01

Associations between maternal and fetal inflammatory biomarkers and anthropometry in the first year of life in offspring of women with GDM

Author/Address of institution:

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Background/Introduction:

Gestational Diabetes Mellitus (GDM) is associated with chronic, low-grade inflammation. Whether this environment affects offspring anthropometry during early childhood remains to be elucidated. The aim of this study was to assess the utility of maternal and fetal (cord blood) inflammatory biomarkers in the prediction of offspring anthropometry up to 1 year in pregnancies with GDM.

Methods:

In this prospective secondary analysis of the MySweetheart trial, we included n=193 women with GDM and their offspring that were followed during pregnancy up to 1 year postpartum and had valid offspring data up to one year. Maternal and fetal (cord blood, N=39) predictors included inflammatory biomarkers-CRP, IL-6, and TNF-α at the first GDM visit and in the cord blood. Offspring outcomes included small and large for gestational age (SGA, LGA), as well as sex- and age-adjusted weight and BMI at birth and at 1 year. Univariate and multivariate regression models were performed.

Results:

Mean maternal age was 33.6 ± 4.8 years, and mean pre-pregnancy BMI was 25.9 ± 5.6 kg/m2. In the models including only maternal predictors, TNF-α at the first GDM visit was negatively associated with offspring weight and BMI at birth and at 1 year, and positively with SGA (all p ≤0.034). In models including only fetal predictors as well as in the combined model, cord blood hs-CRP showed an inverse association with BMI at 1 year (all p ≤0.020). All associations were independent of maternal prepregnancy BMI, age, and ethnicity.

Conclusion:

Both, maternal and fetal inflammatory biomarkers influenced offspring anthropometry during the first year of life, independent of maternal age, pre-pregnancy BMI, and ethnicity. These results suggest that low-grade inflammation associated with GDM during pregnancy may inversely affect offspring anthropometry during infancy.

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

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Background/Introduction:

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

Methods:

This study combined data from two diagnostic studies conducted at three tertiary medical centers. In total, 82 participants (n=39 with AVP-D, n=28 with PP, and n=15 healthy controls [HC]) underwent a psychological evaluation with standardized questionnaires at study inclusion. Anxiety levels were assessed using the State-Trait Anxiety Inventory, mood using the Beck's Depression Inventory, alexithymia using the Toronto Alexithymia Scale, and overall physical and mental health using the Short Form 36 Health Survey (SF-36). Higher STAI, BDI, and TAS scores indicate higher anxiety, depression, and alexithymia levels. Higher SF-36 scores indicate better health and less disability.

Results:

Compared with HC, patients with AVP-D and PP showed increased levels of anxiety (HC 28 points [24, 31] vs. AVP-D 36 points [31, 45], $p<0.01$; vs. PP 38 points [33, 46], $p<0.01$), depression (HC one point [0, 2] vs. AVP-D 7 points [4, 14], $p<0.01$; vs. PP 7 points [3, 13], $p<0.01$), and alexithymia (HC 30 points [29, 37] vs. AVP-D 43 points [35, 54], $p<0.01$; vs. PP 46 points [37, 55], $p<0.01$). Levels of anxiety, depression, and alexithymia showed no difference between patients with AVP-D and PP ($p=0.58$, $p=0.90$, $p=0.50$). Compared with HC, patients with AVP-D and PP reported comparable reduced self-reported mental health scores (HC 84 [68, 88] vs. AVP-D 60 [52, 80], $p=0.05$; vs PP 60 [47, 74], $p<0.01$).

Conclusion:

This is the first study demonstrating comparable increased levels of anxiety, depression, alexithymia, and overall reduced mental health in patients with AVP-D and PP. Based on these data, psychopathological findings should not be used as a hallmark to differentiate between both conditions.

03

Evaluation of the EU-TIRADS system for the risk stratification of thyroid nodules in three Swiss referral centers

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Background/Introduction:

Ultrasound (US) based risk stratification is the recommendend initial step in the workup of thyroid nodules. This prospective cohort study in three Swiss referral centers evaluated the diagnostic accuracy of the EU-TIRADS system and its individual features for the prediction of thyroid cancer.

Methods:

Patients undergoing fine needle aspiration biopsy according to the EU-TIRADS criteria were enrolled in a prospective cohort study in the cantonal hospitals of St. Gallen, Aarau and Lucerne. Cytological evaluation was performed using the Bethesda classification system. Data are reported for nodules with a definitive diagnosis (benign or malignant cytology (Bethesda II, VI) and/or histology). Descriptive statistics (percentages and 95% confidence intervals), chi square and biserial correlation tests are used as appropriate.

Results:

114 of 843 (13.5%) nodules investigated were malignant (PTC 73.7%, FTC 14.0%, MTC 1.8%, ATC 2.6%, other 7.9%). Malignancy rates in the EU-TIRADS categories 2 (n=35, 4.1%), 3 (n=305, 36.2%), 4 (n=254, 30.1%), and 5 (n=249, 29.5%) were 5.7% (0-13.4), 4.6% (2.2-6.9), 9.1% (5.5-12.6)and 30.1% (24.4-35.8; $p<0.0001$). Among the individual high-risk US features the odds ratios (OR, 95% CI) for malignancy were 7.4 (4.5-12.3) for the presence of irregular margins, 7.3 (4.3-12.5) for marked hypoechogenicity, 4.4 (2.7-7.4) for the presence of microcalcifications and 2.5 (1.5-4.1) for the presence of an irregular shape. The number of US high risk features was siginificantly associated with malignancy risk ($r=0.361$, $p<0.0001$) and it increased to 40.1% (31.0-52.2) and 70.6% (48.9-92.2) if >= 2 and 3 were present, respectively. The presence of a benign or low risk US pattern (EU-TIRADS 2 and 3) was associated with a high likelihood for a benign outcome (PPV 95%, 95%CI 93.0-97.5). Maximum nodule size, nodule volume and the maximum size threshold of 4 cm were not associated with malignancy.

Conclusion:

The present analysis confirms the usefulness of US based risk stratification using the EU-TIRADS system in the work-up of thyroid nodules. Consideration of the individual components of the classification system may further improve risk prediction.

04

Tirzepatide Improves HRQoL Compared to Insulin Lispro in Poorly Controlled Basal Insulin-treated Adults with Long-standing T2D (SURPASS-6)

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Background/Introduction:

Tirzepatide (TZP), a first-in-class GIP/GLP-1 receptor agonist, resulted in significant improvements in HbA1c and body weight compared to insulin lispro (iLispro) at 52 weeks in the SURPASS-6 study. We compared the HRQoL of participants with T2D treated with TZP (all doses pooled) versus iLispro, both added to basal insulin, in SURPASS-6.

Methods:

Adults with T2D and inadequate glycemic control were randomized (1:1:1:3) to TZP 5, 10, or 15 mg QW, or iLispro TID, as add-on to optimized insulin glargine, with or without metformin, for 52 weeks in this open-label, multicenter, Phase 3b study. HRQoL was measured at baseline and endpoint (Week 52) using the SF-36v2 acute form comprised of 8 domains and 2 component summary scores.

Results:

Overall, 1428 participants with mean baseline age 59 y, T2D duration 14 y, HbA1c 8.8% and BMI 33.1 kg/m2 were randomized. At endpoint, TZP-treated participants had statistically significantly improved scores across all SF-36v2 domains and component summaries compared to iLispro-treated participants, with the largest differences observed in the General health (LS mean [SE] change 3.0 [0.31] vs. -0.1 [0.32]) and Vitality (1.5 [0.31] vs. -1.1 [0.32]) domains.

Conclusion:

TZP treatment resulted in greater improvements across multiple domains of HRQoL than iLispro in adults with long standing T2D already treated with basal insulin.

05

Prevalence of micro- and macrovascular complications and control of related risk factors in tertiary diabetes care - a SwissDiab Study

Author/Address of institution
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Background/Introduction

Cardiovascular disease is a leading cause of morbidity and mortality in type 2 diabetes mellitus (T2DM), and treatment guidelines have evolved to focus not only on glycemic control but more on overall cardiovascular risk reduction. However, current data on the prevalence of micro- and macrovascular complications among patients with T2DM in Switzerland are limited. The aim of the current study was to assess the prevalence of micro- and macrovascular complications and the control of related risk factors among patients enrolled in the Swiss Diabetes registry (SwissDiab) and a study visit between 2020-2022.

Methods

SwissDiab is a multicenter longitudinal observational study of outpatients with diabetes in tertiary diabetes care at the Cantonal Hospital of St. Gallen (coordinating centre) and Basel, Bern, Geneva, and Zürich University Hospital. Patients with T2DM and a study visit between 01.01.2020-31.12.2022 were included in the current analysis. Data from the latest available visit was used unless missing data justified the use of a previous visit. Patients were advised to arrive fasted (>8 hrs), and blood biomarkers were measured according to routine methods at the laboratory medicine at each hospital. The prevalence of micro- and macrovascular complications was determined, further stratified by sex and diabetes duration (<10 years or ≥10 years). Differences in continuous and categorical traits were determined with Student's t-test and Chi-Square test, respectively. Risk associated with sex and diabetes duration (10 year increment) was further assessed by multivariable logistic regression analysis, additionally adjusted for age.

Results

A total of 431 patients with T2DM were identified. The median (IQR) age was 66.5 (58.2-73.8) years, diabetes duration 15 (9-22) years, HbA1c 7.3 (6.7-8.1)% and 26.5% were females. Lipid-lowering medication was prescribed 86.2% of the patients and 84.6% were on statin therapy (low-intensity, 1.1%; moderate-intensity, 35.1%; high-intensity, 62.7%; information missing for 1.1%). Antihypertensive medication was prescribed 79.9%, oral antidiabetic medication 90.9%, SGLT2 inhibitor 45.1%, GLP-1 receptor agonist 36.5%, and 64.3% were on insulin therapy.

Overall, 80.5% of the patients suffered vascular complications; 74.5% microvascular and 43.9% macrovascular complications. Patients with microvascular and macrovascular complications had a longer diabetes duration than patients without (17 [11-24] years vs 11 [6-17] years and 19 [12-25] years vs 13 [7-20] years, respectively; *P*-values <0.0001). Macrovascular complications were more common among men than women (48.6% vs 30.7%, *P*-value =0.001). Based on a multivariable logistic regression models including diabetes duration, sex and age, each 10-year increase in diabetes duration increased the odds of microvascular complications (OR=1.55, 95% CI [1.11, 2.15]) and macrovascular complications (OR=1.61, 95% CI [1.24, 2.08]), and the risk of macrovascular complications was higher among males than females (OR=2.22, 95% CI [1.37, 3.60]).

Conclusion

Despite relatively good glycemic control, prevalence of micro- and macrovascular complications among patients with T2DM enrolled in SwissDiab was high, the latter more common among males than females. Although the vast majority of patients benefited from pharmacological control of blood pressure and lipids, SGLT2 inhibitors and GLP-1 receptor agonists, both with proven cardiovascular benefits, were prescribed less than half of the assessed patients.

06

Nivolumab-induced Diabetes Mellitus – A Case Report and Literature Review of the Treatment Options

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Background/Introduction:

Immune checkpoint inhibitor (ICI) treatment has become important for treating various cancer types. However, ICI treatment can lead to endocrine immune-related adverse events (irAEs). Here, we report a rare case of a new-onset of diabetes mellitus (DM), caused by nivolumab, and we discuss the feasible treatment options with focus on TNF-antagonism.

Methods:

A 50-year-old man was diagnosed with metastatic renal cell carcinoma. Due to systemic progression, a combined immunotherapy with ipilimumab/nivolumab was initiated, followed by nivolumab monotherapy due to partial response. 14 months after treatment start, the patient presented himself with a new onset of DM with diabetic ketoacidosis. In addition to intravenous fluids and insulin perfusor, the patient received infliximab infusions (TNF-alpha inhibitor) four days and two weeks after the initial diagnosis of DM. However, C-peptid values remained low, indicating a sustained insulin deficiency, and the patient remained on insulin treatment.
Two months later, nivolumab treatment was re-started without destabilization of the diabetic situation.

Results:

-

Conclusion:

The administration of corticosteroids is not recommended in ICI-induced DM. In contrast to previous reports, the administration of infliximab – in an attempt to salvage the function of the beta-cells – was not successful in our patient, possibly due to the absence of insulin resistance. There is so far no evidence for immunosuppressive treatment in ICI-induced DM. Prompt recognition and immediate start of insulin treatment are most important.

07

Case report MODY 2: Non-invasive prenatal diagnostic (NIPD) during early pregnancy allows precision medicine.

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Background / Introduction:
Glucokinase–maturity-onset diabetes of the young (GCK-MODY) is caused by heterozygous inactivating mutations in the *GCK* gene and is characterized by mild hyperglycemia due to a higher blood glucose threshold for insulin secretion. Outside of pregnancy, patients are asymptomatic and do not require treatment since they are not at risk for long-term diabetes complications. Due to the autosomal dominant inheritance, there is a 50% probability that the fetus inherits the maternal mutation. In this case, its insulin secretion is set at the same threshold as the mother's, and no fetal growth excess will occur. When the fetus has not inherited the maternal mutation, maternal hyperglycemia will trigger increased fetal insulin secretion and growth, with a high risk of macrosomia. According to current recommendations, maternal insulin treatment is only recommended if there is a fetal sign of macrosomia, an indirect sign of a fetal non-carrier state. This leads to the need for frequent sonographic checks and carries the risk of beginning the therapy too late. Non-invasive prenatal diagnosis (NIPD) can be achieved with the relative haplotype dosage (RHDO) method, which relies on allelic imbalance caused by small amounts of fetal circulating cell-free DNA in the maternal blood. The knowledge of the fetal genotype helps to start insulin therapy early if necessary or to avoid unnecessary treatment, as intensive maternal insulin treatment carries the danger of severe hypoglycemia for pregnant women and leads to decreased fetal insulin secretion and, consequently, a reduction in birth weight.

Methods / Results:
The 30-year-old patient with *GCK*-diabetes (c.608T>C) was referred to us with the desire to have children. To save time, we decided to determine parental haplotypes before pregnancy. Due to the lack of previous offspring, genotyping was necessary for the mother and father and the maternal grandparents. This method is less efficient than with a previous child but possible in most cases for non-consanguineous couples. Circulating fetal DNA fraction increases during pregnancy, which makes a meaningful result more likely. The non-invasive search for the familial mutation in the fetus from maternal plasma is therefore recommended between 12 to 16 weeks of pregnancy. We performed testing in week 14 and received the result 10 days later.
The analysis showed, with a likelihood of 1.6×10^6 : 1 that the fetus inherited the low-risk maternal haplotype, which does not carry the familial mutation. The patient started with capillary measurements, which surprisingly showed the expected increased fasting blood glucose and postprandial values. Despite the absence of other risk factors (healthy, BMI 23.9 kg/m², family history bland), we suspect a gestational diabetes component. In addition to nutritional advice, we established a treatment with basal and bolus insulin (NovoRapid and Levemir) in 18th week of pregnancy. We tried to reach the recommended values for GDM (fasting blood sugar ≤ 5.3mmol/l, 1h postprandial ≤ 8.0 mmol/l). Due to fluctuating blood sugar levels, a switch from Levemir to Tresiba was done in 28th week of pregnancy and led to stabilisation. From week 26th of pregnancy, the CGM Dexcom G6 was used for therapy monitoring. With a total daily dose of about 50 units of insulin (50 % bolus, 50% basal), we reached a time in range (3.9 – 8 mmol/l) of 75% with an acceptable number of hypoglycemias (2 % between 3 and 3.9 mmol/l) during the third trimester. Frequent sonographic controls (every two weeks) revealed no abnormalities in the growth of the fetus, whose birth is expected at the end of July.

Conclusion:
The non-invasive prenatal diagnostic test for determining fetal glucokinase mutations enables precision medicine during pregnancy. This case report aims to raise awareness about this test.

08

Identification of the molecular changes leading to beta-cell dysfunction and enhanced insulin sensitivity in members of an affected family – HEREDIA-Study

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Background/Introduction:

The classic distinction between type 1 and type 2 diabetes mellitus is being challenged more and more at the time being. There is an increasing number of subtypes and variants of the disease and instead of insisting upon the conventional types and differentiation, experts have begun to focus on therapy outcomes. To better understand the disease, this study aimed to phenotypically and genotypically characterise the particular form of diabetes mellitus in an affected family with pronounced occurrence of the disease in every single of four generations. To achieve this goal, as many of the living family members needed to be included in the study.

Methods:

This was an observational clinical study among members of the affected family. Participants have been recruited on a voluntary basis. The subjects underwent a thorough physical examination, a 75g oral glucose tolerance test with measurements of insulin, c-peptide and glucose, routine blood tests and a retina scan during a single visit. Throughout the course of the following two weeks, the participants wore a continuous glucose monitoring system to track their blood glucose levels in their everyday life.

Results:

15 possible subjects have been informed about all the study details. Out of those, 14 decided to participate in the study. There were no dropouts. 4 out of the 14 participants showed impaired glucose tolerance during the glucose tolerance test. Mean HbA1c was 5.67% (range 4.8% - 6.9%). 85.7% of the participants were of a normal weight (mean body mass index 22.9 kg/m2, range 18.1 - 30.8 kg/m2). Mean insulin sensitivity index was 42.94 (range 14.89 - 125.46). Mean insulin secretion index was 36.63 (range 3.97 - 66.38). Subjects did not present any signs of diabetic retinopathy. The continuous glocose monitoring showed that blood sugar levels could be lowered through exercise. High carbohydrate intake increased blood sugar levels to supraphysiologic levels in affected subjects. Results from genetic analyses are pending. No adverse events have been recorded.

Conclusion:

The disease affects mainly women. It is characterized by slow progression, low insulin secretion and normal insulin sensitivity in lean individuals. Different stages and various degrees of characteristics seem to be present in the family. Only direct descendants of the twin women could be identified as definitely affected. A genetic root cause for the disease seems plausible; however, the results from the genetic analyses need to be taken account of to pass a final judgement.

09

Effect of Romosozumab on Tissue Thickness–Adjusted Trabecular Bone Score in Postmenopausal Women with Osteoporosis and Diabetes: Results From the ARCH Study

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Background/Introduction:

Diabetes mellitus is associated with reduced bone strength and increased fracture risk. Trabecular bone score (TBS), a gray-level texture index derived from lumbar spine (LS) duel-energy X-ray absorptiometry (DXA) scans, has been reported to be decreased in patients with diabetes and is associated with an increased fracture risk, independent of bone mineral density (BMD). In the ARCH trial, romosozumab (Romo), an osteoanabolic with the dual effect of increasing bone formation and decreasing bone resorption, significantly improved bone mass and bone strength leading to superior fracture risk reduction vs alendronate (Aln) alone. Here, we examined the effect of Romo-to-Aln vs Aln-to-Aln on LS BMD and TBS in ARCH patients with diabetes.

Methods:

In ARCH, postmenopausal women with osteoporosis and prior fracture were randomized 1:1 to Romo 210 mg SC monthly or Aln 70 mg weekly for 12 months, followed by Aln 70 mg PO weekly for 24 months in both groups. This post hoc analysis included a subgroup of women from ARCH who had diabetes mellitus at baseline and had LS DXA scan measurements at baseline and ≥1 post-baseline visits (Romo-to-Aln, n=195; Aln-to-Aln, n=165). BMD and TBS (determined by an updated tissue thickness–adjusted TBS algorithm [TBS_{TT}]; TBS iNsight^{TM} v4.0 [Medimaps]) were assessed on LS DXA scans at baseline, Month 12, Month 24, and Month 36.

Results:

Baseline LS BMD was –2.63 for Romo and –2.89 for Aln; baseline LS TBS_{TT} was 1.006 and 1.010, respectively. Treatment with Romo led to significantly greater gains vs Aln at Month 12 in least squares mean percentage change from baseline in LS BMD (12.0% vs 5.0%, $p<0.001$) and TBS_{TT} (4.1% vs 1.5%, $p<0.001$). Greater gains with Romo were maintained after transition to Aln and persisted significantly to Month 36 vs Aln alone for both LS BMD (14.8% vs 7.9%, $p<0.001$) and LS TBS_{TT} (5.2% vs 2.7%, $p=0.019$). In the Romo-to-Aln group, the percentage of women with “normal” TBS values ($TBS_{TT}>1.074$) increased from 23.6% at baseline to 50.0% at Month 36 and those with “degraded” TBS values ($TBS_{TT}\leq1.027$) decreased from 55.8% to 33.9% ($p<0.001$). A similar trend, albeit with smaller improvement, was observed in the Aln-to-Aln group. TBS_{TT} percentage changes were unrelated to LS BMD percent changes from baseline to Month 36 (Romo-to-Aln, $r^2=0.1493$; Aln-to-Aln, $r^2=0.0429$).

Conclusion:

In postmenopausal women with osteoporosis and diabetes, 12 months of Romo followed by 24 months of Aln significantly improved LS BMD and TBS as measured by TBS_{TT} (independently of BMD) to a greater extent when compared with 36 months of Aln alone. These changes may reflect a greater improvement of bone strength by Romo vs Aln in patients with diabetes.

Funding: Amgen Inc. and UCB Pharma

The use of AID systems improves glycemic control in adolescents with type 1 diabetes and attention deficit hyperactivity disorder – a single center case series

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Background / Introduction:
Children and adolescents with type 1 diabetes (T1D) and attention deficit hyperactivity disorder (ADHD) are known to have poorer glycemic control than children with T1D without ADHD. Currently available automated insulin delivery (AID) systems have the potential to support adolescents with T1D and psychiatric comorbidities such as ADHD. The aim of this case series was to describe glycemic control before and after start of AID in youth with ADHD.

Methods:

Children and adolescents with T1D and ADHD followed up at the UKBB who changed their insulin therapy to an automated insulin delivery (AID) system were identified. Demographics and glycemic parameters (mean HbA1c, mean percentage time spent between 3.9 and 10mmol/L (TIR) and mean percentage time spent < 3.9mmol/L (TBR)) one year before and one year after AID start were obtained from medical records and compared using a Wilcoxon rank sum test.

Results:

Five adolescents (3 male and 2 female) with T1D and ADHD started on an AID system between February 2019 and February 2022. Median (range) diabetes duration was 1.1 years (0.8-14.4 years), median age at AID start 13.6 years (11.0-16.6). Median (range) TIR increased from 45.5% (33.8-59,6) to 71% (45.3-76.7), p=0.043, while TBR did not significantly change 2.8% (1.3-11.3) vs 2.3%, (1.5-5.3), p= 0.225. All adolescents except one showed a trend towards lower HbA1c values, median HbA1c was 7.9% (6.9-8.9) before vs. 7.5% (6.5-9.4) after AID start, p=0.5. No episodes of diabetic ketoacidosis (DKA) or severe hypoglycemia (SH) occurred during the two-year follow-up period.

