(SD=11) yrs. Population was mostly female (64%). Percentage change in body weight was -8.4% at 4 months; 34/42 (80.9%) and 12/42 (28.6%) lost ≥5% and ≥10% body weight respectively. We observed significant improvement in glucose profile (5.7 SD=0.9 vs 5.3 SD=0.4 mmol/L, p=0.01; HbA1c 5.5% SD=0.4 vs 5.2% SD=0.3 p=<0.001) with no change in lipids. Interestingly, TSH decreased (2.6 SD=1.3 vs 2.1 ± 0.9 SD=0.4 mmol/L, p=0.05). The following adverse events were reported: constipation (10/42, 23.8%), nausea (8/42, 19.04%), esophageal burning (4/42, 9.5%), local skin reaction (4/42, 9.5 %). Liraglutide was discontinued in one patient because of abdominal pain and increased lipase levels.

Conclusion:

The weight-loss after only 4 months of liraglutide was better than previous real-life studies. Early diet counseling may be a powerful tool to improve liraglutide effect. Reimbursement of treatment does not affect the motivation of patients nor the outcomes and tolerance was excellent.

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Bone microarchitecture and strength in patients with long-standing type 1 diabetes

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Background/Introduction:

Type 1 diabetes (T1DM) is associated with an increased fracture risk, specifically at non-vertebral sites. The influence of glycaemic control and microvascular disease on skeletal health in long-standing T1DM remains largely unknown. We aimed to assess areal (aBMD) and volumetric bone mineral density (vBMD), bone microarchitecture, bone strength and bone turnover in patients with long-standing T1DM, defined as disease duration >25 years.

Methods:

We recruited 59 patients with T1DM (disease duration 37.7±9.0 yrs.; age 59.9±9.9 yrs.; BMI 25.5±3.7 kg/m2; 5-year median HbA1c 7.1% [IQR 6.82-7.40]) and 77 non-diabetic controls. Dual-energy X-ray absorptiometry (DXA), high-resolution peripheral quantitative computed tomography (HRpQCT) at the ultradistal radius and tibia and biochemical markers of bone turnover were assessed. Group comparisons were performed after adjustment for age, sex and BMI.

Results:

Patients with T1DM had lower aBMD at the hip ($p<0.001$), distal radius ($p=0.01$), lumbar spine ($p=0.04$) and femoral neck ($p=0.05$) as compared to controls. CTX, a marker of bone resorption, was significantly lower in T1DM ($p=0.005$). At the distal radius there were no significant differences in vBMD and bone microarchitecture between both groups. In contrast, patients with T1DM had lower cortical thickness (estimate -0.14 [-0.24, -0.05], $p<0.01$) and lower cortical vBMD (-28.66 [-54.38, -2.93], $p=0.03$) at the ultradistal tibia. Bone strength and bone stiffness at the tibia were significantly reduced in T1DM compared to controls. Both the altered cortical microarchitecture and decreased bone strength and stiffness were dependent on the presence of diabetic peripheral neuropathy.

Conclusion:

In addition to a reduced aBMD and decreased bone resorption long-standing, well-controlled T1DM is associated with a cortical bone deficit at the ultradistal tibia with reduced bone strength and stiffness. Diabetic neuropathy was found to be a determinant of cortical bone structure at the tibia potentially contributing to the increased non-vertebral fracture risk.

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Effect of long-term treatment with Glucagon-like peptide 1 receptor agonists on vasoactive hormones in euvolemic participants

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Background/Introduction:

Glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) elicit direct natriuretic action in humans. A decrease in angiotensin II, which has been observed after acute administration of GLP-1 RA, could explain the natriuretic effect and thereby the blood pressure lowering effect. However, dynamics of vasoactive hormones after long-term treatment with GLP-1 RA are inconclusive. Therefore, we aimed to investigate the effect of a three-week treatment with the GLP-1 RA, Dulaglutide, on vasoactive hormones i.e., renin, angiotensin II, aldosterone, MP-proANP as well as urinary sodium excretion in euvolemic participants.

Methods:

We enrolled 54 participants from two double-blind, placebo-controlled, cross-over trials, including 20 (37%) healthy participants and 34 (63%) patients with primary polydipsia at the University Hospital Basel. All participants were treated with either Dulaglutide 1.5 mg or placebo, i.e., 0.9% sodium chloride, in random order, subcutaneously once weekly over a three-week treatment phase. After each treatment phase, blood and urine samples were collected during an eight-hour study visit. The primary objective was to investigate the effect of Dulaglutide on vasoactive hormones.

Results:

Median age (IQR) was 27 years (24, 37) and 68% were female. After a three-week treatment phase, Dulaglutide showed no effect on plasma renin levels [treatment effect: -1.5 ng/L; 95% CI -4.40 to 0.80; p = 0.117], plasma angiotensin II levels [treatment effect: 0.35 pg/ml; 95% CI -0.50 to 1.40 pg/mL; p=0.239], and plasma aldosterone levels [treatment effect: 9.50 pmol/L; 95% -58.00 to 92.00 pmol/L; p=0.561] in comparison to placebo. The fractional excretion of sodium and 24h urinary sodium excretion remained unchanged (p=0.224 and p=0.163). Dulaglutide significantly decreased plasma MR-proANP levels [treatment effect: 10.60pmol/L; 95% CI -14.70 to -7.90; p < 0.001] and systolic blood pressure [median: 3 mmHg; 95% CI -5 to 0; p = 0.036], whereas heart rate increased [median: 5 bpm; 95% CI 3 to 11; p < 0.001].

Conclusion:

In euvolemic participants, a three-week administration of Dulaglutide reduced MR-proANP levels without changes in renin, angiotensin II, aldosterone, and urinary sodium excretion. The reduction in MR-proANP might be an important mediator contributing to the blood pressure lowering effect of GLP-1 RAs.

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Clinical Challenges in Diagnosis of Pheochromocytoma

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Background:
Pheochromocytoma/paraganglioma (PPGL) is a rare tumor entity, which affects approximately 0.8/100,000 persons per year. However, their incidence is certainly underestimated, as almost 50% of tumors are diagnosed at autopsy. In part, this is due to the broad spectrum of clinical presentation, with only 25% of patients demonstrating the typical triad of headache, tachycardia and sweating. In addition, biochemical screening is cumbersome with various preanalytical and analytical factors leading to inconclusive biochemical results, especially in physiological/ paraphysiological circumstances associated with elevated adrenergic activity.

Clinical Case:
A 37-year-old man presented with increasingly debilitating episodes of excessive sweating, combined with nervousness and heat intolerance, initially occurring during physical activity, but over time also when confronted with distinct emotional distress. He attributed his condition to a psychological trauma he faced 7 years ago. As alcohol lead to symptom relief, he increased consumption and developed psychological and physical dependence. On clinical examination, he appeared slightly agitated, with marked sweating on trunk, head and neck. Blood pressure was 117/93 mmHg, BMI 25 kg/m2. The endocrinological workup was unremarkable except for prediabetes [HbA1c 5.8%, reference: 4.4-5.6; fasting glucose 6.4 mmol/l, reference 3.9-5.6], elevated free metanephrines [1.37 nmol/l, n <0.45] and normetanephrines [0.82 nmol/l, n <0.67].
Since the initial clinical presentation was consistent with acute alcohol withdrawal, we decided to repeat blood sampling after prolonged alcohol abstinence, by which time normetanephrines had normalized, but metanephrines remained elevated, albeit to a lesser degree [1.01 nmol/l, n <0.45]. Metanephrines in a 24h urine sample were also conspicuously high [5581 nmol/l, n 325 – 1530]. Subsequent 18F-DOPA-PET/CT imaging revealed a 20x23 mm lesion of the left adrenal gland with increased DOPA uptake (SUV max 9.0), in contact to the left kidney and the paraaortic diaphragm without infiltration.
There was no evidence of other DOPA-avid lesions. After laparoscopic left adrenalectomy, pheochromocytoma was histologically confirmed. On genetic testing, there was no evidence of pathogenic germline mutations associated with hereditary syndromes associated with PPGL.

Discussion:
This patient`s symptoms initially seemed plausibly explained by past psychological trauma, consecutive social phobia and alcohol dependence. Alcohol intoxication or withdrawal with subsequent sympathetic stimulation may lead to elevated metanephrine levels during biochemical assessment, and are therefore potentially relevant confounders given the globally high incidence of alcohol abuse. Alcohol consumption results primarily in increase of adrenaline levels, with a delayed increase of normetanephrines, a pattern that matched the initial biochemical results of our patient. Confronted with persistent elevation of plasma metanephrines even after withdrawal symptoms had resolved, we performed (18)F-DOPA-PET-CT to confirm the suspected diagnosis, since this imaging modality has a reported specificity of up to 100% for PPGL. After left laparoscopic adrenalectomy, the patient became asymptomatic with normalized glucose metabolism and plasma metanephrines, confirming the relationship between clinical presentation and catecholamine excess.

Conclusion:
DOPA-PET is a useful tool in diagnostics of hormonally active PPGL when clinical presentation and biochemical screening are inconclusive