Conclusions:

This case series illustrates that AID can facilitate diabetes management in adolescents with T1D and ADHD. It points towards improved glycemic control and less time in hypoglycemia without an event of DKA or SH. These observational findings warrant verification in a larger cohort with longer follow-up and comparison between children and adolescents with T1D and ADHD with and without AID.

AI companion to transition from a glucocentric approach to personalised cardio-renal-metabolic optimization in type 2 diabetes

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Background/Introduction:

With emerging pharmacotherapies and improved pathophysiological insights, diabetes management is moving from a pure glucocentric view to a more holistic approach centred around people's cardio-renal-metabolic health. The use of Artificial intelligence (AI) opens new avenues to personalise treatment choices while reducing failures related to one-size-fits-all approaches. Such AI-driven platforms that integrate data from electronic health records with data from wearable technologies have the potential to effectively implement precision medicine by clinicians caring for people with diabetes by continuous learning from real world evidence data.

Methods:

Based on the new EASD/ADA guidelines on managing type 2 diabetes and local expert knowledge (including insulin titration and tapering protocols), we developed a neural network that mimics guideline-conform therapeutic management decisions of diabetes specialists with a 95% accuracy. This is used to evaluate the adherence of clinicians using a retrospective data analysis and to learn how to improve glucose control alongside with meeting other treatment goals such as body weight reduction.

Results:

Applying the technology to usual care data from a total of 1,640 patients with diabetes (insulin and non-insulin treated), we find that 60% of a total of 1,548 therapeutic decisions agree with the algorithm. Testing for the impact on glucose control, the weighted average relative reduction in HbA1c over treatment regimens that are in-line with guidelines (-5.62%, N=283) significantly exceeded those that were not (+0.22%, N=362); also, proportion testing for a target relative HbA1c reduction of 5% yields a p-value of 4*10-7 showing clear retrospective outperformance of guidelines therapies over the alternatives, underscoring the potential for optimisation. Results from dual optimization will be discussed in a retrospective analysis, highlighting both the promise and the limitations from AI driven precision medicine therapies that are anchored in medical guidelines and reflect specificities of smaller cohorts justified by glucose and other outcomes (e.g. body weight, lipid control, kidney function) .

Conclusion:

In this proof-concept study, we demonstrated that a neural network can mimic clinical guidelines and learn from therapeutic outcomes to improve diabetes management beyond glucose control. First results provide insights into its usability and therapeutic efficacy in daily clinical practice.

12

Hypercalcemia due to severe Amiodarone-induced Thyrotoxicosis

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Background/Introduction:

Hypercalcemia due to hyperthyroidism has been previously described with usually mild to moderate hypercalcemia. There are only few case reports on amiodarone-induced thyrotoxicosis with associated hypercalcemia. Here, we describe such a case which was successfully treated with total thyroidectomy.

Methods:

Severe thyrotoxicosis was detected in a 60-year old patient with ischemic cardiopathy and supraventricular tachycardia treated with amiodarone (TSH <0.01mU/l and fT4 > 100pmol/l). The patient was asymptomatic and diagnostic work up showed negative TSH receptor antibodies (TRAb) and an enlarged thyroid without any nodules. Thus we diagnosed an amiodarone-induced thyrotoxicosis type 2. Thyrotoxicosis was additionally aggravated by the administration of iodine-based contrast agent prior to reviewing the lab results. Therapy with carbimazole, natrium perchlorate and prednisone was started immediately without improvement of thyroid values and the still asymptomatic patient refused to undergo total thyroidectomy.

Results:

Three weeks later the patient presented himself with emesis and nausea. Thyroid values remained unchanged but newly elevated serum calcium levels (2.89mmol/l) and elevated serum phosphorus levels were detected in the context of a low-normal PTH level and low vitamin D level. The patient was then willing to undergo surgery. Total thyroidectomy without complications was performed with resolution of hypercalcemia within days.

Conclusion:

Amiodarone-induced thyrotoxicosis with associated hypercalcemia is rare. However, patients with known hyperthyroidism and symptoms of hypercalcemia should be screened and treated accordingly. Therein, treatment of hyperthyroidism, especially total thyroidectomy, is beneficial in resolving hypercalcemia.

13

And yet it grows: microprolactinoma in pregnancy - a case report

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Introduction
In female patients with prolactinoma and infertility treatment with dopamin agonists can normalize prolactin levels and restore fertility. Usually this treatment is suspended once pregnancy is confirmed. However, relevant prolactinoma growth in pregnancy can be observed. Therefore, prolactin levels are checked every trimester in macroadenomas. Routine controls of prolactin during pregnancy in microprolactinoma are discussed controversially, as the risk of growth is low.

Methods
Here we describe the case of a pregnancy associated significant enlargement of a microprolactinoma.

Results
A 26 year old patient was referred to our outpatient clinic with a one year history of secondary amenorrhea after stopping the combined oral contraceptive pill, as well as galactorrhea, secondary hypogonadism and elevated prolactin serum levels (240µg/l, ref. 4.8-23.3µg/l). Other pituitary hormones were normal. The pituitary MRI revealed a 9x9mm microadenoma in the right pituitary lobe.
Treatment with cabergoline 0.5mg/week was initiated thereafter. After 4 and 8 weeks there was a complete normalisation of the serum prolactin levels (2.2µg/l and 4.4 µg/l, respectively) and the patient reported a restoration of her mestrual cycle. Only 3 months after treatment initiation she reported a pregnancy in the 7th week of gestation. Therefore, treatment with cabergoline was stopped and follow-up visits every trimenon were scheduled. In the 31st week of gestation there was a significant rise in prolactin to 567µg/l without headaches or visual field defects. On MRI a volumetric 3-fold growth (1.6x1.2x1.1cm) including infiltration of the sinus cavernosus but without extension toward the optic chiasm was reported. Due to this invasive growth, the treatment with cabergoline was resumed at 0.25mg per week. Two weeks later the prolactin levels already decreased by appr. 50%. The further course of the pregnancy was unremarkable and a healthy baby was delivered after the induction of labor at 41+4 weeks of gestation. Despite continuous cabergoline treatment, the patient was able to breastfeed and prolactin levels fell to a nearly normal range 25.9µg/l (ref. 4.8-23.3µg/l) within 10 days postpartum.
A pituitary MRI 6 weeks after the delivery showed a significant reduction of the size of the macroprolactinoma (10mm). As the milk production declined and the patient had started to supplementary feed her baby the dose of cabergoline was increased to 0.5mg per week despite the risk for ablactation in order to suppress the prolactin completely.

Conclusion
A significant growth of pituitary microproalctinomas during pregnancy is rare, occurring only in 2.4% of the cases. Therefore, routine screening of prolactin levels during pregnancy is discussed controversially, as it can be difficult to distinguish the physiological prolactin rise from that associated with adenoma growth. However, as seen in our patient, an elevation of prolactin levels above 400µg/l should raise the suspicion of a significant adenoma growth and warrant further investigations including pituitary MRI scan as well as clinical and visual field testing. In enlarging prolactinomas dopaminergic therapy can be resumed to prevent further growth and alleviate symptoms, as it is considered safe during pregnancy. Our patient was even able to breastfeed while on low dose cabergoline.

14

Tirzepatide reduces the predicted risk of developing type 2 diabetes: post-hoc analysis of the SURMOUNT-1 trial

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Background/Introduction:

The effect of tirzepatide (TZP) on the risk of developing type 2 diabetes (T2D) in people with obesity or overweight is unknown. We aimed to assess the impact of TZP treatment on T2D risk in the Phase 3 SURMOUNT-1 trial through predictive modelling.

Methods:

Cardiometabolic Disease Staging, a validated robust tool providing 10-year risk estimates of T2D, was applied to the SURMOUNT-1 trial to derive risk scores at baseline, 24, and 72 weeks. Mean risk scores and change from baseline to week 72 were calculated from a mixed model.

Results:

A total of 2539 participants were randomized 1:1:1:1 to TZP 5/10/15 mg and placebo (PBO) (mean age=45 years; female=68%; White=71%). Mean risk scores at baseline ranged from 23–24% and did not differ between groups. Mean risk scores for TZP 5, 10, 15 mg, and PBO groups were 13%, 11%, 11%, and 21% at week 24 and 11%, 9%, 9%, and 23% at week 72, respectively. At week 72, the absolute mean risk reductions from baseline were 12%, 14%, 15%, and 1% for TZP 5 mg, 10 mg, 15 mg, and PBO groups, corresponding to median relative risk reductions of 60.3%, 68.3%, 69%, and 10.8%, respectively. This resulted in significantly greater risk reduction between TZP groups vs. PBO (5 mg: 12%, 10 mg: 14%, 15 mg: 14%; $p<0.001$).

Conclusion:

Treatment with TZP significantly reduced the 10-year predicted risk of developing T2D compared to PBO; most of the reduction in predicted risk was achieved by week 24.

Blood pressure changes during smoking cessation on dulaglutide and placebo treatment - A secondary analysis of the randomized, double-blind, placebo-controlled SKIP trial

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Background/Introduction:

Intermittend transient blood pressure increases are observed in people who smoke and have been linked to their high cardiovascular risk. It is unclear if and how blood pressure values change after smoking cessation. While lower blood pressure values have been suggested, some studies point to increased values after smoking cessation, which may be due to post-cessational weight gain. We have recently shown that the glucagon-like peptide-1 (GLP-1) analog dulalgutide conteracts postcessational weight gain.
The aim of this secondary analysis was to investigate blood pressure changes during smoking cessation in dulaglutide versus placebo treated individuals. We hypothesize that dulaglutide treated participants who quit smoking will have the most beneficial effect on blood pressure change (lower values) compared to placebo treated participants or those who continue smoking.

Methods:

This is a predefined secondary analysis of the SKIP trial, a randomized, double-blind, placebo-controlled trial. Participants (n=255) underwent a 12-week smoking cessation program including standard of care (behavioral counselling and varenicline) and weekly injections of dulaglutide 1.5mg or placebo.
The primary endpoint was the change in systolic blood pressure during smoking cessation (week 12 compared to baseline) in dulaglutide and placebo treated individuals while taking into consideration other variables influencing blood pressure such as weight change, sex, age, BMI, and baseline blood pressure (mediation analysis).
Blood pressure was assessed by unattended automated office blood pressure measurement. Smoking status was self-reported and validated with end-expiratory exhaled carbon monoxide measurement. In 38 participants, hemodynamic parameters such as systemic vascular resistance and cardiac index were measured by thoracic impedance analysis (HOTMAN®).

Results:

All participants with available systolic blood pressure measurements at baseline and week 12 were included. Results will display changes in systolic, diastolic blood and mean arterial pressure (MAP), heart rate, systemic vascular resistance and cardiac index according to smoking status and in dulaglutide versus placebo treated participants. The mediation analysis will quantify to which extent above-mentionned variables cause presumed changes in blood pressure.
The data is currently analyzed and will be presented at the congress.

Conclusion:

This analysis will provide further information on blood pressure changes during smoking cessation and identify whether a treatment with dulaglutide, which is known for his weight and blood-pressure lowering properties, has beneficial effects on blood pressure in the context of smoking cessation.

16

Do adults with early-treated PKU sense high phenylalanine levels?

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Background/Introduction:

This study aimed to analyze whether early-treated adults with phenylketonuria (PKU) can subjectively sense an impact of phenylalanine (Phe) on cognition or mood and whether cognitive test performance and mood assessment reflect the patients' self-perception.

Methods:

Data from the PICO study, a randomized, placebo-controlled, double-blind, crossover, non-inferiority trial, were analyzed. Twenty-eight early-treated adults with PKU were given either Phe capsules or placebo capsules orally in two 4-week intervention phases, with a washout period of 4 weeks in between. Neuropsychological assessments were collected at four study visits. At the end of the last study visit, participants were asked if they thought they could discern the Phe and placebo intervention order.

Results:

57 % of adults with early-treated PKU could not subjectively sense elevated Phe levels. Although most of the other 43 % of patients related the sensing to a subjectively negative impact on cognition and mood, cognitive test performance and standardized mood assessment did not reveal significant differences. Moreover, a subjective negative effect on their cognition was reported to the same percentages by patients who correctly assumed to have high Phe levels as by patients who incorrectly thought to have high Phe levels. However, in both groups cognitive test performance and standardized mood assessment were not negatively affected.

Conclusion:

The present study suggests that more than half of adults with early-treated PKU cannot subjectively sense elevated Phe levels. In addition, the self-perception of the impact of Phe is prone to expectation bias and nocebo effect.

Prospective associations between breastfeeding and cardio-metabolic health, inflammation and bone density at 1-year postpartum in women with prior gestational diabetes mellitus.

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Background/Introduction:

International societies recommend breastfeeding for at least 6 months. Breastfeeding is associated with a reduced risk of type 2 diabetes mellitus and cardiovascular diseases in high-risk women with a history of gestational diabetes mellitus (GDM). However, the underlying mechanisms and its impact on overall health outcomes are still unclear. Prospective studies in this population are scarce and rarely accounted for lifestyle behaviours or adverse pregnancy outcomes that can influence breastfeeding initiation and duration. We investigated the prospective associations between breastfeeding and detailed cardio-metabolic outcomes, inflammation and bone mineral density in women with GDM.

Methods:

This secondary analyses of the MySweetheart trial, included 171 women with GDM with valid breastfeeding data. Women were evaluated at the first GDM visit (24-32 gestational weeks), at 6-8 weeks and at 1-year postpartum. Outcome measures at 1-year postpartum included anthropometric measures (weight, weight retention), body composition (fat and lean mass), markers of insulin resistance and secretion, C-reactive protein (CRP) and bone density (DXA). Dietary intakes (food frequency questionnaire) and physical activity (Geneactiv) were assessed during pregnancy and at 1-year postpartum. We compared differences in health outcomes between women who did not initiate or breastfed <6 months vs ≥ 6 months. All analyses were adjusted for potential confounders.

Results:

Women that did not initiate or breastfed < 6 months (n=69) had a higher pre-pregnancy BMI (p=0.012), lower education level (p=0.012) and needed more glucose-lowering treatment in pregnancy (p=0.024), but other potential confounders (age, other socioeconomic, medical, lifestyle characteristics and adverse pregnancy outcomes) did not differ. Total breastfeeding duration correlated with lower weight, weight retention, fat mass, visceral adipose tissue, but also lower fat free and lean mass at 1-year postpartum, as well as lower CRP, HOMA-IR, HOMA of β-cell index (HOMA-B) and Area under the Curve (AUCins/glu) (all p≤0.002). Breastfeeding duration also correlated with higher overall insulin sensitivity (MATSUDA), and insulin resistance-adjusted insulin secretion (ISSI-2) at 1-year post-partum (all p≤0.011), but not with bone density. All correlations except for AUCins/glu, MATSUDA, and ISSI-2 remained significant after adjusting for confounders. In the adjusted models, breastfeeding for ≥6 months was associated with lower weight, weight retention, fat mass and CRP (all p≤0.046). Insulin secretion and bone density did not differ compared to those who did not initiate or breastfed for <6months.

Conclusion:

In this prospective study of women with GDM, breastfeeding duration predicted lower cardio-metabolic risk and inflammation at 1-year postpartum. After adjusting for significant confounders, breastfeeding for ≥6 months was associated with lower weight, weight retention, fat mass and inflammation but not with higher insulin secretion, reduced lean mass or bone density at 1-year postpartum.

18

Cardiovascular risk stratification using Lipoprotein (a) in youth with type 1 diabetes

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Background/Introduction:

Type 1 diabetes (T1D) is the most frequent metabolic disease in childhood and cardiovascular diseases (CVD) remain the leading cause of T1D adult mortality. Elevated Lipoprotein(a) (Lpa) is an independent and robust risk factor for CVD in adults. Recently, pediatric studies have shown that high levels of Lpa in youth represent a two-fold higher risk of atherosclerotic cardiovascular disease as adults compared with a group with normal Lpa levels. Our study aimed to assess the distribution of Lpa levels in a pediatric cohort with T1D and use it for CVD risk stratification.

Methods:

Retrospective analysis of medical charts from T1D patients followed between 2012 and 2023 at the University Hospital of Geneva. Lpa levels were measured one year after diabetes diagnosis, then annually. Descriptive data were compared according to Lpa values (low (0-80mg/l), normal (80-300mg/l), high (300-500mg/l), and very high (>500mg/l). One-way ANOVA was performed to compare the effect of Age, HbA1c, LDL, HDL, Total Cholesterol, C-peptide, and BMI on Lpa groups. Lpa plasma concentrations were assayed by immunonephelometry on a Atellica® NEPH 630 (Siemens Healthcare). The local ethics committee approved the study.

Results:

We included 122 patients (44% girls) with a mean age at Lpa measurement of 9 years (2-17 years). 35 patients (28.7%) had low, 52 (42.6%) normal, 19 (15.6%) high, and 16 (13.1%) very high Lpa levels. The mean Lpa value was 263 mg/l. High LDL levels (>3.36mmol/l) were found in 5.7%, 9.6%, 5.3%, and 31.3% in the low, normal, high, and very high Lpa groups, respectively. A one-way ANOVA revealed a statistically significant difference in HbA1c ($p=0.0194$), LDL ($p=0.0012$), and Total Cholesterol ($p=0.005$) between Lpa groups.

Conclusion:

We identified elevated Lpa levels (>300mg/l) in 28.7% of the children with T1D. This is higher than the 10% reported previously in pediatric reference groups. Our data show a positive association between HbA1c, LDL, total cholesterol, and levels of Lpa. As Lpa is a causal risk factor for CVD, we recommend measuring it in diabetic children for CVD risk stratification and implementing a CVD risk reduction program for modifiable factors while awaiting targeted therapies.

Diagnostic accuracy of free T3 in defining the severity of thyorid disorder

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Background/Introduction:

Thyroid disorders are frequently diagnosed in endocrine practice. The first-line test for the global thyroid function is the measurement of thyrotropin (TSH). Direct measurement of thyroxine (T4) and triiodothyronine (T3) is recommended to refine the diagnosis. T3 and T4 in human plasma are mainly protein-bound. Non-protein bound, free T4 (fT4) is routinely measured with direct immunoassays. However, the validity of direct immunoassays for free T3 (fT3) as compared to total T3 assays has been questioned. We investigated the clinical performance of a fT3 assay and compared it to total T3.

Methods:

We analyzed data from three prospective studies performed at our institution between 2015 and 2022. The cross-sectional MATcH-study comprised 162 healthy volunteers, 48 hyperthyroid and 33 hypothyroid individuals. The longitudinal HEAT-study followed 19 hyperthyroid patients from diagnosis to normalization of thyroid function. The longitudinal ThyroBAT-study examined 41 hypothyroid patients and again after three months of euthyroid state. We measured resting energy expenditure (REE, by indirect calorimetry) and thyroid hormones (TH) (Elecsys, Roche Diagnostics) in all patients. We adjusted REE by dividing the measured REE through the estimated REE (Mifflin formula).

Results:

We calculated receiver operating characteristics (ROC) for fT3, T3 and fT4. All parameters were equally accurate to differentiate hyperthyroidism from euthyroidism (AUC fT3 0.957, T3 0.968 and fT4 0.952, $p<0.0001$). We compared the correlation of TH to the normalized REE (adjREE). R2 in hyperthyroid and euthyroid subjects together of the MATcH-study was for fT3 0.256, for T3 0.207 and for fT4 0.224 (p-values<0.0001). To distinguish hypothyroidism from euthyroidism the ROC yielded an AUC for fT3 of 0.754, for T3 0.664 and for fT4 0.798 (p-values<0.0001). The results for the linear regressions for TH and adjREE of the MATcH-study in hypothyroid and euthyorid subjects together was for fT3 0.0797, for T3 0.0301 and for fT4 0.111 (p-values<0.05).

Conclusion:

FT3 and total T3 were both valid to differentiate hyperthyroidism and hypothyroidism from euthyroidism. FT3 correlated well with the adjREE in hyperthyroid patients and can therefore be used as a reliable parameter to assess the severity of hyperthyroidism. The peripheral TH are less accurate for the diagnosis of the degree of hypothyroidism.

Development and external validation of a risk prediction model of natural menopause onset using routinely available predictors

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Background/Introduction:

We aim to develop and externally validate the first risk prediction model of natural onset of menopause using only ready-to-use predictors.

Methods:

Participants- Premenopausal women aged 28 years and older with information on menopausal status and candidate predictor variables.
Main outcome measure- Self-declared age at the last menstrual period.
Model development- The model was developed on the CoLaus Cohort (Switzerland) using backward elimination approach. Internal validation was performed by bootstrapping 500 samples. External validation was performed on the PREVEND cohort (Netherlands) by recalibrating the baseline survival estimate. C-statistic, calibration slopes and Expected/Observed probabilities were calculated as measures of model internal and/or external performances.

Results:

The final analysis included 750 and 976 participants from the CoLaus and the PREVEND cohort respectively. Of them 445 (59.%) and 369(38%) respectively experienced menopause over a medium follow-up period of 10 years. The final model included age, alcohol consumption, smoking status, education level and Systolic Blood Pressure (SBP). Older participants, who did not consume alcohol, were smokers, had a lower level of education and a lower SBP were at higher risk of developing menopause in the next 10 years. Upon external calibration the model exhibited good discrimination, with a C-statistic of 0.89 and Expected/Observed probability of 0.83.

Conclusion:

We present the first internally and externally validated risk prediction model of natural menopause onset consisting of age, smoking status, educational level, alcohol consumption and systolic blood pressure, all readily available predictors with a good predictive performance.

21

Tumor-to-Tumor Metastasis of a Colloidal Adenocarcinoma (NSCLC) to a Papillary Thyroid Carcinoma: A Case Report

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Background/Introduction:

Thyroid nodules are a frequent condition and prevalence increases with age. Consequently, thyroid nodules are often coincidentally discovered in older patients during evaluation of other diseases. The majority of nodules are benign. However, up to 30% of the PET-CT-positive nodules are considered malignant. Although malignant, differentiated thyroid carcinomas, which account for >80% of malignant thyroid neoplasms, have relatively good prognosis. Conversely, metastasis to the thyroid gland is a rare condition, predominately caused by more aggressive malignancies. Only 0.4% of all thyroid malignancies are due to direct metastasis and invasion of the thyroid gland by another malignant tumor. Possible primaries thereby include renal cell carcinoma, colorectal carcinoma, lung and breast cancer as well as melanoma.

Methods:

We present the case of a colloidal adenocarcinoma (NSCLC) metastasizing to the thyroid gland within a papillary thyroid carcinoma, including initial clinical and biochemical findings, imaging, histological findings and short-term follow up.

Results:

A 66-year-old year old euthyroid male patient presented for further evaluation of a FDG-positive nodule of the thyroid gland found in a PET-scan performed due to a suspect pulmonal lesion (11 cm). Ultrasound examination of the thyroid gland revealed a single, unilateral, 14mm-measuring, hypoechoic thyroid nodule (TI-RADS 4) and the patient was euthyroid. The ultrasound did not reveal any suspect cervical lymph nodes. In light of the unclear pulmonal lesion and due to the FDG-positivity, a fine needle aspiration (FNA) was performed, despite a lesion size < 15mm-cutoff for FNA in moderately suspicious nodules. FNA showed features of a follicular neoplasm (Bethesda IV). According to tumor board decision pulmonary lobectomy was performed in a first step, revealing a PD-L1-negative colloidal adenocarcinoma of the lung. The recommended adjuvant chemotherapy was rejected by the patient. Instead he agreed on targeting the additional FDG-positive thyroid leason. Hemithyroidectomy revealed a multifocal papillary thyroid carcinoma with two lesions of 25 and 3 mm.Interestingly, the larger lesion contained a small metastasis of the known NSCLC with identical morphology. The thyroid carcinoma was BRAF- and PAX8-positive, whereas the metastasis was positive for CDX2 and CK-20.

Conclusion:

Nonthyroidal metastases to the thyroid gland are rare and there are only a few reports of tumor-to-tumor metastasis of an NSCLC into a papillary thyroid carcinoma. Histology remains paramount to avoid such small manifestations of a potentially more aggressive neoplasm from being overlooked, especially in patients with known cancer disease.

22

Real-world use of oral semaglutide in adults with type 2 diabetes: Results from the PIONEER REAL Switzerland multicenter, prospective, observational study

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Background/Introduction:

Oral semaglutide, the first oral glucagon-like peptide 1 receptor agonist (GLP-1 RA), demonstrated high efficacy in reducing HbA1c and body weight (BW) in the phase 3a PIONEER program. As part of the PIONEER REAL program conducted in 13 countries, PIONEER REAL Switzerland is a non interventional real-world study investigating clinical outcomes associated with oral semaglutide use in adults with type 2 diabetes (T2D).

Methods:

PIONEER REAL Switzerland is a 34 - 44-week, multicenter, prospective, open-label, non-interventional, single arm, phase 4 study in adults with T2D naive to injectable glucose-lowering medication, initiated on once-daily oral semaglutide in routine clinical practice. Changes in HbA1c (primary endpoint) and BW (secondary endpoint) were assessed from baseline (BL) to end of study (EOS). Proportion of participants achieving HbA1c <7% and the composite endpoints HbA1c reduction ≥1% with BW reduction ≥3% or ≥5% at EOS were assessed along with additional exploratory endpoints. Primary analyses were based on the in-study observation period.

Results:

Of 187 participants initiating oral semaglutide, 170 (90.9%) completed the study and 145 (77.5%) remained on treatment with oral semaglutide at EOS. At BL, participants had a mean (Standard deviation, SD) age of 62 (10.42) years, HbA1c of 7.8 (1.53) %, BW of 95.3 (17.93) kg, BMI of 33.2 (4.78) kg/m2 and 56.7% were receiving concomitant glucose-lowering medications. HbA1c was significantly reduced from BL to EOS (estimated mean change [95% confidence interval (CI)] ─0.9% [-1.12; -0.73], p<0.0001), as well as absolute and relative BW (estimated mean change [95% CI] -4.7kg [-5.60; -3.86] and ─4.9% [-5.73; -4.04] respectively; both p<0.0001). At EOS, 63.8% of participants had an HbA1c <7%, while an HbA1c reduction ≥1% plus BW reduction ≥3% or ≥5% was reached by 38.3% and 28.9% of participants, respectively. At EOS, clinical success assessed by the physician was reported in 123 (74.1%) participants. A total of 139 Adverse Events (AE) were reported in 65 participants (34.8%). Most AEs were mild or moderate. The most frequently reported AEs were gastrointestinal disorders (89 events in 50 participants) and 31 AEs in 20 (10.7%) participants led to the discontinuation of oral semaglutide. A total of 6 serious AEs were reported; all were unlikely to be related to oral semaglutide.

Conclusion:

In the PIONEER REAL Switzerland study, adults with T2D treated with oral semaglutide in the real-world setting of Swiss routine clinical practice, experienced clinically significant improvement in glycemic control and BW reduction, without any new safety findings.

23

Weight maintenance after Time-Restricted Eating vs. Standard Dietary Advice interventions – A one-year follow-up

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Background/Introduction:

Several human studies showed increased weight loss with time-restricted eating (TRE) compared to standard dietary advice (SDA). TRE tends to reduce energy intake by 10–30% but most studies were conducted over 12 weeks. Therefore, the efficacy of TRE on weight loss and weight maintenance needs investigation over longer periods. We have previously shown a 1–2% weight loss after 6 months of 12h TRE with no significant difference with SDA (Phillips et al., Nutrients 2021). Here, we aim to assess weight maintenance until month 12 in the same study population. We hypothesize that weight maintenance from month 6 to 12 is similar with TRE and SDA.

Methods:

Patients with at least one feature of the metabolic syndrome (central obesity, hypertension, hyperlipidaemia, elevated fasting glucose) whose eating duration was > 14h were randomized to 12h TRE vs. SDA for 6 months, with an optional follow-up until month 12. We compared the weight change from month 6 to 12 with the Wilcoxon signed rank test and the two groups using the Mann-Whitney U test. Predictors of weight change were tested using ordinary least square regression.

Results:

Of the 45 patients who completed the intervention, only 23 (TRE n = 13, SDA n = 10, 74% women) could be followed until month 12 due to Covid-19 restrictions and drop-outs. We did not observe weight regain from month 6 to 12 after TRE (mean –1.1%, SD 3.8, p = 0.74), nor after SDA (mean –1.8%, SD 2.1, p = 0.01), with no significant difference between groups (p = 0.20). Regarding predictors of weight change, we did not find any difference in weight maintenance according to age, sex, body mass index, place of birth, menopause, smoking, alcohol consumption and eating behaviour. Participants who abandonned the intervention from month 6 to 12 had a tendency towards weight regain compared to those who continued the intervention (p = 0.07).

Conclusion:

Both 12h TRE and SDA for 6 months were not followed by weight regain in the 6-month follow-up period. Based on this study and the growing literature on TRE benefits, either method seems to be a good choice for weight loss, but also for weight maintenance. Longer studies with different TRE implementations are needed for better comparison with other approaches to achieve weight loss and weight maintenance.

24

Propylthiouracil-induced cutaneous ANCA-associated vasculitis – a case report of a rare side effect

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Background/Introduction:
Thiamazole and its prodrug carbimazole are recommended as first line treatment in most patients with Graves' disease. Propylthiouracil (PTU) is usually reserved if adverse effects occur and during the first trimenon in pregnant women. Anti-neutrophil cytoplasmatic antibody (ANCA)-associated vasculopathy is a rare but major complication of PTU therapy.

Methods:
We describe the clinical presentation, diagnostic work-up, treatment and follow-up of a patient with PTU-induced cutaneous ANCA-associated vasculopathy. Additionally, we focus on the current literature of this topic.

Results:
A 53 years old woman presented with thyrotoxicosis and a diagnosis of Graves' disease was established. After one month of antithyroid drug therapy carbimazole (CBZ, 35 mg/day) she developed stomatitis, headache and arthralgia and treatment was switched to PTU (300 mg/day). After 14 months of PTU treatment several painful subcutaneous hyperpigmented nodules in a sporotrichoid pattern appeared on the left shin followed by new lesions on the right calf. Rapidly, the nodules turned into bullae filled with seropurulent fluid and ulcerated spontaneously. A dermatological work-up did not show any evidence for a microbial aetiology and the subsequent histopathologic analysis of a skin biopsy specimen revealed granulomatous dermatitis with septal and lobular panniculitis. Serological testing showed an increased ANCA titer with activity to several components of myeloid granules (PR3- ANCA and MPO-ANCA). A further workup did not show any evidence of other organ involvement. PTU-induced cutaneous ANCA-associated vasculitis was diagnosed and PTU immediately stopped. As the patient refused definitive therapy for Graves' disease, CBZ was resumed and well tolerated. The efflorescences were treated with topical clobetasol propionate for two weeks which was subsequently tapered and switched to topical tacrolimus. An antiseptic soft cream was applied to ulcerated skin lesions to prevent bacterial superinfection. Additionally, compression bandages were applied. Seven months later, no active inflammatory skin lesions were noted. Antithyroid drug therapy was stopped after further ten months of therapy with CBZ and the patient remained euthyroid.

Conclusion:
In accordance with the existing literature, our case shows that PTU-induced ANCA-vasculitis limited to the skin can be treated solely by stopping PTU and the use of topical anti-inflammatory therapy, but screening for systemic disease is of key importance. Moreover, positivity for both main ANCA subtypes seems a common finding. Switching antithyroid drug therapy from PTU to CBZ is a reasonable option as no cross-reaction has been documented so far. Early cessation of PTU appears to be crucial in the treatment of PTU-induced ANCA-vasculitis of the skin in order to reduce the risk of organ involvement.

25

A rare cause of Achilles tendon xanthomas

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Background/Introduction:
Tendon xanthomas occur mostly in genetic hypercholesterolemic syndromes. In patients with concomitant normal lipid profile cerebrotendinous xanthomatosis (CTX) must be suspected.

Methods:
We describe the initial presentation, diagnostic work-up and early treatment response of a young patient with CTX (OMIM #213700).

Results:
A 17 years old male of Afghanian origin was referred to the orthopedic service because of progressive thickening of both Achilles tendons with some pain while running. A biopsy of the yellowish and fibrillary altered tendons showed giant cell inflammation with cholesterol crystals and a MR scan confirmed fatty infiltration of both tendons. Plasma lipids were normal, however, the patient was referred for further work-up. A diagnosis of CTX was suspected and confirmed by increased concentrations of urinary bile alcohols (cholestan-5-tetrol and -pentol) and blood cholestanol, 7-dehydrocholesterol and 8-dehydrocholesterol. Genetic testing revealed a homozygous pathogenic variant (c.2T>C) of the CYP27A1 gene. Screening for multi-organ involvement documented a moderate development disorder including learning disability but fortunately no further central nervous system, ocular, cardiovascular, skeletal system, pulmonary or enterohepatic involvement. Treatment with chenodeoxycholic acid 250 mg t.i.d was started and resulted in improved biochemical control with decreased concentrations of serum cholestanol and cholesterol precursor metabolites and urinary bile alcohols were found to have normalized. Clinical and genetic family screening identified two 15 and 20 year old sisters homozygous for the pathogenic variant and a pathognomonic biochemical profile, but without clinical manifestations in the younger and possible neurological involvment in the older sister. Treatment with CDCA will be started upon approval of coverage by the health insurance providers. Two sisters are heterzygous carriers.

Conclusion:
CTX is a rare autosomal recessive, inborn error of bile acid metabolism with an estimated prevalence of < 5/100’000 worldwide that may be diagnosed both in children and early adulthood. Defective sterol 27-hydroxylase results in enhanced production of cholesterol and cholestanol which accumulates in tissues throught the body, notably the CNS, lens and tendons. If untreated the disease has a devastating clinical course with progressive neurological involvement including ataxia, spasticity, seizures and dementia as well as other organ involvement (xanthomas, cataracts, diarrhea). Early and long-term treatment with CDCA, a naturally occuring FXR agonist and inhibitor of bile acid synthesis, corrects the biochemical abnormalities and may slow or even halt disease progression. Clinical and genetic family screening is mandatory to allow early diagnosis and treatment before the onset of irreversible neurological manifestations.

Adaptive potential of fully closed-loop insulin system for the management of inpatient metabolic challenge

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Background/Introduction:

Subcutaneous (SC) fully closed-loop (FCL) insulin delivery systems represent a promising opportunity for perioperative diabetes management in the hospital, offering excellent glycaemic control and reducing hospital staff workloads. Understanding the ability of FCL systems to adapt to abrupt changes in metabolic demand is critical to ensuring successful and safe implementation in the hospital setting. In this case series, we examine four instances in which FCL was challenged by unique inpatient clinical situations.

Methods:

Four cases of patients who underwent major abdominal surgery and received perioperative SC FCL insulin therapy are described. Therapy was initialised using the estimated daily insulin dose and patients' body weight at a set glucose target of 7.0 mmol/L. Each case involved an abrupt metabolic challenge: (1) total parenteral nutrition (TPN) initiation, (2) enteral tube feeding (TF) initiation, (3) concurrent intraoperative administration of sandostatin and dexamethasone, and (4) hyperkalaemic emergency requiring combined IV insulin/dextrose administration. The FCL system controller effort was evaluated by measuring fold change of mean insulin delivery rate between 6 hours before and 6 hours after each metabolic challenge, except in the case 3. In this instance, only 1 hour of pre-challenge data were available. Continuous glucose monitor (CGM) values from the corresponding timeframes were evaluated to assess the ability of FCL system to accommodate these situations.

Results:

Case 1: Initiating TPN (125g carbohydrates (CHO) over 24h) after 1 day of fasting and 2 days of clear fluids increased insulin delivery rate 2.8-fold. The CGM peaked at 11.2 mmol/L, returning to <10 mmol/L after 2 hours. Case 2: Starting TF (44.3g CHO over 24h) following 3 days of fasting resulted in a 1.8-fold increase in insulin delivery rate. CGM peaked at 14.0 mmol/L and returned to <10 mmol/L in 1.5h. Case 3: Intraoperative administration of 4mg IV dexamethasone and 0.2mg SC sandostatin led to a 2.7-fold increase in insulin delivery rate. CGM peaked to 12.1mmol/L and returned to euglycaemia in 1h. Case 4: Correcting hyperkalaemic emergency with 10 units of IV insulin and 200ml 20% IV dextrose increased insulin delivery rate 1.9-fold. Mean CGM increased from 8.3 mmol/L to 12.9 mmol/L, returning to <10 mmol/L after 7 hours. There were no manipulation of the system except when the glucose target was changed to 5.8 mmol/L after the initiation of nutrition support. No hypoglycaemia (<3.9mmol/L) occurred during any of the cases.

Conclusion:

The SC FCL system adapted to a diverse set of metabolically demanding cases, including initiation of TPN, TF and administration of steroid with somatostatin analogue. Although mean CGM values increased, they quickly returned to <10mmol/L. Potassium shift with IV insulin/dextrose (40g) required more time for glucose values to reach the target range. Nonetheless, the system demonstrated broad adaptive capacity without requiring additional input, underscoring its benefit in the hospital setting.

27

Pre-exercise ingestion of caffeine and low-dose glucose reduce the risk of exercise-associated hypoglycemia in people with type 1 diabetes treated with insulin degludec

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Background/Introduction:

The prevention of hypoglycaemia during exercise is a challenge for people with type 1 diabetes (T1D). Current guidelines promote the adaption of insulin therapy and/or carbohydrate consumption in the context of exercise. However, for individuals using ultra-long acting insulin analogues adjustment of basal insulin concentrations in the context of exercise is not straightforward, and novel but practical approaches may be helpful. The present study assessed whether pre-exercise ingestion of caffeine with a low amount of glucose reduces the risk for hypoglycaemia during exercise in people with T1D using insulin degludec.

Methods:

Sixteen participants (mean age 30.4 ± 8.9 y, 5 female, HbA1c 64.8 ±23.2) completed a randomized, three-arm, double blinded prospective trial. Each participant conducted three sessions of aerobic exercise with prior consumption of either caffeine + 10 grams of glucose + aspartame (CAF), or 10 grams of glucose + aspartame (GLU), or aspartame (ASP) alone. Blood glucose was measured every 5 minutes until either the occurrence of hypoglycaemia or the end of the exercise session (60 to 75 minutes).

Results:

The intake of CAF significantly reduced the risk for hypoglycaemia during exercise by 85.7%, as compared to aspartame ($p<0.05$). Mean glucose during exercise was significantly higher after intake of CAF, as compared to GLU and ASP ($p<0.001$) but hyperglycemia was avoided (mean glucose with CAF 8.3 ± 1.9 mM). Individual rating of perceived exertion was significantly lower after ingestion of CAF, if compared to GLU ($p=0.023$). In addition, plasma concentrations of lactate increased significantly after intake of CAF as compared to ASP ($p<0.001$).

Conclusion:

Caffeine added to a limited amount of glucose (10g) significantly lowered the risk of exercise-associated hypoglycaemia in people with T1D treated with ultra-long acting insulin analogues while avoiding hyperglycemia. Moreover, caffeine reduced the perceived exertion, indicating an improved exercise tolerance, while increasing lactate, pointing towards a beneficial metabolic effect (alternative substrates).

The NEMESIS-Study: Correlation of DNA methylation of neuroendocrine tumors with their grading, differentiation and prognosis.

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Background/Introduction:

Neuroendocrine tumors (NETs) represent a diverse group of neoplasms with increasing incidence arising from neuroendocrine cells, displaying heterogeneous clinical behavior and prognosis. Interestingly, the heterogeneity observed at the histopathological level is also encountered in terms of genetic and epigenetic alterations. DNA methylation has emerged as a critical regulator in tumorigenesis and tumor progression through its role in transcriptional regulation without altering the DNA sequence. The purpose of this study was to correlate DNA methylation profiles with pathological and clinical features of NETs in order to develop a methylation-based classifier for NETs.

Methods:

To address these aims we performed DNA methylation and copy number analyses on 32 fresh frozen pancreatic- (Pa), small-intestinal- (SI), and lung-NET tissue samples from the Tissue Biobank of the University Hospital of Basel. All samples were reviewed and excision sites chosen by a highly experienced pathologist. DNA methylation profiling was performed using Infinium MethylationEPIC. The results were then visualized and cross-compared to other microarray-based methylation datasets using the EpiDip Data tool. Furthermore, additional data of the patients, concerning baseline clinical, histopathologic, and immunohistochemical characteristics, as well as outcome measures were retrospectively collected.

Results:

In total, samples and data of 16 Pa-NETs, 8 SI-NETs and 8 Lung-NETs, 50% female were analyzed. Mean (SD) age was 62 (12) years. The majority of the included samples were grade 1 NETs (n=9 in Pa-NETs, n=4 in SI-NETs and n=7 typical carcinoids in Lung-NETs). Mean follow up time was 60 (43) months. During this period, 4 (12.5%) patients died.
Interestingly, despite previous data showing distinct differences between the three tumor entities, current methylation profiles were very similar and no distinction possible.

Conclusion:

In contrast to the majority of the existing data, no distinct methylation profiles were observed despite different tumor origin and grading. Further analyses are planned to better characterize the findings.

29

Effects of Glucagon-Like Peptide-1 Analogs on Sexuality: A randomized, double-blind, placebo-controlled trial with crossover design (The DESIRE Study)

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Background/Introduction:

GLP-1 analogs are prescribed for diabetes and obesity due to their well-known insulinotropic, satiation-promoting and appetite-suppressant effects. Several studies also investigated if GLP-1 analogs reduce the rewarding effect to addictive drugs such as alcohol, nicotine, cocaine, amphetamine or opioids. Pre-clinical studies suggest that sexual desire, as another type of natural reward, could also be affected by GLP-1 analogs.

Methods:

This was a single-center, randomized, double-blind, placebo-controlled, crossover trial conducted at the University Hospital Basel in Switzerland. We enrolled healthy eugonad men of normal weight (BMI 18.5-25kg/m2 or BMI 25.1-30kg/m2 and waist circumference <102 cm), aged between 18 and 50 years who reported an active and satisfactory sex life. Participants were randomized to dulaglutide and placebo in random order. The primary outcome was the difference in change in sexual desire, assessed via the Massachusetts General Hospital - Sexual Functioning Questionnaire (MGH-SFQ), after four weeks of treatment with dulaglutide compared to placebo. As secondary outcome, we examined the effect of dulaglutide as compared to placebo on hormones of the hypothalamic–pituitary–gonadal (HPG) axis (total and free testosterone, follicle-stimulating hormone, luteinizing hormone, sex hormone-binding globulin).

Results:

Between May 2021 and February 2022, 24 out of 26 randomized participants completed the study. At baseline, all participants reported to have a “satisfying” (66.7%) or “very satisfying” sex live (33.3%) and the majority was sexually active (masturbation 14/24 or with partner 17/24) at least once weekly. Our data do not support the hypothesized effect of dulaglutide on sexual desire (estimated difference in change of the MGH-SFQ sum score from baseline to end of treatment under dulaglutide and under placebo 0.58 [95% CI -0.83-2.00], p-value = 0.402). Further, there was no evidence for a significant difference in the change in the analyzed hormones of the HPG axis between dulaglutide and placebo.

Conclusion:

In healthy men, the study showed no evidence of negative impacts of the widely used GLP-1 analogue dulaglutide on sexual desire and hormones of the HPG axis.

Postpartum glucose intolerance after gestational diabetes mellitus: tailored prediction according to data-driven clusters and predefined subgroups.

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Background/Introduction:

The heterogeneity of diabetes has led to the development of a new diabetes clustering classification system with distinct risks for complications. In women with gestational diabetes (GDM), considerable heterogeneity also exists, but a similar clustering classification and its impact on future diabetes risk has not been investigated. In this study, we aimed to identify tailored predictors during pregnancy and at 6-8 weeks postpartum (pp) for incident glucose intolerance (GI, prediabetes and diabetes) at 1-year postpartum for data-driven clusters and predefined subgroups.

Methods:

This study utilized data from the MySweetheart trial (NCT02890693), and included 179 women with GDM who underwent a 75g oral glucose tolerance test (oGTT) and had HbA1c measurement at 1-year pp. Subgroups were determined in pregnancy and the early pp according to (a) a cluster analysis based on age, BMI, homoeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-B) indices; and for clinical ease according to (b) normal weight (NW) vs overweight/obesity (OW/OB); (c) high vs low HOMA-IR and (d) high vs low HOMA-B. The following predictors of GI were tested: medical history, clinical and laboratory measures at 24-32 weeks of gestation and at 6-8 weeks pp; eating behavior and nutritional intake at 24-32 weeks of gestation and several oGTT-derived insulin resistance and secretion indices at 6-8 weeks pp.

Results:

Sixty-seven (37.4%) women were diagnosed with GI at 1-year pp. During pregnancy and at 6-8 weeks pp, we identified two clusters (“insulin-resistant” and “insulin-deficient”). Compared to the “insulin-deficient” cluster, the risk of GI in the “insulin-resistant” cluster during pregnancy was increased by 2.6 fold (CI: 1.42-5.62, p=0.003), and at 6-8 weeks pp by 3.3 fold (CI: 1.57-7.10, p=0.002). In pregnancy, history of previous GDM and/or fasting glucose were the most relevant predictors of GI for women in the “insulin-deficient” cluster, and for women with NW, low HOMA-B/HOMA-IR (all p≤0.035). HOMA-IR was the most relevant predictor for women in the “insulin-resistant” cluster and those with OW/OB, high HOMA-B/HOMA-IR (all p≤0.019). In the early pp, ISSI-2 (insulin-resistance adjusted secretion) was the most important predictor for GI for women in the “insulin-deficient” cluster and those with low HOMA-B/HOMA-IR (all p≤0.008) and pre-pregnancy BMI for those in the high HOMA-IR/HOMA-B subgroups (both p≤0.024). PP predictors for GI were more heterogeneous for the "insulin-resistant" cluster and the other subgroups.

Conclusion:

We identified an “insulin-resistant” and an “insulin-deficient” cluster in women with GDM with distinct risks for future GI. These clusters underline the main pathophysiological pathways in this population and may help for risk stratification. Predictors of GI vary according to clusters and subgroups and parallel their characteristics, emphasizing the need for a tailored risk assessment.

The landscape of long-term problems in adult patients with glycogen storage disorder type I

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Background/Introduction:

Apart from the main metabolic disturbances, patients with glycogen storage disorder type I (GSDI) frequently develop complications such as liver adenomas and nephropathy. Additionally, due to the frequent intake of carbohydrates, and in some cases a tendency for overtreatment, there is a risk of developing overweight. We aimed to analyze the presence, extent and progression of these complications in a cohort of GSDI patients, in association with metabolic parameters.

Methods:

Clinical and laboratory data of 20 adult patients (8 female, 12 male, 17 GSDIa, 3 GSDIb, median age 34, range 21 - 57) from routine clinical care, including data from continuous glucose monitoring (CGM), were collected prospectively within the frame of the Swiss Hepatic Glycogen Storage Disease Registry and analysed cross-sectionally.

Results:

Liver adenomas were present in the majority of patients (70%), but none had radiological signs of malignant transformation. Progression was found in about half of patients with adenomas, yet it was not associated with more unstable glucose control. Nephropathy with albuminuria was present in 55% of patients, mostly KDIGO grade A1-2, but A3 in 3 patients, with preserved GFR in 85% of patients. Severe albuminuria A3 completely resolved in one patient after liver transplantation, indicating that metabolic control is an important factor determining the clinical course of nephropathy. Normal weight was associated with more unstable glucose profiles in CGM curves compared to overweight (BMI > 25kg/m², 8/20) patients, with lower glucose time in range, indicating a more severe metabolic phenotype.

Conclusion:

Long-term complications are present in the majority of adult GSDI patients, and may progress also in patients with apparently stable metabolic control. Overweight is a frequent problem, mostly affecting patients with a less severe metabolic phenotype in the present cohort, indicating that diet must be adapted judiciously to avoid overtreatment. Monitoring and management of complications remains a central element in the follow-up of adult patients with GSDI.

32

Comparison of romosozumab and teriparatide effects on cortical and trabecular bone using 3D modeling from DXA images in postmenopausal women transitioning from bisphosphonate therapy

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Background/Introduction:

In STRUCTURE, greater gains in hip and spine areal bone mineral density (BMD) and estimated hip strength were observed with romosozumab (Romo) vs teriparatide (TPTD) treatment over 12 months in patients at high risk for fracture when transitioning from bisphosphonates (BPs). Significant gains in integral and cortical volumetric BMD (vBMD) at the hip by quantitative computed tomography (QCT) were also observed with Romo but not TPTD over 12 months, while gains in trabecular vBMD (TvBMD) were not significantly different between groups. QCT is useful for assessing changes in bone parameters but is not widely available in clinical practice. To overcome the limited availability of QCT, we used duel-energy X-ray absorptiometry (DXA) based modeling of the hip to assess estimated changes in cortical and trabecular parameters and to map the distribution of changes in bone parameters to visually monitor treatment effect over time in STRUCTURE.

Methods:

STRUCTURE enrolled 436 postmenopausal women with osteoporosis (OP) who had received oral BP therapy for ≥3 years and alendronate for ≥1 year prior to screening; women were then randomized 1:1 to receive open-label Romo or TPTD for 12 months. Data from women who had total hip DXA scans at baseline, Month 6, and Month 12, and had provided consent for future research, were included in this analysis. We applied 3D-SHAPER software (v2.11 3D-SHAPER Medical) to generate patient-specific QCT-like 3D models for the total hip DXA scans in these women. Percentage change from baseline to Month 6 and Month 12 in cortical vBMD (CvBMD), cortical thickness (Cth), cortical surface BMD (CsBMD), and TvBMD were evaluated. Percentage changes were assessed by repeated measures model adjusting for baseline covariates.

Results:

Data from 308 women from STRUCTURE (Romo, 160; TPTD, 148) who had evaluable 3D assessments at baseline, Month 6, and Month 12 were analyzed. Greater increases were observed following treatment with Romo vs TPTD in CvBMD (least squares mean % change from baseline: 0.9% vs –1.0% [Month 6] and 1.2% vs –1.2% [Month 12]), Cth (0.8% vs –0.7% [Month 6] and 1.2% vs –0.3% [Month 12]), CsBMD (1.7% vs –1.7% [Month 6] and 2.4% vs –1.5% [Month 12]), and TvBMD (4.2% vs 1.0% [Month 6] and 5.9% vs 2.5% [Month 12]) ($p<0.001$ at Month 6 and Month 12 for all parameters with Romo vs TPTD). Notably, TPTD treatment led to loss in CvBMD, Cth, and CsBMD.

Conclusion:

These results support the superiority of Romo compared with TPTD on hip cortical and trabecular bone compartments at Month 6 and Month 12 in women with severe postmenopausal OP who were previously exposed to BP therapy. The results further support the use of Romo over TPTD as first-choice therapy in women remaining at high fracture risk despite BP therapy.

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33 S

Patients with type 1 diabetes mellitus and currently recommended LDL-cholesterol, non- HDL-cholesterol and apoB targets – a SwissDiab study

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Background/Introduction

As a result of younger age of onset and a longer lifetime burden of disease, adult patients with type 1 diabetes mellitus (T1DM) have been shown to have similar, and in some cases higher, cardiovascular risk than adult patients with type 2 diabetes mellitus. The aim of this study was to assess the proportion of patients with T1DM that reach currently recommended lipid treatment targets in the Swiss Diabetes Registry (SwissDiab). Specifically, low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apoB).

Methods

SwissDiab is a multicenter longitudinal observational study of outpatients with diabetes in tertiary diabetes care at the Cantonal Hospital of St. Gallen (coordinating centre) and Basel, Bern, Geneva, and Zürich University Hospital. Participating patients with T1DM and a study visit 01.01.2021 or later were included in the current analysis. In case more than one visit was available the most recent was used, unless missing data justified the inclusion of a previous visit. Patients were advised to arrive fasted (>8 hrs), and HDL-C, LDL-C, total cholesterol, triglycerides, and apoB were measured according to routine methods at the laboratory medicine at each hospital. In addition to directly measured LDL-C (LDL-C_M), LDL-C was also calculated based on the Friedewald (LDL-C_F) and the Sampson equation (LDL-C_S). Only patients with all five lipid parameters (LDL-C_M, LDL-C_F, LDL-C_S, non-HDL-C, and apoB) were included. Atherosclerotic cardiovascular risk category and lipid targets were determined based on the 2021 European Society of Cardiology (ESC) guidelines on cardiovascular disease prevention in clinical practice.

Results

Of 322 eligible patients, 103 (32.0%) were excluded due to missing data (the majority missing apoB). Of the 219 patients included, the median (IQR) age was 43.4 (31.8-58.2) years, diabetes duration 16 (10-25) years, HbA1c 7.3 (6.8-8.0)%, 39.7% were females, and 33.8% were prescribed lipid-lowering therapy (33.3% statin). Based on the ESC guidelines, 11.4% of the patients were at very high risk, 75.3% at high risk, and 13.2% at moderate ASCVD risk.

The recommended LDL-C target was met by 8.2% (LDL-C_M), 11.9% (LDL-C_F) and 11.0% (LDL-C_S) of the patients. Non-HDL-C and apoB targets were met by 30.6% and 59.8%, respectively. Whereas 39.7% of the patients did not meet any of the lipid targets, 8.2% (LDL-C_M), 11.4% (LDL-C_F), and 11.0% (LDL-C_S) of the patients met all three lipid targets.

Conclusion

Currently recommended LDL-C targets were met by a small minority of the patients with T1DM enrolled in SwissDiab, whereas a substantially higher proportion reached non-HDL-C and apoB targets. Contrary to what has previously been observed among patients with T2DM in SwissDiab, the method used to determine LDL-C levels did not considerably influence the proportion considered at target. Further studies are needed to inform the optimal lipid management strategy to guide cardiovascular risk reduction in adult patients with T1DM.

Effect of dulaglutide in promoting abstinence during smoking cessation: The 12 month follow-up of a randomized, double-blind, placebo-controlled, parallel group trial.

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Background/Introduction:

Smoking cessation is difficult, despite making use of established smoking cessation therapies. Preclinical studies and one clinical pilot study suggest glucagon-like peptide-1 (GLP-1) analogues to modulate addictive behaviors and nicotine craving. In our study, using the GLP-1 analogue dulaglutide versus placebo as an adjunct to smoking cessation therapy, we found no effect on abstinence rates after 12 weeks of treatment, but a beneficial effect on short-term post-cessation weight gain (difference in weight change between dulaglutide and placebo −2.9 kg (95% CI: [−3.59, −2.3]) at week 12). The aim of the present study is to report long-term abstinence rates and weight developments after 24 and 52 weeks.

Methods:

This is a follow-up study of the SKIP trial conducted at University Hospital Basel. Smokers willing to quit and showing at least a moderate nicotine dependence were included and randomized to either a 12-week treatment with dulaglutide 1.5mg once weekly or placebo subcutaneously additional to standard of care (varenicline 2mg/day and behavioural counselling). After 12 weeks, dulaglutide or placebo and smoking cessation therapy were discontinued and the participants were followed up at week 24 and 52 to assess point prevalence abstinence rate by self-report and end-expiratory carbon monoxide measurement and weight changes.

Results:

In total, 255 participants were enrolled and randomized between June 2017 and December 2020 (dulaglutide group n = 127; placebo group n = 128). After completion of the 12-week treatment with dulaglutide or placebo and smoking cessation therapy, 63% (80/127) participants on dulaglutide and 65% (83/128) on placebo were abstinent. These abstinent rates declined to 43% (54/127) and 41% (52/128), respectively, after 24 weeks and to 32% (41/127) and 32% (41/128), respectively, after 52 weeks. After the discontinuation of dulaglutide or placebo and smoking cessation therapy, body weight increased in both groups, however, tending to be less in the dulaglutide group (difference in weight change between dulaglutide and placebo -1 kg (95% CI: [-2.02, 0.01]) at week 24 and -0.35 kg (95% CI: [-1.72, 1.01]) at week 52).

Conclusion:

Dulaglutide is helpful to counteract post-cessation weight gain, however, 3 months of treatment proved to be not sufficient to maintain prolonged beneficial effects after one year. As post-cessation weight gain is highest in the first year of smoking cessation, future studies should consider a longer treatment duration of ideally one year.

Impact of autofluorescence imaging on involuntary parathyroidectomy in thyroid surgery

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Background/Introduction:

Thyroid surgeries are at risk of involuntary parathyroidectomy, especially for oncologic cases and when coupled to a central neck dissection. This can cause transient or permanent hypoparathyroidism and affect the post operative quality of life. Recently developed near-infrared autofluorescence (NIRAF) imaging can detect the intrinsic autofluorescence of the parathyroid glands. Growing evidence show that the use of NIRAF imaging in thyroid surgeries may reduce the rate of involuntary parathyroidectomy. However, information on the benefits of NIRAF imaging on thyoid surgeries associated with a central neck dissection in oncologic cases are lacking.

Frozen section exams can provide intraoperative histopathological information and help the surgeon in his decision making. These exams can be used intraoperatively to differentiate parathyroid glands from other tissues. In some cases, NIRAF imaging may reduce the use of frozen section by facilitating parathyroid tissue discrimination.

Methods:

A retrospective monocentered case-control study including lobectomies, total thyroidectomies and total thyroidectomies with central neck dissection performed at the Lausanne University Hospital between november 2016 and december 2022 was carried out. Operative and pathology reports were reviewed to count the amount of parathyroid gland fragments and frozen section exams in patients operated with NIRAF imaging (cases) and without (controls). The main cohort including all three operation types, as well as a subcohort including only total thyroidecomies with central neck dissections, were analyzed using a $\chi 2$-test and a propensity score and ATT weights.

Results:

The main cohort contained a total of 136 patients, while the subcohort contained 44 patients. Involuntary parathyroidectomies were reduced by 23.5% in the main cohort ($p=0.029$) and by 61.4% in the subcohort ($p=0.005$). Frozen section exams were reduced by 28.1% ($p=0.009$) in the main cohort and by 48.0% ($p=0.0398$) in the subcohort. The Odds Ratio to suffer no involuntary parathyroidectomy was 3.15 (CI: 1.32 - 7.53) in the main cohort and 17.86 (CI: 3.15 - 101.15) in the subcohort. The Odds ratio to get no frozen section in the main cohort was 8.92 (2.02 - 39.44) and 14.14 (1.63 - 123.00) in the subcohort.

Conclusion:

In the limits of our study, our data show that NIRAF imaging seems to significantly lower the rate of involuntary parathyroidectomies and frozen section exams in thyroid surgery. These rates seem to be particularly reduced in case of total thyroidecomiy with central neck dissection performed on oncological cases. Our data suggest that NIRAF imaging seems to be an effective aid to reduce thyroid complications at the Lausanne University Hospital.

36

Anemia and platelet disorders revealing a severe sitosterolemia, a case report

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Background/Introduction:

Sitosterolemia is an uncommon autosomal recessive genetic disorder resulting from a mutation in the ABCG5 or ABCG8 genes, which encodes sterol efflux transporters in the gut and biliary system. This leads to plasma and tissue accumulation of plant sterols and stanols. Because it is often underdiagnosed, the actual prevalence of the disorder is uncertain. The clinical presentation range from asymptomatic individuals to those with severe hypercholesterolemia leading to accelerated atherosclerosis, xanthomas and hematological disorders. The treatment includes dietary intervention to limit plant sterols, and lipid lowering therapies (LLT) that affect sterols absorption ezetimibe and bile acid sequestrants.

Methods:

A 55-years-old patient has been diagnosed with moderate isolated hypercholesterolemia with a total cholesterol of 5,8 mmol/l, LDLc 3.4 mmol/l, HDL 1.9 mmol/l and triglycerides 0.9 mmol/l. Physical examination revealed a corneal arcus (figure 1). Cardiac evaluation by EKG revealed ischemic lesions in inferior territory confirmed by cardiac MRI which was likely associated with an episode of a chest pain at the age of 52.

Results:

A LLT by rosuvastatin up to 30 mg per day was started with a moderate effect on the cholesterol levels (total cholesterol 4.9 mmol/l, LDL 2.8 mmol/l). Consequently, a combination therapy with ezetimibe was initiated.The follow-up laboratory showed a thrombocytopenia with a platelet count of 90 G/l, initially attributed to the ezetimibe treatment, which was discontinued. However, this had no effect on the platelet count. A peripheral blood smear showed a non-autoimmune macrothrombocytopenia and anemia with stomatocytosis, which raised the suspicion of sitosterolemia. This diagnosis was confirmed by a laboratory tests with campesterol at 121 mg/l (normal range: 1.07 - 7.67 mg/l) and sitosterol at 279 mg/l (normal range: 0.64 - 4.03 mg/l).
Ezetimibe therapy at 10 mg per day was reintroduced along with a low plant sterol diet. Laboratory re-evaluation showed that the campesterol had reduced to 45 mg/l and sitosterol to 115 mg/l. In response, the ezetimibe dose was increased to 20 mg per day (off-label) and cholestyramine 3g/day was added to the treatment regimen. Further lab tests to monitor sitosterol levels, analyze blood smears, and perform genetic analysis are scheduled for the next appointment.

Conclusion:

Sitosterolemia is a rare disease, often unrecognized. It should be considered in patients with hypercholesterolemia with unexplained hemolytic anemia with macrothrombocytopenia, especially if associated to clinical signs of familial hypercholesterolemia. A resistance to statin therapy with an important decrease of cholesterol levels in response to ezetimibe or bile acid sequestrants should raise this diagnosis.

37

TRENDS IN POTENTIALLY AVOIDABLE HOSPITALIZATIONS FOR DIABETES IN SWITZERLAND, 1998 TO 2018: DATA FROM MULTIPLE CROSS-SECTIONAL STUDIES

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Background/Introduction:

Timely and appropriate outpatient care can prevent potentially avoidable hospitalizations (PAH) for diabetes. We analysed the trends, determinants, and consequences of PAH for diabetes in Switzerland over two decades.

Methods:

Hospital discharge data for years 1998 to 2018 were used. PAH were defined according to the Organization for Economic Cooperation and Development (OECD) criteria.

Results:

Data from 99,804 hospitalizations for diabetes were used, of which 9457 (9.5%) were PAH. The percentage of PAH decreased from 14.7% in 2006 to 6.7% in 2018. Compared to non-PAH, patients with PAH were more frequently women (46.9% vs. 40.5%), in the younger age categories, more frequently non-Swiss (20.6% vs. 19.0%), without health insurance (3.5% vs. 2.4%), more frequently admitted in an emergency setting (84.6% vs. 56.4%), at the patient's initiative (26.6% vs. 16.9%) or via emergency services (28.1% vs. 12.4%) and had a lower comorbidity index (all $p<0.001$). Patients with PAH were more frequently admitted to the intensive care unit (31.9% vs. 5.7%) and their length of stay was shorter, median and [interquartile range], 8 [5-13] vs. 9 [5-15] days. PAH represented 2,807 hospital days in 1998, increasing to 6,400 in 2002 and decreasing to 3,172 days in 2018, corresponding to approximately nine hospital beds continuously occupied for this condition. The estimated cost for PAH of diabetes in 2018 amounted to 5.3 million CHF.

Conclusion:

In Switzerland, PAH for diabetes represent a small and decreasing percentage of all hospitalizations for diabetes. Most PAH could be prevented, thus reducing cost and sparing health systems.

38

Unnecessary thyroid surgery rate for suspicious nodule in the absence of molecular testing

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Background/Introduction:

Molecular tests for suspicious thyroid nodules decrease rates of unnecessary surgeries but are not widely used due to reimbursement issues. The aim of this study was to assess the rate of unnecessary surgery performed in real life setting for Bethesda III, IV and V nodules in the absence of molecular testing.

Methods:

This is a single-center retrospective study of consecutive patients undergoing fine needle aspiration cytology (FNAC) with rapid on-site evaluation between January 2017 and December 2021.
Unnecessary surgery was defined as surgery performed because of Bethesda III, IV or V results in the absence of local compressive symptoms with final benign pathology and as second surgery for completion thyroidectomy.

Results:

Among 862 patients (640 female, mean age 54.2 years), 1010 nodules (median size 24.4 mm) underwent 1189 FNAC. Nodules were EU-TIRADS 2, 3, 4 and 5 in 3%, 34%, 42% and 22% of cases, respectively. FNAC was Bethesda I, II, III, IV, V and VI in 8%, 48%, 17%, 17%, 3% and 6%, respectively. Surgery was performed in 36% of Bethesda III nodules (benign on pathology: 81%), in 74% of Bethesda IV nodules (benign on pathology: 76%) and in 97% of Bethesda V nodules (benign on pathology: 21%). Surgery was considered unnecessary in 56%, 68% and 21% of patients with Bethesda III, IV and V nodules, respectively.

Conclusion:

In this real data cohort surgery was unnecessary in more than half of patients with Bethesda III and IV nodules and in 21% of patients with Bethesda V nodules.

39

Incidental, symptomatic, and genetic screening-pheochromocytomas: how different are they?

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Background/Introduction:

Pheochromocytomas (sporadic or hereditary) are rare tumors arising from the adrenal medulla. Their diagnosis can be suspected in case of catecholamine secretion related or tumor related symptoms. Other reasons leading to diagnosis include screening in patients with a germline pheochromocytoma-related mutation or incidental findings during abdominal imaging performed for unrelated reasons. The objective of our study was to describe clinical characteristics of pheochromocytomas according to circumstances of diagnosis in a cohort of patients treated in a tertiary academic center.

Methods:

This is a retrospective monocentric study of consecutive cases of histologically proven pheochromocytomas operated between November 2007 and October 2022 in Geneva University Hospital. Reasons leading to diagnosis were documented together with patients' baseline characteristics including symptoms at diagnosis, tumor size and catecholamine levels.

Results:

Fifty-four patients (28 female; mean age: 47.9 years (range: 14-86)) with 61 pheochromocytomas (bilateral pheochromocytomas in 7 patients) were included. High blood pressure and elevated catecholamines were present in 32 (59%) and 50 (93%) cases, respectively. Mean maximal diameter was 39.9 mm (range: 10-145 mm). Reasons leading to diagnosis were symptoms related to catecholamine secretion or tumor size in 22 patients (41%), periodic screening because of a known germline mutation in 6 patients (11%) and was incidental in 26 patients (48%). Compared to symptomatic pheochromocytomas, patients with incidental pheochromocytomas had similar median age (48.5 versus 46.5 years). Those with germline mutations leading to the diagnosis were younger (median age 33.5 years). Regarding blood pressure, patients with incidental findings had more often normal blood pressure, compared to those with germline mutations and those with symptomatic pheochromocytomas (58%, 50%, and 42% respectively). Most pheochromocytomas were secreting (93%) in our cohort; two patients with incidental PC and one with diagnosis for abdominal pain were not. Incidental pheochromocytomas were smaller (mean maximal diameter of 30 mm (SD:13.4) versus 40.5 mm (SD: 29.2).

Conclusion:

Pheochromocytomas presenting as incidentalomas are frequent, accounting for 48% of cases in our cohort. As expected, those tumors were smaller and only 42% of patients had hypertension upon diagnosis. Patients with germline mutation leading to diagnosis tend to be diagnosed earlier.

40

Trends in use of anti-diabetes medications among hospitalized patients with type 2 diabetes– a single-center cohort study

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Background/Introduction:

In the recent years, novel anti-diabetes medications with proven cardiovascular benefit, such as sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide 1 receptor agonists (GLP-1RA), have entered the Swiss market. However, little is known about current patterns of anti-diabetes medication use among people with type 2 diabetes hospitalized for an acute medical condition. We therefore evaluated trends in use of anti-diabetes medications at hospital admission and assessed changes in prescribing patterns during hospitalization.

Methods:

Using electronic health record data from the Cantonal Hospital Aarau in Switzerland, we conducted a retrospective cohort study including 5,024 adult hospitalizations with type 2 diabetes who were prevalent or incident users of any of the following anti-diabetes medication classes (metformin, dipeptidyl peptidase-4 inhibitors, sulfonylureas, GLP-1RA, SGLT-2i, short-acting insulin or long-acting insulin) between 2019 and 2022. Quarterly trends in use of anti-diabetes medications were plotted overall and stratified by cardiovascular disease (CVD) and chronic kidney disease (CKD).

Results:

Between 2019 and 2022, at hospital admission, we observed a numerically increase in the proportion of hospitalized people with type 2 diabetes who received any anti-diabetes medication (from 76.6% in 2019Q1 to 82.5% in 2022Q4; p=0.07). While, among prevalent users, the largest increase in use over time was found for SGLT-2i (from 6.2% to 29.0%; p<0.001), the strongest decrease was observed for sulfonylureas (from 11.7% to 6.6%; p=0.04). In the most recent quarter of the study period, between hospital admission and discharge, metformin tended to be discontinued most frequently (difference in proportion, -6.3% in 2022Q4; p=0.4), while SGLT-2i were the most frequent newly prescribed medication class (difference in proportion, +7.3%; p=0.03). In people with CVD, during 2022Q4, metformin was the most frequently used medication at hospital admission (44.1% in 2019Q1, 55.1% in 2022Q4; p=0.07), with SGLT-2i being the most frequently used anti-diabetes medication class at hospital discharge (11.2% in 2019Q1, 49.1% in 2022Q4, p<0.001). Among people with CKD, long-acting insulin was the most used medication class at hospital admission and discharge, even though the use of SGLT-2i became more frequent in the recent years. Trends were similar when we restricted the analyses to incident users.

Conclusion:

Among adult medical inpatients with type 2 diabetes, the proportion with any anti-diabetes medication increased numerically during the study period. While SGLT-2i were increasingly used over the recent years and became the most frequently prescribed medication class in people with CVD at hospital discharge, the use of sulfonylureas consistently decreased.

41

Effects of Home-Based Exercise Gaming on Cardio-Metabolic and Cognitive Health in Physically Inactive Individuals

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Background/Introduction:

Sedentary behaviour accounts for a substantial number of chronic disease and premature death. A variety of barriers impedes physically inactive people from engaging in regular physical activity. Exergames may represent a promising option to facilitate access to and motivation for regular physical activity. In this study, we examined the effects of a home-based exergame training over 6 weeks on cardio-metabolic and cognitive health in physically inactive individuals.

Methods:

Twenty participants were equipped with a home-based exergame system. Each participant performed at least 3 weekly exercise sessions at ≥ 80% of their individual, maximum heart rate, over 6 weeks. Exercise duration increased biweekly until 75 minutes of vigorous exercise were performed in week 5 and 6. VO2max, cardio-metabolic profiling, and neuro-cognitive tests were performed at baseline and study end.

Results:

After 6 weeks of home-based exergaming, VO2max increased significantly, while resting and maximum heartrate, systolic, diastolic, as well as mean blood pressure during CPET decreased significantly. In addition, significant reductions in LDL-C together with an increase TG and mean CGM glucose were observed. Moreover, dynamic balance and reaction time significantly improved after 6 weeks of exergaming.

Conclusion:

6 weeks of home-based exergaming induced a significant and clinically relevant increase in VO2max as a determinant of cardiovascular health, accompanied by further improvements in cardiovascular, metabolic and neuro-cognitive parameters. Exergaming may, therefore, offer an innovative approach to increase regular physical activity, improve metabolic risk profile, and prevent chronic diseases.

Effect of Protein Supplementation on Plasma Sodium Levels in the Syndrome of Inappropriate Antidiuresis – a Monocentric Open-Label Proof-of-Concept Study - the TREASURE Study

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Background/Introduction:

The syndrome of inappropriate antidiuresis (SIAD) can be treated with oral urea. Proteins are metabolized into urea by the liver. We hypothesized that dietary protein could increase free water clearance through urea-induced osmotic diuresis and aimed to investigate the effect of a high-protein supplementation on plasma sodium levels in chronic SIAD.

Methods:

This is a monocentric open-label proof-of-concept trial conducted at the University Hospital of Basel, Switzerland, between 10/2021 and 02/2023. Adult outpatients with chronic SIAD of any etiology were eligible. Patients received 90 g protein daily for 7 days in the form of protein powder dissolved in a maximum of 1l of liquid of choice. After a wash-out period of at least a week, patients received 30 g of oral urea daily for 7 days. The primary endpoint was the increase in sodium levels from baseline to the end of the 7-day protein supplementation.

Results:

Seventeen patients were included (14 females, median age 68 [61, 79]). After 7 days of 90 g daily protein supplementation (n = 17), plasma sodium levels increased by a median of 3 mmol/l [0, 5] (P = 0.01), plasma urea by a median of 3 mmol/l [1.7, 4.9] and urinary urea corrected for urine creatinine by a median of 21.2 mmol/mmol [6.2, 29.1]. After 7 days of oral urea (n = 10), sodium levels increased by a median of 2 mmol/l [1, 3], plasma urea by a median of 5.8 mmol/l [2.7, 9.2] and urinary urea corrected for urine creatinine by a median of 31.0 mmol/mmol [18.7, 45.1].

Conclusion:

Our findings suggest that a high-protein supplementation with protein powder increases plasma sodium levels in patients with chronic SIAD through protein-induced ureagenesis and osmotic diuresis.

43

A 4-week high phenylalanine exposure alters cortical grey matter in adults with phenylketonuria

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Background
Phenylketonuria (PKU) is an inborn error of metabolism resulting from deficiency of the enzyme phenylalanine hydroxylase. Recent cross-sectional evidence suggests that early-treated patients with PKU exhibit alterations in cortical grey matter compared to healthy peers. However, the effects of acute high Phenylalanine (Phe) exposure in adulthood need to be further elucidated. In this double-blind, randomized, placebo-controlled crossover trial, we investigated the impact of a 4-week increase in Phe intake on cortical thickness and its relationship to cognitive performance in early-treated adults with PKU.

Methods
A total of 28 adult patients with early-treated classical PKU were included in the study. Structural T1-weighted magnetic resonance images (MRI) at 3 Tesla were acquired before and after the Phe and placebo interventions (four timepoints) and were preprocessed and evaluated using a novel deep-learning-based morphometry analysis tool (DL+DiReCT). Plasma levels of Phe, tyrosine, and tryptophan, as well as performance in executive functions and attention, were assessed at each timepoint.

Results
Median Phe levels increased from 799 µmol/L before to 1455 µmol/L after the Phe intervention. Structural MRI analyses revealed a significantly thinner cortex in 19 out of 60 brain regions after the Phe phase compared to the placebo phase. The largest decreases were observed in the right inferior temporal gyrus (point estimate=-0.091mm, 95% CI=-0.132, -0.049, p_{FDR}=0.004) and the right pars orbitalis (point estimate=-0.095mm, 95% CI=-0.147, -0.044, p_{FDR}=0.007). Changes in cognitive performance were statistically significantly associated with changes in cortical thickness after the Phe phase. In detail, decreases in performance in sustained attention and cognitive flexibility were correlated with decreases in cortical thickness of the right transverse temporal gyrus (r_s=-0.69, p_{corr}=0.042, 95% CI=-0.84, -0.44) and the left pars opercularis (r_s=-0.69, p_{corr}=0.023, 95% CI=-0.86, -0.41), respectively. Similarly, increases in blood Phe levels were related to decreases in cortical thickness, although these associations did not survive False Discovery Rate correction.

Conclusion
These findings provide evidence that a 4-week high Phe exposure in adults with PKU results in widespread reductions of the cortical grey matter, potentially contributing to a decrease in cognitive performance in these patients. Further research is needed to determine the potential long-term impacts of high Phe levels on brain structure and function in adults with PKU.

Prevalence and predictive factors of erythrocytosis in persons with testosterone replacement therapy.

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Background/Introduction:

Testosteron-induced erythrocytosis (TIE) or polyglobulia is a known side effect of testosterone replacement therapy (TRT) and describes the increase of the erythrocyte count / hematocrit (HCT) above the normal and sex-specific range. TIE may be associated with serious clinical consequences (i.e., venous thromboembolism) and severe forms of TIE sometimes necessitate an adaption of the dosing regimen or the stopping the TRT respectively.

Methods:

In this single center, retrospective study we studied over a follow-up period of several years the prevalence and development of TIE and assessed risk-factors for development of polyglobulia under TRT. Laboratory values were collected at baseline, approximately 3, 6 and 12 months after TRT initiation and at last follow-up (LFU). Logistic regression was used to analyze predictive factors (i.e., age, BMI, smoking status, baseline HCT) for clinical relevant TIE (HCT ≥0.5).

Results:

We included 247 patients with TRT (T-undecanoat n=194, T-enanthate n=18, T-gel n=35) in our analysis. Median age was 44 years (IQR 33-59), median follow-up was 2.9 years (IQR 1.0-5.5). Compared to baseline, HCT-values at LFU increased siginficantly by 0.04 (p=<0.0001). A total 57% of the patients in the cohort reached a HCT-value >0.46, 23% >0.5 and 5%>0.54 but only in 46% of the cohort the pathological value was reached within the first year after start of the TRT, in the other 54% TIE appeared later. Logistic regression analysis demonstrated that BMI was significantly associated with development of a HCT ≥0.5 (p=0.013).

Conclusion:

TIE represents a common clinical problem in patients with TRT, nearly a quarter of our patients developed a clinical relevant polyglobulia and the majority of cases appeared after 1 year of TRT. BMI is a significant predictor of a HCT value ≥0.5.

45

Greater weight loss achieved with shorter eating windows in time-restricted eating (TRE) – A pooled analysis of individual data from five TRE trials

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Background/Introduction:

Time-restricted eating (TRE) has emerged as an alternative weight loss approach, yet the impact of TRE specific implementation, such as the duration of the eating window, or its relation with sleep onset and wake-up time, remains unclear. In this work, we explored the effects of different TRE eating windows on changes in body weight.

Methods:

We pooled individual data from 5 TRE open-label trials (randomized controlled trials: SeeFoodStudy, SwissChronoFood; single arm trial: NY-TREAT, UCSD, TREMNIOS) conducted in 3 different countries (USA, Switzerland and Poland) with a follow-up of 3-6 months and timestamped food/drink ingestion recorded using the MyCircadianClock app. In regression models we assessed the associations between TRE and weight loss according to the allocated (8h, 10h, 12h vs. habitual eating windows ≥ 14h) and achieved eating windows. The latter was defined as the period during which 95% of all calorie-containing ingestion events took place and was used to assess the adherence over follow-up.

Results:

We included 119 adults (68% women; mean age 47 ± SD 13 years; baseline eating duration 15.1 ± 1.4 h) who were assigned to TRE (n = 90) or control intervention (i.e., continuation of habitual diet or provision of standard dietary advice for healthy eating, n = 29). Participants on TRE shortened their eating window by 3.9 ± 2.0 h ($p < 0.001$) and lost 2.3 ± 3.1 kg ($p < 0.001$), while controls did not significantly change their eating window (-0.3 ± 0.9 h, $p = 0.07$) and maintained their body weight (-1.0 ± 3.1 kg, $p = 0.09$). Those allocated to 8h-TRE experienced greater weight loss than those on 12h-TRE (difference: +1.7 kg, 95%CI 0.2-3.1, $p = 0.02$) and controls (difference: +2.3 kg, 95%CI 0.8-3.7, $p = 0.002$). These associations remained largely significant ($p = 0.003$ to 0.059) after adjustment for age, sex and BMI at baseline, either sequentially, or in backward selection of predictors (AIC cutoff $p \leq 0.157$). When analyzing adherence to TRE intervention, shorter achieved eating windows were associated with greater weight loss (0.3 kg, 95%CI 0.1-0.5, for each 1-hour reduction, $p = 0.009$).This association remained significant after adjustement for age and sex ($p = 0.03$), but was attenuated after further adjustment for BMI at baseline ($p = 0.058$).

Conclusion:

These findings suggest that TRE with a shorter eating window (8h-TRE) is associated with greater weight loss. Future studies are needed to explore the underlying mechanisms of these observations.

Clinical use of the Diabeloop® DBLG1 system in patients with type 1 diabetes: Impact on HbA1c, time in range and patient-reported outcomes – a single centre study.

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Background/Introduction:

Automated insulin delivery (AID) systems represent a mainstay in modern diabetes treatment. The Diabeloop® DBLG1 algorithm combines the Accu-Check® Insight insulin pump with a Dexcom G6® sensor. In this single centre study we report our experiences with this newer AID system in a real world setting in terms of glucose control and patient reported outcome measures (PROMs).

Methods:

We included patients with type-1-diabetes using the DBLG1 algorithm between 2021 and 2023. Data regarding diabetes control (i.e., HbA1c, time in range [TIR]) were collected retrospectively at baseline (before implementation of AID system) and after 3±2, 6±2 and 12±2 months and at last follow-up (LFU) from the electronic health records and the algorithm database (YourLoops®). PROMs were prospectively assessed with a specific developed questionnaire.

Results:

A total of 32 patients (17 female, 15 male) were studied. Median age was 35.5 years (interquartile range [IQR] 31-46.5), diabetes duration was 19.5 years (14.1-24.5), duration of follow-up was 21 months (15.2-22). HbA1c values at baseline, 3±2, 6±2, 12±2 months and LFU were 7.9% (7.3-8.8), 7.2% (6.8-7.7; p=0.0006 compared to baseline), 7.1 (6.7-7.8, p<0.0001), 7.4 (6.9-7.8, p=0.0003) and 7.2 (6.8-7.7, p<0.0001). Median TIR values at 3±2, 6±2, 12±2 months and LFU were 69.5% (60.8-18.8), 69% (63.5-76), 69% (60-76) and 67%(62.3-76.3). PROMs demonstrated a good acceptance of the system and the perception of more stable glucose values with a reduction of the hypoglycemia rate.

Conclusion:

Implementation of the DBLG1 algorithm in type-1-diabetics led to a significant reduction of HbA1c and a persistent stable glucose control over a follow-up of 21 months.

47

PCSK9 inhibitors resistance in heterozygous familial hypercholesterolemia: a case report

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Background/Introduction:

PCSK9 inhibitors (PCSK9i) (evolocumab, alirocumab and inclisiran) are very potent lipid-lowering therapies (LLT) that induce a 50-60% decrease in low-density lipoprotein cholesterol (LDLc) in randomized controlled trials. Some patients with heterozygous familial hypercholesterolemia (FH) show a certain resistance to PCSK9i, but the mechanisms of resistance are not totally elucidated. Here we present a rare case of a patient with FH with a resistance to PCSK9i.

Methods:

A 61-years-old female patient with a history of severe hypercholesterolemia (maximal LDLc of 9,26 mmol/l), hypertension, and asymptomatic atherosclerotic disease (30% stenosis of the left anterior descending coronary artery) was referred to the lipid clinic of CHUV for statin intolerance. Despite their efficacy, with an LDLc nadir of 3,9 mmol/l, rosuvastatin and atorvastatin induced statin-associated muscle symptoms.

Results:

We introduced PCSK9i subsequently, evolocumab 140 mg q2weeks, then alirocumab 150 mg q2weeks and finally inclisiran 284 mg, with only 23% decrease of LDLc (nadir LDLc 7,1 mmol/l) which corresponds to a resistance to PCSK9i (defined as < 30% decrease in LDLc in response to PCSK9i). We then performed an exome sequencing that identified a heterozygote slice-site mutation in intron 7 of the LDL receptor gene, NM_000527.5:c.1061-2A>G, associated with a silent mutation in intron 13, NM_000527.5:c.1941G>A (p.Leu647=). This splice-site mutation corresponds to a null mutation giving rise to a non-functional LDL receptor protein. This mutation provides a resistance to PCSK9i whose action is to increase the number of functional receptors on the surface of the hepatocyte. Conversely, statins and others LLT efficacy were not largely affected by this mutation. The patient was finally treated with simvastatin 10 mg/day, ezetimibe 10 mg/day, divistyramine 6g twice per day and bempedoic acid 180 mg/day, with an excellent effect on LDLc that decreased by 65%, reaching 2,75 mmol/l.

Conclusion:

Previous reports regarding the resistance to PCSK9i of LDL receptor null mutation carriers are contradictory. A recent study comparing the effect of PCSK9i in patients with null and non-null heterozygous LDL receptor mutation found no significant difference in terms of % of LDLc decrease. To our knowledge, this is the second observation of a patient carrying this mutation and showing a resistance to PCSK9i. The exact mechanism of this resistance is still to be elucidated.

Metformin prevents glucocorticoid-induced bone resorption in healthy subjects

Author/Address of institution:

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Background/Introduction:

Glucocorticoids are crucial for treating various medical conditions due to their beneficial immunosuppressive effects. However, glucocorticoids also carry a high risk for osteoporosis. Notably, within just a few months of glucocorticoid therapy, bone density can be significantly reduced, and up to 5% of patients undergoing such treatment may experience fractures. There is promising evidence from preclinical studies and observations in patients with type 2 diabetes that metformin may prevent glucocorticoid-induced osteoporosis. We aim to investigate whether metformin prevents glucocorticoid-induced osteoporosis as assessed by biochemical markers of bone turnover in healthy subjects.

Methods:

In a randomized, placebo-controlled, cross-over trial, we compared metformin to placebo during high-dose glucocorticoid treatment in 18 lean, healthy males. All participants received prednisone 30mg/d for two 7-day periods separated by a 28-day washout period. During one period, participants additionally had metformin; during the other, they received a placebo. In an exploratory analysis, we assessed changes in bone turnover markers before and after glucocorticoid treatment in both study phases.

Results:

18 male subjects (mean age 27, standard deviation [SD] ±5.2 years, BMI 22.9 ±1.8 kg/m2) were enrolled in the study. During glucocorticoid treatment, serum C-terminal telopeptide (CTX) increased with placebo but remained stable with metformin (placebo: 0.2±0.2 ng/ml; metformin 0.06±0.2 ng/ml, p=0.003). Serum procollagen I Intact N-terminal (PINP) decreased with both treatments (placebo: -20.6 ±11.8 ng/ml; metformin -22.3 ±16.7 ng/ml, p=0.7). Serum osteocalcin decreased with both treatments (placebo -10.8 ±6.9 ucg/L; metformin -12.1 ±9.4 ucg/L, p= 0.3).

Conclusion:

Our study demonstrated that metformin has a protective effect during GC-therapy with diminished bone resorption, while no effect on bone formation can be observed. These findings indicate that metformin may have a promising role in mitigating some of the detrimental effects of glucocorticoids on bone health.

49

Primary papillary carcinoma of the thyroglossal duct cyst- a case report

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Background/Introduction:

Thyroglossal duct cysts (TGDCs) are among the most common congenital masses of the neck and are the result of failure of closure of the thyroglossal duct by the ninth week of gestation.
They are present in approximately 7% of the population, with 50% of TGDC containing ectopic functional thyroid tissue. Carcinoma arising from the thyroglossal duct cyst (TGDCa), however, is rare, with the incidence being less than 1%.

Methods:

A 40 year-old woman presented to our clinic with a chief complaint of a midline neck mass. A neck ultrasound performed demonstrated an 12x27x23mm midline neck mass with both solid and cystic components. The thyroid gland was normal. The fine-needle aspiration biopsy (FNAB) revealed a papillary carcinoma.

Results:

The cyst and part of the hyoid bone were removed. Histopathology of the surgical excision specimen showed a thyroglossal duct cyst with a maximum diameter of 9mm containing a primary invasive papillary carcinom. Due to the patient's thrombophilia and low grade microcarcinoma a total thyroidectomy was not performed.

Conclusion:

Thyroglossal duct carcinoma, most commonly papillary carcinoma, is a rare condition that should be considered in patients presenting with cystic midline neck masses.

50

C-reactive protein during pregnancy and in the early postpartum predicts adverse metabolic health outcomes at 1-year postpartum in women with gestational diabetes

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Background/Introduction:

Women with gestational diabetes mellitus (GDM) have higher insulin resistance and/or reduced secretion and an increased risk of future diabetes, which may be due to a pathological activation of the innate immune system. C-reactive protein (CRP) is induced by inflammatory cytokines and reflects innate immune activity. We investigated the prospective associations between CRP during the perinatal period with adverse metabolic outcomes at 1-year postpartum in women with previous GDM.

Methods:

Women with gestational diabetes mellitus (GDM) have higher insulin resistance and/or reduced secretion and an increased risk of future diabetes, which may be due to a pathological activation of the innate immune system. C-reactive protein (CRP) is induced by inflammatory cytokines and reflects innate immune activity. We investigated the prospective associations between CRP during the perinatal period with adverse metabolic outcomes at 1-year postpartum in women with previous GDM.

Results:

CRP during pregnancy and at 6-8 weeks postpartum predicted increased weight, body fat and visceral adipose tissue (VAT), insulin resistance (higher HOMA-IR, lower MATSUDA), absolute insulin secretion (HOMA-B, AUCins/glu), a reduced adjusted insulin secretion (ISSI-2) and a higher prevalence of the MetS at 1-year postpartum (all $p \leq 0.036$). These relationships particularly those concerning CRP during pregnancy, were independent of weight (for VAT, insulin resistance and secretion indices, MetS; all $p \leq 0.032$) and of body fat (for VAT, MATSUDA, MetS; all $p \leq 0.038$).

Conclusion:

CRP during pregnancy and in the early postpartum predicted an adverse metabolic profile in women with prior GDM at 1-year postpartum independent of weight. The prospective association of CRP with increased insulin resistance and reduced adjusted insulin secretion hint to the role of inflammation in the development of impaired metabolism after GDM and could be used as an early marker for risk stratification.

51

The Effect of Tirzepatide During Weight Loss on Metabolic Adaptation, Fat Oxidation and Food Intake in People with Obesity

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Background/Introduction:

We hypothesized that tirzepatide (TZP) causes body weight loss by reducing food intake and, according to pre-clinical studies, decreasing metabolic adaptation during weight loss. In a randomized blinded clinical trial in people with obesity (PWO) undergoing caloric restriction, we investigated the effect of TZP vs Placebo (PBO) on energy metabolism after targeting a 10% (±2%) weight loss.

Methods:

In this 18wk phase 1 study, 55 PWO, were randomized (1:1) to TZP 15 mg or PBO (mean baseline body weight 102.5 vs 103.1 kg, respectively). The primary objective was to investigate the change from baseline in sleeping metabolic rate (SMR) measured by whole-room indirect calorimetry. Secondary measures were changes in 24-hr sedentary energy expenditure, 24-hr respiratory quotient (RQ), sleeping RQ, substrate utilization, body composition (BC) and food intake.

Results:

TZP caused greater weight loss than PBO (-16.7 kg vs -8.3 kg; $p<0.001$). The decreases in SMR (TZP: -135 kcal/day; PBO: -154 kcal/day; P=0.573) and 24-hr energy expenditure (TZP: -300 kcal/day; PBO: -297 kcal/day; P=0.948) were not different between groups after adjusting for changes in body weight and BC. However, TZP significantly reduced 24-hr RQ (TZP: -0.030; PBO: 0.005; $P<0.0001$) and sleeping RQ (TZP: -0.028; PBO: -0.001; P=0.0031) compared to PBO; thus, significantly increasing fat oxidation (TZP: 12.8 g/day; PBO: -1.6 g/day; $P<0.0001$) while decreasing carbohydrate and protein oxidation rates.

Conclusion:

TZP significantly reduced food intake, did not affect metabolic adaptation but significantly increased fat oxidation.

52

Diagnosing AVP-Deficiency (Central Diabetes Insipidus) using Copeptin: Head-to-head Comparison of Arginine and Hypertonic Saline Stimulation

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6 University Hospital Zürich, 7 Federal University Minas Gerais, 8 University Milan, 9 University Cambridge, 10 University Hospial Cambridge, 11 Ludwig-Maximilians Universität München, 12 University Hospital Würzburg

Background/Introduction:

The distinction of arginine-vasopressin-deficiency (AVP-D, central diabetes insipidus) from primary polydipsia (PP) is challenging. Hypertonic saline-stimulated copeptin permits diagnosis of AVP-D with a high accuracy, but requires close sodium monitoring. Arginine-stimulated copeptin showed similar diagnostic accuracy, but with a simpler test protocol.
We performed a head-to-head comparison hypothesizing arginine-stimulation to be non-inferior to hypertonic-saline stimulation in diagnosing AVP-D.

Methods:

Randomized multicenter study conducted between 2018-2022. Patients with AVP-D or PP underwent diagnostic evaluation with hypertonic saline and arginine stimulation. Serum copeptin levels were measured 60 minutes after arginine and once sodium was ≥149 mmol/L after hypertonic saline infusion. The main outcome measure was the overall diagnostic accuracy using the pre-defined copeptin cut-offs 3.8 pmol/L for arginine and 4.9 pmol/L for hypertonic saline stimulation.

Results:

Of the 158 patients who underwent both tests, 69 (44%) were diagnosed with AVP-D (41 complete and 28 partial) and 89 (56%) with PP.
The diagnostic accuracy [95% CI] to differentiate AVP-D from PP patients was 74.4% [67.0, 80.6] for arginine- compared to 95.6% [91.1, 97.8] for hypertonic saline-stimulated copeptin. Accordingly, arginine stimulation was inferior to hypertonic saline stimulation (estimated difference -21.2% [-28.7, -14.3]).
Adverse events were mild for both tests, but 72% of patients preferred arginine to hypertonic saline stimulation. Arginine-stimulated copeptin ≤3.0 pmol/L diagnosed AVP-D with a specificity [95%CI] of 90.9% [81.7, 95.7], while levels >5.2 pmol/L diagnosed PP with a specificity of 91.4% [83.7, 95.6].

Conclusion:

In the diagnostic evaluation of AVP-D, copeptin upon hypertonic saline stimulation was superior to arginine stimulation and remains the test with the highest diagnostic accuracy.

53

Persistent postoperativ hyporeninemic hypoaldosteronism after adrenalectomy for primary aldosteronism - a case report

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Background/Introduction:

Primary aldosteronism is the most common cause of secondary hypertension and affects 5-10 % of people with high blood pressure. Most frequent subtypes are unilateral aldosterone-producing adenomas and bilateral idiopathic hyperaldosteronism. The diagnostic algorithm involves laboratory measurements (plasma aldosterone, plasma renin concentration, aldosterone/renin ratio (ARR)), confirmatory tests (saline infusion test), localisation studies of adrenal gland and adrenal vein sampling. In young patients (< 35-40 years of age) with unequivocal laboratry results and typical adenoma in image studies, there is no need for confirmatory tests nor vein sampling. Unilateral primary aldosteronism can be treated medically or with laparoscopic adrenalectomy.

Methods:

Case report

Results:

We introduce a 35 year old female patient who presented with resistent hypertension and severe hypokalemia. With a plasma aldosterone of 4200pmol/L, a suppressed renin and a ARR of > 8400 (pmol/L/mIU/L) after withdrawing the interfering medication, we made the diagnosis of primary aldosteronism. A MRI Scan of the adrenal glands revealed a 2 cm adenoma in left adrenal gland. Because of the young age and unequivocal laboratory results, the patient went straight to adrenalectomy. Postoperatively the patient presented with normal blood pressure, there was no need of antihypertensives nor potassium supplementation. Two months after the operation, the patient suffered from dizziness. Clinical work up showed symptomatic hypotension. After unsuccessful medical trial with sympatomimetic drugs by her general particioner she was referred back to our clinic. Laboratory analysis showed persisting hyporeninemic hypoaldosteronism. After starting treatment with fludrocortison, her blood pressure normalized and the patient felt well. In the follow up consultation 7 month postoperatively the hyporeninemic hypoaldosteronism persisted, but the patient appeared asymptomatic with the established fludorocortison replacement therapy.

Conclusion:

Clinically relevant hypoaldosteronism requiring treatment following adrenalcetomy for primary aldosteronism is a rare phenomenon. It is due to prolonged suppression of renin and contralateral aldosteron production in the zona glomerulosa. Persistent hypoaldosteronism is an uncommon finding.

Epidemiology and Management of Neuroendocrine Tumors of Unknown Origin in Switzerland

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* equally contributed

Background/Introduction:

Neuroendocrine neoplasms (NEN) are relatively rare tumors which are characterized by the expression of somatostatin receptors. They are usually located in the lungs, pancreas or gastrointestinal tract. However, in some NENs the origin remains unidentified and they are referred to as cancer of unknown origin (CUP). CUP are associated with a worse prognosis compared to when the location of the primary is known. Since only 10-14% of neuroendocrine neoplasms are CUP, the subject is comparatively poorly studied nationally and internationally. Therefore, this study aims to improve the understanding of CUP in the Swiss population based on a larger sample size.

Methods:

The data used were provided by the prospective SwissNET registry from 2008-2022, including 3153 NEN-patients. All subjects with a diagnosis date before 01.10.2021 were included, ensuring a follow-up time of at least one year. Only patients registered as CUP were selected. The primary aim of this analysis was the evaluation of demographic characteristics, tumor grading, the diagnostic modalities used and treatments applied. The secondary aim was to evaluation overall survival time.

Results:

During the observation period, 226 (7.2%) patients were diagnosed with CUP. 11 individuals were excluded due to non-valid data, resulting in a sample size of 207. In our cohort, the prevalence of CUP was higher in men (54.6%, n = 113) than in women (45.4%, n = 94). The median (IQR) age of onset was 67.7 years (59.0, 77.2). In 45.9% (n = 95) of cases, the CUP was characterized as functional. At the time of diagnosis, 44 (21.3%) patients were classified as grade 1, 59 (28.5%) as grade 2, 10 (4.8%) as grade 3 NEN and 49 (23.7%) as NEC. Computed tomography (CT) was the most commonly used diagnostic imaging modality (58.9%, n = 122). 68Ga-DOTATOC PET was performed in 34.3% (n = 71) of cases. For treatment of CUP, somatostatin analogues were used most frequently (42%, n = 87), followed by chemotherapy (31.9%, n = 66). Peptide receptor radionuclide therapy (PRRT) was used in 30.4% (n = 63) and surgery in 29.5% (n = 61) cases. Overall, 63.3% of patients died during the observation period. Median (CI) survival time was 15.5 months (11.5, 20.0).

Conclusion:

This is the first description of prevalence, demographics, investigation, therapy, histology and survival of patients with CUP NENs in Switzerland. Despite more aggressive treatment than known in other NENs, overall survival time was shorter than reported in the literature in NENs with known origin. One reason for shorter survival may be the high rate of NEC at time of presentation.

55

Effects of the modified release hydrocortisone preparation Efmody® on hormones, spermatogenesis and body weight in males with congenital adrenal hyperplasia

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Background:
Hormone replacement in congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) aims at mimicking the physiologic secretion patterns of cortisol and aldosterone. However, available glucocorticoid preparations do not allow to achieve an adequate cortisol peak during the early morning hours, a milder peak during the evening, and low cortisol serum levels at night. As a consequence, intermittent ACTH hypersecretion may induce the development of testicular adrenal rest tumours (TART), and recurring phases of adrenal androgen excess may suppress central hypothalamic-pituitary-gonadal axis activity, which both may impair spermatogenesis and thus male fertility.

Patients and methods:
Twenty males with salt-waisting (SW) or simple virilising (SV) CAH (confirmed by biallelic *CYP21A2* mutations) consented to switching ongoing standard treatment to the recently licenced modified-release hydrocortisone formulation Efmody®. In n=17 semen samples (analysed according to WHO standards) and hormonal parameters (measured by LC-MSMS) were evaluated at baseline and over a period of 12 months of MR-HC treatment. Three men discontinued MR-HC due to suspected adverse effects, including joint pain, increased appetite and deteriorated mood.

Results:
The median age of men included in the evaluation was 28 years (20-47). The median Efmody® dose required for optimal cortisol replacement was 16 mg/m^2 (10-22.7), corresponding to 30 mg/day (25-50), with one third of the daily dose taken at 7:00 h and two thirds taken at 23.00h. The dose of fludrocortisone was not changed. 17-OHP serum concentrations significantly decreased from a median of 9.1 nmol/l (1.3-374), to a median of 3.4 (0.95-69.6); p= 0.013, and androstenedione from 2.0 nmol/l
(0.76-33.8) to 1.3 (0.16-10.81); p= 0.113; n.s.. Median sperm concentrations rose from 6.3 mill/ml (0- 53.6) to 12.7 mill/ml (0-74.8); p= 0.1; n.s.; while total sperm counts significantly increased from a median of 20.8 (0-111.7) to 44.3 (0-111.7); p= 0.026. Serum LH rose from a median of 3.6 U/l (0.4-11.4) to 4.7 U/l (0.7-11.5), in concert with median serum testosterone concentrations which increased from
14.5 (7.2-24.8) to 19.8 nmol/l (8.1-48.7), while median INSL3 concentrations did not change: 2.34
ng/ml (0.22-16,1) vs. 2.32 (0.15-19.8). Median BMI decreased slightly, but significantly, from 27,2
(22,6-51,6) to 27,0 (22,7-46,9) kg/m^2.

Conclusions:
The modified release hydrocortisone preparation Efmody® seems to be a valid alternative to conventional glucocorticoid replacement in men with CAH, with potential beneficial effects on hypothalamic-pituitary-adrenal and -gonadal axis hormone concentrations, semen quality and body weight.

56

Personalized diurnal nutrition improving insulin sensitivity and reversing Type-2-diabetes

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Background/Introduction:

Insulin resistance plays an important role in many chronic diseases and is recognized as the core problem in type 2 diabetes. Insulin sensitivity is dominantly influenced by diurnal gene expression for fat oxidation, which is maximal during the day and lower in the evening. In contrast, de novo lipogenesis activity is maximal in the evening and lower throughout the day. It counteracts insulin sensitivity. Hence, the tolerance of saturated fat intake is higher during the day and lower in the evening to account for insulin sensitivity. Therefore, the food consumed throughout the day should be matched to biological fat oxidation capacity and insulin sensitivity.

Methods:

A 4-day digital diary of the EGB WebApp was used to analyze the daily food intake of a group of 80 individuals with different BMI, gender, and age. The group was assessed for insulin resistance risk using the medical indices TyG and TG: HDL. To restore metabolic health, a personalized diet was applied to achieve the best possible insulin sensitivity. The calculated normalized food intake, based on DGE recommendations at the BMI of 23 was used as control for each participant respectively.

Results:

The studied group of 80 individuals with varying BMI from 19 to 45 had similar dietary patterns regardless of BMI. All participants showed reduced insulin sensitivity.
Analyzing the food intake of the BMI groups compared to the norm showed, that the average daily caloric intake was lower in all BMI groups. In contrast, saturated fat intake was increased, whereas intake of "mufas" and "pufas" was decreased, although total fat intake was near normal. The diet distributed throughout the day was lower than the recommended intake of calories and saturated fat in all participants in the morning and at noon. In contrast, in the evening, caloric intake was elevated and saturated fat intake was highly increased. This was observed independently of BMI. The coefficient for saturated fatty acids as a ratio between calorie and saturated fat intake was strongly increased in the evening, whereas this was not the case in the morning and at noon. No deviation from this pattern was observed in the different BMI groups. Restoring metabolism through a diurnally optimally adjusted dietary intake that compensated for the observed deviations and allowed for a good saturated fat coefficient improved or normalized insulin resistance. Also prediabetes or diabetes could be normalized with good efficiency.

Conclusion:

We hypothesize that a persistent mismatch of the dietary pattern to the daily biological needs, independent of BMI, leads to phenotypic differentiation to insulin resistance, prediabetes, and diabetes. A personalized dietary pattern targeting insulin sensitivity improves or normalizes insulin resistance as well as prediabetes in a short time regardless of the BMI and efficiently reverses diabetes. Weight loss in the higher BMI groups was effective with a dietary focus on insulin sensitivity.

Impact on diabetes control and patient reported outcomes with a newer implantable continuous glucose monitoring system (Eversense® CGM System): a single center experience.

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Background/Introduction:

The aim of this study is to evaluate the efficacy, safety and patient reported outcomes measures (PROMs) in patients using the implantable Eversense® CGM System in a real world setting with prolonged follow up and assessed at a single diabetes center (Luzerner Kantonsspital).

Methods:

This was a prospective and retrospective observational study that included patients with type 1 diabetes mellitus and in which at least one Eversense® glucose sensor was implanted between 2017 and 2022. The outcome measure was the change of the HbA1c levels from baseline (before implantation of the sensor) to 6±2, 12±2 months at last follow-up after implantation. Other outcome measures were adverse events related to the implantation procedure (i.e., infection, bleeding, difficulties with in- or explantation respectively), and PROMs (assessed with a questionnaire).

Results:

33 patients participated in this study; median follow-up time was 50 [IQR 22.3-58.5] months. In total 178 sensor implantations were performed. Compared to baseline there was a HbA1c-reduction of -0.2%, -0.5% and -0.2% after 6, 12 months and at last-follow-up respectively (p=ns). The results of the questionnaire also showed a subjective improvement in hypoglycemia rates, a better perception of hypoglycemia and in general a better diabetes management. Common issues with the device were technical errors and issues with the removal procedure. However, no major complications were recorded.

Conclusion:

The use of the Eversense® CGM System resulted in a reduction of the HbA1c value. PROMs showed a subjective positive impact on hypoglycemia rates as well as greater confidence in managing hypoglycemia and diabetes in general and an easy handling of transmitter and Mobile App. Technical issues (early sensor breakdown and difficult sensor removal) have to be considered but are nowadays and with the use of the newest sensor generation very rare, major complications were absent.

58

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

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Background/Introduction:

Late dumping syndrome (LDS) represents a serious complication after Roux-Y-gastric-bypass surgery (RYGB) and is characterized by postprandial hypoglycemia. A newer minimally invasive endoscopic procedure, the transoral outlet reduction (TORe, endoscopic overstitch), reduces the diameter of the gastrojejunostomy as mechanical barrier and is performed in patients with weight-regain after bariatric surgery. To date, exact data on the mechanisms of LDS, gastric emptying velocity and clinical course after TORe is missing. This is the first study investigating these issues in patients with LDS undergoing TORe.

Methods:

Patients with severe LDS (severe hypoglycemia 1-3 hour after meal) were studied prospectively. Investigations included dynamics of insulin-/C-peptide-, incretin- and glucagon-secretion studied by mixed meal test (MMT), patient reported outcomes (PRO, Arts'-/Sigstad-score), continuous glucose monitoring (CGMS), scintigraphic measurement of gastric emptying velocity (separately studied with solid/liquid phase). These assessments were carried out before (V0) and 12 (V1), 24 (V2) and 48 (V3) weeks after TORe. Biochemical data of MMT is pending, results will be awaited in September 2023.

Results:

We included 11 patients (9 female, 2 male) with RYGB. Median age was 47 years (IQR 43-48), time after surgery was 7 years (3-11). Weight at V0 was 85.3kg (70.4-87.4) and at V3 82kg (71.2-96-8, p=0.249 compared to baseline). TORe significantly reduced the frequency and severity of LDS assessed after TORe: significant reduction in dumping scores (Arts'- and Sigstad-score), numerical reduction of hypoglycemic episodes and a significant increase in mean glucose values (assessed by CGMS) in all but one patient. Scintigraphic studies demonstrated a significant prolongation of gastric emptying time of the solid but not of the liquid phase.

Conclusion:

The prolongation of the gastric emptying phase by TORe improves clinical parameters of LDS and increases blood glucose. Data has to be fortified with the pending biochemical parameters. TORe seems to be a promising new treatment option in patients with LDS.

Increased pituitary 18F-FDG uptake in patients with diffentiated thyroid cancer under hypothyroidism versus rhTSH stimulation

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Background/Introduction:

In patients with differentiated-thyroid-carcinoma (DTC), 18F-FDG PET/CT is performed for assessment of radioactive iodine (RAI) non-avid disease. RAI therapy requires preparation by either thyroid hormone withdrawal (THW) or recombinant human thyroid-stimulating hormone (rhTSH) stimulation. In patients prepared by THW, increased pituitary uptake of 18F-FDG in the absence of pituitary disease may reflect physiological activation of pituitary thyrotroph cells by hypothyroidism. This study aimed to compare pituitary 18F-FDG uptake in DTC patients under THW vs. rhTSH-stimulation.

Methods:

A total of 57 patients with DTC undergoing 18F-FDG PET/CT (40 under THW, 17 under rhTSH stimulation) were retrospectively analyzed. Pituitary metabolism was expressed as maximum standardized-uptake-value (SUVmax) and as SUVratio using the right cerebellum as reference. The correlation between pituitary 18F-FDG uptake and serum TSH level was also assessed.

Results:

Pituitary hypermetabolism (SUVmax ≥4.1) was present in more patients in the THW group compared to the rhTSH group (25/40, 62.5% vs. 4/17, 23.5%; p=0.01). Pituitary metabolism was significantly higher in the THW group compared to the rhTSH group, as assessed by either SUVmax (mean±SD: 4.61±1.22, 95%CI: 4.22-5.00 vs. 3.34±0.86, 95%CI: 2.9-3.8; p<0.001) or SUVratio (0.52±0.11, 95%CI: 0.49-0.56 vs. 0.42±0.07, 95%CI: 0.38-0.46; p<0.001). Serum TSH levels correlated positively with SUVmax (r=0.41, p<0.01) and SUVratio (r=0.44, p<0.01) in the THW group only.

Conclusion:

The present findings support the hypothesis that pituitary hypermetabolism on 18F-FDG PET/CT in DTC patients under THW is a common physiological response to hypothyroidism. Awareness of this physiological hypermetabolism is important to avoid potential pitfalls in image interpretation that could trigger unnecessary investigations.

60

Cerebral blood flow and its association with white matter lesions in adults with phenylketonuria

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Background/Introduction:

Phenylketonuria (PKU) is an inborn error of metabolism affecting the conversion of phenylalanine (Phe) to tyrosine. Previous research has found reduced cognitive performance and functional and structural brain alterations (including white matter lesions) in individuals with PKU. However, less is known about cerebral blood flow (CBF) and its possible associations with cognition, white matter lesions, and metabolic parameters in patients with PKU, which was therefore aimed to investigate in this study.

Methods:

Arterial spin labeling perfusion MRI was performed to measure CBF in 30 adults with early-treated classical PKU (median age 35.5 years) and 59 healthy controls (median age 30.0 years). For all participants, brain Phe levels were measured with 1H spectroscopy, and white matter lesions were rated by two neuroradiologists on T2 weighted images. For patients only, concurrent plasma Phe levels were assessed after an overnight fasting period. Furthermore, retrospective Phe levels were collected to estimate historical metabolic control. On the day of the MR exam, each participant underwent a neuropsychological evaluation assessing IQ and performance in executive functions, attention, and processing speed.

Results:

No significant group difference was observed in global CBF between patients and controls ($F(1, 87) = 3.81$, $p = .054$). Investigating CBF on the level of cerebral arterial territories, the most prominent reduction in CBF was observed in the left anterior subdivision of the MCA ($F(1, 87) = 4.27$, $p = .015$, FDR corrected). Further, white matter lesions in patients were associated with cerebral blood flow reductions in the affected structures. Particularly, patients with lesions in the occipital lobe showed CBF reductions in the left PCA ($p = 0.015$, effect size $r_{rb} = 0.28$). Cerebral blood flow did not correlate with cognitive performance or metabolic parameters.

Conclusion:

The relationship between cerebral blood flow alterations and white matter lesions indicates a complex interplay between vascular health and white matter lesions in patients with PKU. It highlights the importance of considering a multifactorial model when investigating the impact of PKU on the brain.

Granulomatosis with polyangiitis affecting the hypophysis: A case report

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Background
Granulomatosis with polyangiitis (GPA) is a necrotizing granulomatous vasculitis of small vessels. They are also referred to as ANCA-associated vasculitis because of their strong association with antineutrophil cytoplasmic autoantibody (ANCA). The upper and lower respiratory tract and the kidneys are most commonly and severely involved, but any organ or tissue can potentially be affected. Involvement of the central nervous system is estimated to occur in approximately 10 % of patients with GPA. The affection of the hypophysis is infrequent. A review of the literature resulted in less than 50 published cases. We describe the clinical and biochemical presentation, imaging findings, and short-term follow-up under therapy of a patient with GPA affecting the hypophysis.

Case presentation
A 54-year-old woman presented at the emergency department with intermittent fever and new headache for two weeks. Furthermore, she described adynamia, night sweats, and weight loss of four kilograms in one year. Clinical examination showed a pale and febrile patient in a hemodynamically stable status and no clear infectious foci. Laboratory results revealed light signs of inflammation. MRI cranium demonstrated a cystic sellar lesion. A Rathke's cyst was suspected, and due to contact with chiasma, the patient was referred to neurosurgery. Additional imaging with MRI of sella (see Figure 1) showed a pituitary enlargement with central necrotic-cystic changes and diffusion restriction, thickening of the pituitary stalk, and an absent bright spot for the posterior pituitary. Differential diagnoses were hypophysitis (see Table 1) and an abscess (due to the diffusion restriction). Biochemically partial hypopituitarism (corticotropic, thyrotropic, and gonadotropic) was detected, initially with no diabetes insipidus. A substitution therapy of the insufficient hypophysis axes was established. Under cortisol substitution, diabetes insipidus was unmasked, and corresponding therapy was initiated. Further investigation due to unknown fever was computed tomography of the chest showing a cavitary pulmonary nodule in the anterior segment of the left upper lobe and multiple small subpleural nodules in the lower lobes bilaterally. Bronchoscopy of the pulmonary nodules resulted in the histologic diagnosis of a GPA. Biochemically, ANCA was positive. In this context, the sella region and stalk findings were interpreted as part of the GPA, skipping further and possibly harmful diagnostic and surgical interventions. Treatment of the GPA with rituximab and high-dose glucocorticoid was initiated. The patient quickly reported improved clinical symptoms under this regimen and the concordant hormonal substitution. MRI images seven months later revealed a remission of the initial sellar findings (see Figure 2). Laboratory results showed persistent partial hypopituitarism and diabetes insipidus.

Conclusion
GPA affecting the hypophysis is rare. In this case, the leading symptoms of GPA were due to pituitary gland involvement and fever. Given the MRI findings of the sella region and in context with the histologic confirmation of pulmonary GPA, we could establish the diagnosis of a pituitary GPA. The remission of the radiologic findings under systemic therapy was affirmative. There is no clear evidence of the long-term prognosis of pituitary function due to the small number of patients reported in the literature. A full recovery is rarely given, even under systemic therapy and good disease control.

62

Cognition after a 4-week high Phenylalanine intake in Adults with Phenylketonuria – a Randomized Controlled Trial

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Background/Introduction:

Phenylketonuria (PKU) is an autosomal recessive metabolic disorder characterized by increased phenylalanine (Phe) concentrations in the blood and brain. Despite wide agreement on treatment during childhood, recommendations for adults are still controversial.
We aimed to assess the impact on cognition, mood, and depression of a 4-week increase in Phe intake simulating normal dietary Phe consumption in early-treated adults with PKU was investigated in a double-blind, randomized controlled trial (RCT).

Methods:

In a single-site crossover trial, 30 adult patients with classical PKU diagnosed at birth were recruited. All of the patients underwent a 4-week period of oral administration of Phe (1500–3000 mg Phe/day) and a 4-week placebo period in a randomized order with age, sex, and place of usual medical care as stratification factors. Analyses were based on the intention-to-treat (ITT) and per-protocol (PP) approach to claim noninferiority (non-inferiority margin –4%), with working memory accuracy as the primary endpoint and additional cognitive domains, mood, and depression as secondary endpoints.

Results:

For the primary endpoint, a 4-week increase of Phe intake was noninferior to placebo with respect to working memory accuracy in both the ITT (point estimate 0.49; lower limit 95% CI: −1.99) and the PP analysis (point estimate −1.22; lower limit 95% CI: −2.60). Whereas some secondary outcomes (working memory reaction time, manual dexterity, mood, and depression) did not significantly differ between the Phe and placebo period, others (inhibition, cognitive flexibility, and sustained attention) did. Adverse events were more frequent during the Phe than during the placebo period (95% CI: 1.03 to 2.28, P=0.037).

Conclusion:

In conclusion, in early-treated adult patients with PKU, a 4-week increase in Phe intake was noninferior to continuing Phe restriction with respect to working memory accuracy, whereas some of the secondary outcomes differed between the Phe and Placebo periods. Future randomized, double-blinded intervention studies should address the impact of a long-term increase in Phe intake across different periods of adulthood. It might also be crucial to identify patients with particular vulnerability to high Phe, which would allow treatment recommendations to be individually adapted.

63

Prevalence of Undetected Heart Failure in Patients with Diabetes Mellitus

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Background/Introduction:

Heart failure (HF) is a common complication of diabetes mellitus (DM) with up to 22% of DM patients known to be affected. Early diagnosis of HF enables targeted and effective treatment to limit disease progression and improve prognosis. However, HF is frequently undetected in DM patients. Although periodical (N-terminal pro) b-type natriuretic peptide (NT-proBNP) measurements are not yet standardized, recent international guidelines advocate their application for the early detection of HF in DM patients. Currently, the prevalence of undetected HF in DM patients and their prognosis is unknown.

Methods:

Consecutive patients referred for cardiac work-up using myocardial perfusion imaging were enrolled between 2010 and 2016 in a large prospective diagnostic study at the University Hospital Basel (BASEL VIII; NCT01838148). A post-hoc analysis was performed to evaluate the prevalence of undetected HF and its prognostic implications in DM patients. Patients with known DM were included in this study and patients on dialysis were excluded. NT-proBNP levels were measured at presentation and processed blinded to medical history and study results. HF was centrally adjudicated by independent cardiologists according to current guidelines using all available clinical and study-specific data. Follow-up was performed at 1, 2, 5 and 8 years. The primary prognostic endpoints were death and major adverse cardiovascular (CV) events (MACE; CV death, acute myocardial infarction, acute HF).

Results:

In total, 925 DM patients were enrolled with 283 (31%) being insulin-dependent. Median age was 69 years (inter-quartile-range, IQR 61-76) and 240 (26%) were female. Median NT-proBNP levels were 181 ng/l (IQR, 71-509). At presentation, 42 (4.5%) of DM patients had a history of HF. Of the 883 (95%) DM patients without known HF, 429 (49%) had elevated NT-proBNP levels after adjustment for gender, age, body mass index (BMI), kidney function and heart rate (age in years <60, 39%; 60-70, 45%; 70-80, 54%; >80, 62%). Undetected HF was adjudicated in 272 (31%) of DM patients without known HF (age in years <60, 28%; 60-70, 27%; 70-80, 33%; >80, 39%). Overall, 157 (37%) of DM patients without known HF and elevated adjusted NT-proBNP levels did not have HF. At 8 years, death (41% vs. 27%, $p<0.001$) and MACE (57% vs. 31%, $p<0.001$) was significantly more common in patients with undetected HF as compared to patients without HF. This was confirmed per age strata. NT-proBNP remained an independent predictor of death and MACE in multivariable Cox-regression after adjustment for patient characteristics (age, gender, smoking history, BMI, kidney function) and medical history (cardiovascular, pulmonal, cancer).

Conclusion:

In patients with DM and suspected myocardial ischemia, the prevalence of undetected HF was over six times higher than that of diagnosed HF. Regular NT-proBNP screening for undetected HF in DM patients could allow prompt treatment initiation, potentially limiting disease progression and improve prognosis.

64

Tirzepatide vs. Semaglutide 2.4 mg for overweight and obesity: an indirect treatment comparison

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Background/Introduction:

Tirzepatide (TZP), a first-in-class GIP/GLP-1 receptor agonist, that induces clinically meaningful body weight reduction in people with obesity or overweight. In the absence of a head-to-head trial, the purpose of this study was to compare the efficacy of TZP versus semaglutide 2.4 mg using an indirect treatment comparison (ITC) with placebo as the common comparator.

Methods:

Mean percent change in body weight from baseline and odds ratio (OR) of achieving ≥5% weight loss target were compared between TZP (10 and 15 mg) at week 72 and semaglutide 2.4 mg at week 68 using matching adjusted indirect comparison (MAIC) of the efficacy estimand where patients in SURMOUNT-1 were reweighted to adjust for the differences seen in gender proportion between SURMOUNT-1 and STEP-1. In addition, five different sensitivity analyses were conducted to assess the robustness of the primary analysis findings.

Results:

For the efficacy estimand, both TZP doses resulted in significantly greater reductions in percent change in body weight compared to semaglutide 2.4 mg (TZP 10 mg mean difference: -4.67%, 95% confidence interval [CI] (-5.91%, -3.43%); TZP 15 mg mean difference: -5.92%, 95% CI (-7.16%, -4.68%); $p<0.001$ for both). Similarly, significantly more participants achieved ≥5% weight loss with TZP 10 mg (OR 2.61, 95% CI (1.48, 1.57); $p<0.001$) and 15 mg (OR 2.75, 95% CI (1.57, 4.81); $p<0.001$) compared to semaglutide 2.4 mg. The results from the five sensitivity analyses were consistent with those of the primary analysis ($p\leq0.012$), except analysis of patients achieving ≥5% weight loss between TZP 10 mg and semaglutide 2.4 mg in the treatment regimen estimand using the Bucher method ($p=0.074$).

Conclusion:

IIn this ITC, greater weight loss was seen with TZP 10 and 15 mg versus semaglutide 2.4 mg.

86

Use of Steroid Profiling Combined with Machine Learning for the Diagnosis of Mild Autonomous Cortisol Secretion

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Background/Introduction:
Diagnosis of mild autonomous cortisol secretion (MACS) is limited by inconsistency of low-dose dexamethasone suppression test (DST) results on follow-up. Applications of artificial intelligence combined with mass spectrometry-based steroid profiling might address the problem.This study assessed whether plasma steroid profiling combined with machine learning might assist the diagnosis of MACS in patients with adrenal adenoma.

Methods:

This research was designed as multicenter prospective cohort study with a retrospective component. Two hundred and fourty five patients with an adrenal mass were screened for MACS at multiple tertiary care referral centers. The disease was excluded in 191 patients and confirmed in 54 at the end of the three-year follow-up phase. Statistiscal tests and machine-learning algorithms were applied to a panel of 14 plasma steroids measured by mass spectrometry. Areas under receiver operating characteristic curves, sensitivity, specificity, and other diagnostic performance measures were evaluated.

Results:

Patients with MACS showed lower (P<0.0001) plasma concentrations of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, progesterone and androstenedione than subjects without MACS. The highest concentration (P<0.0001) in plasma steroids among patients with SC were observed for 11-deoxycortisol and 11-deoxycorticosterone. Nevertheless, concentrations of cortisol in patients with MACS were higher (P<0.05) than in those with a non- functional (NF) adrenal mass. A machine learning-designed mode of 14 steroids predicted MACS in patients with adrenal lesions at a diagnostic sensitivity and specificity of > 94%. The external validation utilizing the follow up as well as pre- and post-operative data set validated the prediction model with a superior accuracy of up to 93% compared to that of the DST (71%)

Conclusion:

Distinct plasma steroid profiles combined with machine learning may provide a simplified and improved screening method for establishing the diagnosis of MACS.

87

A rare case of hyperfunctioning papillary thyroid carcinoma in patient with type 1 Marine- Lehnhart syndrome

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Background/Introduction
Graves' disease (GD) accompanied with autonomously functioning thyroid nodule (AFTN) is a rare condition defining the Marine-Lehnhart syndrome (MLS). The vast majority of hyperfunctioning nodules in MLS are benign. In an even rarer event, the MLS might harbor malignant nodules.

Methods
We present the case of a 41-year-old male with an extremely rare simultaneous presentation of papillary thyroid cancer (PTC) within a sole progressively growth hyper-uptake nodule suggestive of type 1 MLS.

Results
The patient was referred to our medical center due to presence of typical thyrotoxicosis symptoms including unexplained weight loss, excessive sweating, tremors, and palpitations. He occasionally developed a sore and swelling throat. Laboratory assessment revealed a suppressed TSH along with elevated free Thyroxine (fT4) and free Threeidodothyronine (fT3). The TSH receptor antibody (TRAK) and Thyreoglobulin were both positive. Thyroid gland enlargement was depicted in the ultrasonography. A large heterogenous hyperechogenic and highly vascularized thyroid nodule was found within the left thyroid gland. The nodule matched the Thyroid Imaging Reporting and Data Systems (TIRADS) 3 classification. A thyroid scintigraphy scan showed an elevated Technetium uptake. An anti-thyroid agent (Carbimazole) was administrated resulting in a biochemically remission after 6 weeks. Two years after the first visit a progressive thyroid enlargement was evident. A total thyreoidectomy was performed in favor of radioiodine therapy. Histopathology assessment reported a papillary thyroid cancer without any evidence of extra thyroidal invasion. A subsequently arranged scintigraphy scan revealed lymph node metastases on the left side of the neck two months after thyreodectomy.

Conclusion
Due to extremely limited supporting data, fine needle aspiration biopsy is usually not indicated to rule out malignancy in case of hyperfunctioning state of thyroid nodule particularly in patient with MLS. Therefore, a careful physical examination and ultrasonographic evaluation should be performed in all patients. In cases of positive biopsy result, hyperfunctioning nodules should be searched for lymph node metastasis.

65

Inhibition of the epigenetic regulators HDAC and LSD1 increases SSTR2 expression and radioligand binding of 18F-SiFAlin-TATE in NET cells.

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Background/Introduction:

Peptide receptor radionuclide therapy is a highly effective, targeted treatment option in advanced neuroendocrine tumor (NET) disease. However, patients expressing low levels of SSTR2 do not benefit from this powerful tool. Recently, several preclinical studies have revealed that histone deacetylase (HDAC) inhibitors can upregulate the expression of SSTR2 and enhance somatostatin ligand binding to tumor cells. In this preclinical study, we explored the effects of single and combined treatment of NET cells with the HDAC inhibitor entinostat and the LSD1 inhibitor LSD1-IN-7 benzenesulfonate (CC-90011) on cell viability, SSTR2 expression, radiosensitivity and radioligand binding.

Methods:

The human NET cell lines BON1 and NCI-H727 were treated with entinostat, CC-90011 or a combination of both. Cell viabiliy assays were used to determine the number of viable cells. Radiosensitivity was tested in combination with γ-irradiation at doses of 0, 1, 2, 4, or 6 Gy by colony formation assay. Somatostatin receptor type 2 (SSTR2) expression was investigated by Western Blot, quantitative PCR and immunohistochemistry, while 18F-SiFAlin-TATE uptake was investigated by radioligand binding assay.

Results:

A 144h treatment of BON1 and NCI-H/727 cells with entinostat decreased cell viability to 52 ± 11% and 59 ± 9%, respecitvely. In contrast, LSD1 did not significantly decrease cell viability, however, the combination of LSD1 and entinostat was slightly more potent compared to entinostat alone. Neither entinostat nor CC-90011 nor the combination of both increased the sensitivity to conventional radiation therapy of NET cells. Entinostat and CC-90011 alone but most strongly the combination of both induced SSTR2 expression (up to 12-fold), resulting in significantly increased binding of 18F-SiFAlin-TATE.

Conclusion:

This preclinical study demonstrates entinostat, CC-90011 and especially the combination of both, to potently upregulate SSTR2 expression and radioligand binding in NET cells. These in vitro findings indicate that epigenetic modifiers might be a putative strategy to improve the treatment efficacy of peptide receptor radionuclide therapy in NET.

66

Nrf2 pathway activation potentiates the iodine-induced transcriptional activation of cell proliferation and growth pathways in murine thyroid

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Background/Introduction:

Thyroid is an organ that relies heavily on the presence of reactive oxygen species (ROS) for its physiological function which is the thyroid hormone production that involves oxidation of iodine. Lack or excess of iodine in the diet can both lead to aberrant thyroid function and increased thyroid size (goiter). Nrf2 is a transcription factor that coordinates the expression of cytoprotective and antioxidant genes. We have shown that Nrf2 orchestrates the antioxidant response in thyroid upon iodine overload and regulates the expression, iodination and processing of thyroglobulin, the major thyroid protein andprecursor of thyroid hormones. Constitutive activation of Nrf2 pathway by knocking down its cytoplasmic inhibitor Keap1 led to diffuse goiter in mice.Herein, we investigated the transcriptional response of thyroid to iodine in a setting of gain-of-function of Nrf2 signaling.

Methods:

3 months-old male C57Bl6J wild-type (WT) or Keap1 knockdown mice (KD) were exposed to 0.05% sodium iodide in their drinking water for 7 days (n=6-8 per genotype per treatment). Thyroids were used for RNA and protein extraction. RNA-seq analysis and immunoblotting were performed.Pituitary gland was also isolated for TSH mRNA expression. Pathway analysis of differentially expressed genes was performed using the Ingenuity Pathway Analysis (IPA) software. Pathways that were enriched with a p-value<0.05 were considered significant.

Results:

Nrf2 pathway activation by Keap1 knockdown led to increased TSH levels, to reduced iodination of thyroglobulin and to increased NIS mRNA and protein expression after iodine exposure.Iodine increased the expression of 773 genes in WT and 638 in KD mice at least 1.5-fold with 224 being common between the two genotypes. 380 and 497 genes in WT and Keap1KD mice respectively showed decreased expression by at least 1.5-fold after iodine exposure with 105 being common. At baseline, 511 genes are upregulated and 365 downregulated at least 1.5-fold in KD mice compared to WT. Iodine exposure of WT and KD mice leads to distinct gene expression clusters enriched for functions related to cell stress response and to cell proliferation.The top 30 enriched pathways in which all these differentially expressed genes participate include, among others, cell proliferation pathways (cell cycle, cancer-related pathways). It appears that all these cell proliferation-related pathways tend to show a similar pattern: upregulation in KD versus WT mice at baseline and further increase upon iodine exposure mainly in KD.

Conclusion:

The enhanced enrichment of cell proliferation and cell cycle-related pathways in KD mice may provide a plausible explanation for the observed goiter phenotype.The transcriptomic response of thyroid to excess iodine in the setting of enhanced Nrf2 signaling provides further insights into the roles of Nrf2 pathway in thyroid economy and physiology.

67

The beta-2-adrenoreceptor agonist fenoterol increases resting enery expenditure without activation of brown adipose tissue in humans.

Author/Address of institution:

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Background/Introduction:

In a global obesity pandemic understanding the physiology and regulation of human energy expenditure is fundamental for development of approaches to counteract weight gain. Brown adipose tissue (BAT) may directly dissipate energy from lipids and carbohydrates into heat and its activity is associated with a favorable metabolic phenotype in human adults. Animal research has established the classical activation of BAT by its primary stimulus, cold exposure, via the sympathetic nervous system and noradrenalin acting on its β3-adrenoreceptor (β3-AR). In humans stimulation of the β3-AR even with high doses of the β3-AR agonist Mirabegon leads to a rather weak activation of BAT as compared to a cold stimulus. In vitro studies in cell lines from human BAT have pointed towards the β2-AR as a possible activator of human BAT. Here, we studied the effect of the potent and selective β2-AR agonist fenoterol on human energy expenditure (EE) and BAT activity.

Methods:

Healthy normal weight volunteers were initially screened for the presence of BAT. 12 individuals with an increased cold-induced thermogenesis of >5% of resting energy expenditure were included. They received the following interventions over two hours in random order: A) standardized mild cold stimulus; B) intravenous infusion of the selective β2-agonist Fenoterol. Energy expenditure was measured continously with indirect calorimetry, skin and core temperature were recorded and BAT activity was quantified in the supraclavicular BAT depot by ^{18}F-FDG-PET/CT after each intervention. Blood was sampled for metabolic analysis.

Results:

Resting EE at baseline was similar before the two interventions 1516±347 kcal/24h before cold-exposure and 1502±281 kcal/24h before Fenoterol. Cold exposure resulted in a mean increase in EE of 195 kcal/24h (P=0.044 vs. baseline) and Fenoterol infusion increased EE by 358 kcal/24h (P<0.0001). The mean standardized uptake value (SUVmean) of supraclavicular BAT was 3,06 (IQR 2,19;3,64) g/ml after cold exposure but only 1,66 g/ml [1,63;1,70] after Fenoterol infusion. Correspondingly, the active BAT volume was 90 (26;190) ml vs. 3 (1;16) ml, respectively.
Analysis of the lipidome revealed increased lipolysis both after cold exposure and fenoterol (p<0.0001 for both treatments) with a marked increase in mono- and poly-unsaturated fatty acids. The effect on lipolysis was more pronounced after fenoterol (p<0.0001). Beta-oxidation did not increase after cold-exposure or fenoterol treatment. The main side effect of fenoterol was a feeling of warmth and a mild tachycardia.

Conclusion:

This study indicates that BAT is not primarily activated via the β2-AR in humans. Further research on the mechanisms of activation of human BAT are warranted. Reasons for the observed fenoterol induced increase in REE could be increased futile metabolic cycles e.g. lipid cycling.

68

High fat high sucrose exposure during lactation but not during the post-weaning period programs impaired glucose homeostasis

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Background/Introduction:

Nutrition during critical developmental windows plays a pivotal role in shaping long-term metabolic health. Exposure to a Western diet in early life may lead to altered metabolic programing, potentially influencing the risk to develop obesity and type 2 diabetes. In particular, exposure to an obesogenic diet may induce a metabolic program that only emerges upon dietary challenges later in life. Accordingly, understanding the long-term impact of nutritional insults in different stages of early life may provide strategies for primary prevention. Therefore, the present study aimed to determine which time window in the post-natal period is the most critical for long-term metabolic health.

Methods:

C57BL/6J mice were exposed to a high-fat high-glucose (HFHS) diet for 3 weeks during lactation or at beginning of the post-weaning period. A subset of these mice was re-exposed to a HFHS diet at the age of 18 weeks until 30 weeks of age. Intraperitoneal insulin and glucose tolerance test were performed to assess insulin sensitivity and glucose tolerance at 6, 12 and 30 weeks of age. After sacrification, liver and fat depot weights were measured and tissue was collected for analysis. Insulin-stimulated plasma glucose levels were measured by ELISA. RNA was isolated from epididymal adipose tissue and gene expression was analysed via RT-PCR to measure expression of target genes. The ΔΔCt method was used to determine gene expression in tissue relative to the housekeeping gene 18S.

Results:

At the age of 12 weeks, mice with lactational exposure to a HFHS diet revealed a significantly impaired glucose tolerance compared to control mice, while glucose tolerance of post-weaning exposed mice was similar to the control group. Moreover, a second bout of HFHS diet impaired glucose tolerance and increased body and adipose tissue weight in mice with lactational exposure to a significantly greater extent than in post-weaning exposed mice. Preliminary data suggests that increased adipose tissue inflammation is mechanistically involved in impaired glucose tolerance of lactation exposed mice.

Conclusion:

Exposure to HFHS during lactation but not during the post-weaning period programs impaired glucose homeostasis, suggesting that the lactational window may be the most critical in terms of metabolic programing.

The dose makes the poison: A high-fat diet based on extra virgin olive oil does not exhibit protection against glucose intolerance and tissue inflammation.

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Background/Introduction:
Obesity is known to be linked with glucose intolerance and systemic low-grade inflammation. Previously, we found that one week of high-fat diet (HFD) containing coconut oil or lard triggers an innate immune response in the gut, marked by a shift towards pro-inflammatory macrophages. Extra virgin olive oil (EVOO) has garnered attention for its potential anti-diabetic and anti-inflammatory properties, presenting a promising prospect for dietary interventions aimed at mitigating metabolic diseases. Our study aimed to explore the metabolic and immunological effects of an EVOO-based HFD, providing insights into the interplay between the immune system and metabolic pathways.

Methods:
Male mice aged 5-8 weeks were fed a coconut- or EVOO-based HFD or control diet for one week, after which the mice underwent metabolic assessments, including glucose and insulin tolerance tests *in vivo*, as well as glucose-stimulated insulin secretion tests in isolated islets *ex vivo*. Flow cytometry was utilized to phenotype immune cells in the gut, adipose tissue, and liver.

Results:
Despite induced hyperinsulinemia in both HFD groups, the EVOO-based HFD exhibited more significant glucose intolerance after one week of exposure. Neither HFDs showed evidence of systemic inflammation or elevated cholesterol levels at this early stage, but mice fed with the coconut-based HFD displayed elevated triglyceride levels. In the adipose tissue (AT), we noted a rise in pro-inflammatory M1b macrophages with both HFDs. Frequencies of AT regulatory T cells, known to regulate immunity and metabolism, were only increased in EVOO HFD-fed mice. In the gut, being the primary site of food exposure, both HFDs led to heightened levels of innate lymphoid cells 1 and reduced natural killer cells. While both HFDs showed a significant increase in the pro-inflammatory macrophage subpopulation P2, the coconut HFD also led to an increase in overall pro-inflammatory $CCR2^{+}$ macrophages. In the liver, innate lymphoid cells 2 were decreased upon both HFDs. However, no discernible differences were observed in the liver immune cell populations when comparing coconut- and EVOO-based HFD.

Conclusion:
EVOO HFD does not offer protection against glucose intolerance and tissue-specific inflammation compared to a coconut-based HFD in the given timeframe. Our study highlights the distinct metabolic and immune responses triggered by different dietary fat sources.

70

Adrenal Abcg1 controls cholesterol flux and steroidogenesis

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Background/Introduction:

Cholesterol is the precursor of all steroids, but how cholesterol metabolism is controlled in steroidogenic tissues is poorly understood. The cholesterol exporter ABCG1 is an essential component of the reverse cholesterol pathway and its systemic inactivation results in neutral lipid redistribution to macrophages and liver and prevents accumulation of fat depots upon high fat diet. However, the function of ABCG1 in steroidogenic organs is not explored.

Methods:

To model this question, we inactivated the ortholog Abcg1 gene specifically in the mouse adrenal cortex using the adrenal-specific Aldosterone Synthase-CRE driver.

Results:

The absence of any change in lipid profile suggested that the adrenal Abcg1 is not involved in cholesterol export to a clincally relevant extent. Instead, Abcg1 disruption led to an adrenal-specific increase in transcripts involved in cholesterol uptake and de novo synthesis. This did not result in the accumulation of lipid droplets: rather, excess intracellular cholesterol was redirected to steroid production (+ 74%) and basal corticosterone production (+ 80%). Importantly, this phenotype was not recapitulated by inactivation of the cholesterol exporter Abca1.

Conclusion:

Altogether, our data show that adrenal Abcg1 controls cholesterol uptake and biosynthesis and regulates glucocorticoid production. Our results suggest that human Abcg1 variants should be investigated for their impact on steroid production.

Impact of Chronic Colonization by *Tritrichomonas spp*. on Gut Inflammation and Glucose Homeostasis in C57BL6/N mice

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Background/Introduction: *Tritrichomonas spp*., a unicellular, tri-flagellated, and highly motile commensal protozoa of 5-10 µm in size, is commonly screened for in mouse colony health surveillance programs and considered non-pathogenic. However, recent studies suggest a potential link between Tritrichomonad protists and the exacerbation of gut inflammation in colonized mice. We previously found a pro-inflammatory shift in gut immune cells associated with impaired glycemic control. Therefore, we propose that colonization of C57BL/6N mice with *Tritrichomonas spp*. may lead to a persistent inflammatory gut microenvironment, affecting glucose metabolism and insulin secretion.

Research Design and Method: C57BL/6N male mice colonized with *Tritrichomonas spp*. from weaning were compared to age- and weight-matched uncolonized controls. Mice were fed a standard diet or a 58 kcal% coconut-based high fat diet (HFD) for 3 months. The metabolic phenotype was monitored by glucose and insulin tolerance tests. To confirm *Tritrichomonas spp*. colonization, the caecum content was examined under a light microscope, and qPCR performed. Immune cells of the innate and adaptive immunity from different tissues were characterized by flow cytometry. Cytokine secretion within the gut was assessed by *ex vivo* colonic explant culture. For assessing the gut microbiota, DNA from the caeca was isolated and analyzed using 16S rRNA amplicon sequencing.

Results: Colonization of *Tritrichomonas spp.* led to impaired glucose tolerance and hyperinsulinemia in mice fed a standard diet and HFD. Colonization precipitated gut inflammation as shown by a decrease in anti-inflammatory CCR2- macrophages, reduction in CD103+ DCs and increase in CD4+ and T-regulatory cells upon Tritrichomonas infection. HFD accentuated these inflammatory changes in gut environment upon colonization. An inflammatory milieu instigated by *Tritrichomonas* was supported by increased IL-1β in colon explants from colonized mice. Nlrp3-/- mice were protected from inflammatory and metabolic derangements instigated by Tritrichomonad protists. The inhibition of IL-1β reversed *Tritrichomonas spp.*-induced glucose intolerance, suggesting a role of the NLRP3 inflammasome in the disease pathogenesis and IL-1β as a potential therapeutic target.

Conclusion: Colonization of the tolerated gut commensal protist, *Tritrichomonas spp*., leads to an inflammatory gut environment and impairs glucose tolerance in mice, which is exacerbated by HFD. NLRP3 inflammasome activation contributes to the disease mechanism. Further research is needed to elucidate whether and how gut microbiota and their metabolites influence mucosal immunity, affecting glucose tolerance and insulin sensitivity.

72

Ablation of Gut-derived Peptides in Mice Induces Local Malabsorptive Diarrhea and Systemic Metabolic Adaptations Due To a Lack of Insulin

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Background/Introduction:
Gut-derived peptides such as glucagon-like peptide (GLP) 1 have recently gained attention due to their agonist's game-changing ability to lower body weight in obese patients. However, less is known about the role of endogenous gut-derived peptides. Acute pharmacological blockade of GLP-1 receptors decreases glucose-induced insulin secretion and thus increases glycemia. Genetic ablation of the GLP precursor proglucagon specifically in the gut decreases circulating GLP-1 but has no metabolic consequences, suggesting that endogenous GLPs are dispensable in healthy rodents. GLP-2 is involved in gut development and an agonist thereof is used clinically to treat defective nutrient uptake associated with short bowel syndrome. Apart from GLPs, several other gut-derived peptides exist with unclear metabolic functions.

Methods:
We generated mice with villus-specific genetic knockout of PC1/3, the protease that processes peptide precursors. The resulting mice lack gut-derived active peptides.

Results:
Gut-specific PC1/3 knockout mice showed two major phenotypes: First, they developed local inflammation, diarrhea and malabsorption, especially during the first few weeks of their lives and under high-fat diet feeding. Second, these mice showed strongly reduced circulating basal insulin levels and a compensatory increase in insulin sensitivity, leading to improved glucose-tolerance. On normal chow diet, body weight was mildly decreased. Knockout mice were completely protected from high-fat diet-induced body weight gain and associated complications. Food and water intake were unchanged under basal and forced conditions but energy was lost via the feces.

Conclusion:
Endogenous gut-derived peptides do not regulate satiety or food intake but lack thereof induces local inflammation and malabsorption. Fully processed peptides are needed for proper basal insulin release and not only for glucose-induced insulin secretion as it is currently postulated. Reducing basal insulin protects from high-fat diet induced body weight gain. Thus, gut-derived peptides have important local and systemic functions and a lack thereof induces severe metabolic disturbances.

IL-27 increases energy storage in white adipocytes by enhancing glucose uptake and fatty acid esterification

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Background/Introduction:

Interleukin (IL)-27 was recently identified as a promising target for anti-obesity therapy since it increased thermogenesis in white adipocytes. However, it remains unknown whether IL-27-mediated energy dissipation in adipocytes is paralleled by elevated energy supply from lipids and/or carbohydrates. Herein, we hypothesized that IL-27 increases lipolysis and glucose uptake in white adipocytes thereby providing energy substrates for thermogenesis.

Methods:

Mature 3T3-L1 or subcutaneous white adipocytes were treated with different concentrations (10 or 100 ng/ml) of recombinant IL-27 or isoproterenol (1 uM) for 4 hours. Subsequently, basal and insulin-stimulated glucose uptake was determined using 14C-deoxyglucose, and free fatty acid (FFA) as well as triglyceride (TG) levels were measured in cell lysates and in the supernatant. Markers of lipolysis, glucose uptake and beta-oxidation were assessed using Western blotting and qPCR. Moreover, glycolytic and mitochondrial ATP production was measured by Seahorse Flux Analyzer.

Results:

Unexpectedly, treatment of 3T3-L1 adipocytes with IL-27 dose-dependently reduced intracellular and extracellular FFA concentration, whereas isoproterenol significantly increased it as expected. In line, phosphorylation of hormone-sensitive lipase (HSL) was not affected by IL-27. Similar results were obtained in subcutaneous white adipocytes. Moreover, IL-27 increased intracellular TG content but neither mitochondrial ATP production nor expression of enzymes involved in beta-oxidation in 3T3-L1 adipocytes indicating that elevated esterification rather than oxidation causes FFA disappearance. In addition, IL-27 significantly increased GLUT1 protein levels, basal glucose uptake as well as glycolytic ATP production suggesting that IL-27-mediated increase in glycolytic flux provides the glycerol backbone for TG synthesis.

Conclusion:

IL-27 increases glucose uptake and TG deposition in white adipocytes and, thus, may prevent ectopic fat accumulation by increasing energy storage in white adipose tissue.

74

Interleukin-18 signaling is involved in human and mouse NASH progression

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Background:
Nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) are frequent hepatic disorders associated with obesity and diabetes. Interleukin-18 (IL-18) is a pro-inflammatory cytokine of the IL-1 superfamily whose activity is under the inhibitory control of IL-18 binding protein (IL-18BP). IL-18 triggers both an IL-1-like intracellular signaling and a specific induction of IFN-γ. Our work aims to analyze the hepatic gene expression of IL-18 signaling members in patients with NAFLD/NASH and to experimentally investigate in dietary NASH mouse models i) the therapeutic value of IL-18 blockade and ii) IFN-γ-dependent and IFN-γ-independent consequences of unopposed IL-18 signaling due to IL-18BP deficiency.

Methods:
We mined the Gene Expression Omnibus (GEO) database GSE135251 originating from patients with NAFLD and NASH for IL-18 signaling members and performed correlation analysis with clinical traits. Experimentally, we fed C57BL/6J wild-type male mice with choline-deficient amino acid-defined high fat diet (CDAHFD) for 3 weeks, in treating them three-times per week either with saline or with 0.5 mg/mouse of neutralizing mouse anti-mouse IL-18 monoclonal antibody. We generated a double KO mouse line deficient in both IL-18BP and Interferon-gamma (IFN-γ) in crossing *Il18bp*$^{-/-}$ mice with *Ifng*$^{-/-}$ mice and fed them with CDAHFD for 6 weeks. Circulating transaminases/lipids levels were measured. Liver integrity was studied through classic histology (HE/sirius red staining), immuno-staining for inflammatory markers and gene expression analysis (qPCR).

Results:
We previously reported that under nutritional stress, *Il18bp*$^{-/-}$ mice exhibit aggravated liver inflammation and fibrosis independently of steatosis compared to wild-type mice. Here, we show that IL-18BP expression is increased in liver of patients with NAFLD and NASH, positively correlating to fibrosis stages and NAFLD activity score. While not impacting transaminases levels, neutralization of endogenous IL-18 with isogeneic monoclonal antibody reduce both inflammation and parenchymal fibrosis in CDAHFD-fed mice. *Il18bp*$^{-/-}$*Ifng*$^{-/-}$ mice exhibit similar liver weight and ALT levels but slightly increased circulating AST levels compared to *Il18bp*$^{-/-}$ mice. Abrogation of IFN-γ signaling reduced inflammatory foci number but not parenchymal fibrosis (which is at contrario elevated) in *Il18bp*$^{-/-}$*Ifng*$^{-/-}$ mice vs. *Il18bp*$^{-/-}$ mice on CDAHFD. Hepatic gene expressions of type 1 immune markers and lymphocytes/macrophages markers were decreased in *Il18bp*$^{-/-}$*Ifng*$^{-/-}$ mice vs. *Il18bp*$^{-/-}$ mice.

Conclusion:
Our clinical and experimental observations implicate IL-18BP in NAFLD/NASH progression, in particular regarding inflammation and fibrosis. Neutralizing IL-18 and/or increasing IL-18BP amount/activity represent interesting therapeutic perspectives to treat NAFLD/NASH.

Alpha cells facilitate cephalic phase insulin release

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Background/Introduction:

The glucose-independent rise of insulin levels immediately at the start of a meal is known as the cephalic phase of insulin release and is a neurally mediated physiological reflex. We recently found that IL-1β mediates cephalic phase insulin secretion by modulating parasympathetic neuronal transmission. It has been established that pancreatic islets are richly innervated by the parasympathetic nervous system, yet the mechanism underlying neuronally-mediated insulin release at basal glucose, as seen in cephalic phase, remain to be studied.

Methods:

We assessed the role of glucagon in cephalic phase insulin secretion using a transgenic mouse model in which alpha cells are selectively ablated. Further, we isolated pancreatic islets of wild-type mice, as well as alpha cell-ablated mice, and assessed insulin and glucagon secretion at low glucose after stimulation with IL-1beta, a muscarinic agonist (carbachol) and both combined.

Results:

We found that IL-1beta given actuely not only stimulates insulin secretion at fasting glucose levels in vivo, but also stimulated glucagon secretion. Further, studies with transgenic mice that lack glucagon-producing alpha cells, had a loss of IL-1beta stimulated insulin secretion, implying that alpha cells may mediate this response. Next we observed that these alpha cell ablated mice fail to exhibit a cephalic phase insulin response. In vitro, we found that muscarinic activation stimulated glucagon secretion at basal glucose, but not insulin secretion. Co-stimulating islets with the muscarinic agonist and IL-1beta stimulated insulin secretion at basal glucose, and strikingly this was not the case in alpha cell-ablated islets. However, we could restore IL-1beta and muscarinic-induced insulin secretion by adding glucagon to the media of alpha-cell ablated islets.

Conclusion:

Cephalic phase of insulin release mediated by IL-1beta stimulation of parasympathetic nerves requires pancreatic alpha cells. This neuronally-mediated beta-cell response may be rely on glucagon, thereby positioning alpha cells an important facilitator of neuronally-stimulated insulin secretion at fasting glucose.

76

Fostering residents' understanding of patients with diabetes by self-tracking glucose with a sensor

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Background/Introduction:

Self-experimentation to understand patients' perspectives has been an underappreciated and underresearched domain, which may be worth exploration to gain a better understanding of patients with chronic diseases. Studies using simulations, wearing bariatric suits or age simulators or wearing health tracking devices report that these experiences provide physicians a good opportunity to experience their emotions and feelings from a patient's perspective.
Both patients and health care professionals need education to harness the full benefits of modern glucose monitoring technology. To the best of our knowledge, there is no published research evaluating use of glucose sensors as an educational tool in medical education. Therefore, our objective is to explore individual experiences of residents after wearing a glucose sensor.

Methods:

Qualitative research study in a single-center (hospital Zollikerberg) in Switzerland
Population: Residents working in internal medicine at hospital Zollikerberg
Intervention: Self-tracking glucose with a glucose sensor
Outcome: Narrative overview of usefulness of this experience to residents regarding awareness, appreciation and understanding of patients with diabetes

Results:

Study will beginn in 08/2023. We expect preliminary results with insight into key points in 11/2023.

Conclusion:

To our knowledge, this is the first study exploring the use a glucose sensor as an awareness tool by allowing residents to experience how self-tracking their glucose feels like. I am excited to see how it unfolds.

77

One-anastomosis gastric bypass with a long biliopancreatic limb leads to improved glucose tolerance

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Background:
Bariatric surgery is the most effective treatment for morbid obesity and obesity induced disorders. One anastomosis gastric bypass (OAGB) has gained attention as a simple, but effective surgery strategy. However, little is known about the influence of the length of the bypass on metabolic and endocrine effects.

Research Design and Method:
C57B6/J male mice were fed high fat diet (HFD) starting from 5 weeks onwards. 8 weeks after the dietary intervention, the mice received an One-Anastomosis Gastric Bypass (OAGB) with either a short biliopancreatic limb (BPL, 22.7% of total bowel length), or a long BPL (29.8%). A control group undergoing sham surgery was food restricted (0.5-1g HFD/day) to limit body weight gain. Weight loss and metabolic parameters were assessed 2 and 5 weeks after surgery and obesity-related comorbidities and endocrine effects at sacrifice.

Results:
Total weight loss after OAGB surgery was independent of the lengths of the BPL. A long BPL was associated with improved insulin sensitivity on day 14, as indicated by lower glucose-stimulated insulin, and with improved glucose tolerance at 5 weeks. In addition, total cholesterol was reduced in mice with a long BPL, but there was no difference in the resolution of non-alcoholic fatty liver disease (NAFLD) and adipose tissue inflammation. The long PBL group also trended towards a reduced hypothalamic-pituitary-adrenal axis and aldosterone. Furthermore, primary bile-acids trended to be increased generally in mice after OAGB, while secondary bile-acids were reduced.

Conclusion:
Weight loss is not dependent on the length of the BPL. However, glucose metabolism is improved with a long BPL as well as lipid and endocrine outcome. These results indicate that tailoring the length of BPL in humans might help to optimize metabolic outcomes after bariatric surgery.

78

Effects of Weight Loss and Dietary Changes on Glucose Homeostasis and Tissue Immune Cell Homeostasis

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Background:
Obesity has been linked to changes in gut microbiota and intestinal immune cell composition. However, it remains unclear whether these changes persist following weight loss or a dietary change. Our study aimed to evaluate whether weight loss through caloric restriction or improved diet can lead to the reversal of both metabolic and immunological changes.

Research Design and Method:
Male C57B6/J mice were fed high-fat diet (HFD) for 8 weeks and then subjected to one of the following dietary interventions: continued HFD, HFD with caloric restriction to limit weight gain, or switched back to standard diet (SD). Additional control mice were continuously fed a SD. Metabolic assessments were performed before, and at two, five and seven weeks after the intervention. Immune cells of different tissues were characterized by flow cytometry upon sacrifice.

Results:
Two weeks after the dietary intervention, body weights became comparable between mice on HFD/caloric restriction, HFD/SD and continued SD. At that time, mice with HFD/caloric restriction and mice with HFD/SD had improved glucose tolerance and insulin secretion, similar to mice on continued SD. Glucose tolerance of mice with HFD/caloric restriction deteriorated over time, however, insulin remained low and gluconeogenesis reduced, indicating sustained insulin sensitivity. Inflammatory adipose tissue macrophages (ATMs) decreased and anti-inflammatory ATMs and AT eosinophils increased after weight loss. Similarly, eosinophils increased in the liver upon weight loss. Immune cell changes driven by improved diet (switched back to SD or continued SD) included higher neutrophils in the liver and regulatory T cells and Th2 cells in the AT.

Conclusion:
Weight loss is associated with reduced insulin levels and immune cell alterations concerning ATMs and eosinophils in AT and liver. In contrast, improving the diet specifically leads to increased neutrophils in the liver and T-cell subsets in adipose tissue. Gaining a better understanding of how weight loss and dietary changes impact metabolic and immunological parameters will help to elucidate their interrelation.

79

Treatment Response to Liraglutide in Overweight or Obese Subjects Aged 60 Years and Above

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Background/Introduction:

The use of GLP-1 agonists in the medical treatment of obesity is continually expanding. Liraglutide was the pioneering drug in this class to be approved for obesity treatment at a daily dose of 3 mg. However, our understanding of its efficacy in individuals aged over 60 years remains limited, especially since the existing data mainly focus on diabetic patients who receive lower doses of liraglutide (1.8 mg/day) and few patients over 60 years old seek an obesity treatment. As the basal metabolic rate and muscle mass tend to decrease with age, it is of significant scientific interest to evaluate the response of this older population to liraglutide treatment in terms of weight loss and body composition changes.

Methods:

In this prospective observational cohort study, we included all patients over the age of 60 who initiated liraglutide treatment (3 mg/day) by subcutaneous injections between May 2020 and September 2022, at the Obesity Center, Service of Endocrinology at Lausanne University Hospital (CHUV).All patients participate in a multidisciplinary program and benefit from professional nutritional/dietary advice, physical activities propositions and from psychological counseling if needed.Patient body weight progression was systematically monitored at baseline, then again at the 4- and 10-month intervals during liraglutide treatment. Additionally, a body composition analysis was carried out using Dual X-ray Absorptiometry (DXA) at two time points: prior to the onset of the treatment, and 10 months subsequently.

Results:

Out of the 15 patients included 9 were women and 6 men. The median age of the subjects at the beginning of the treatment was 64 years, the mean +/- SD body weight was 107.2 kg +/- 15.2 kg and the mean BMI (body mass index) was 39.2 +/- 5.9 kg/m2.After 4 months on liraglutide the body weight was significantly reduced to 99.2 +/- 13.7 kg ($p<0.0001$) compared to baseline (7.4 +/-1.3 % weight loss). At 10 months on the treatment the body weight was further reduced to 95.5 +/- 14.8 kg ($p<0.0001$) (11 +/-3.2 % weight loss compared to baseline). The fat mass index (FMI) based on DXA measurements was significantly reduced ($p<0.0001$) from 18.6 +/- 5.3 kg/m2 at baseline to 15.8 +/- 4.4 kg/m2 at 10 months on liraglutide treatment. The visceral adipose tissue mass was also reduced from 2.9 +/- 1.6 kg to 2.3 +/- 1.2 kg respectively ($p=0.0001$). The appendicular lean mass index (ALMI) was reduced as well ($p=0.0006$) but to a lesser degree from 9.2 +/- 1.4 kg/m2 at baseline to 8.6 +/- 1.2 kg/m2 at 10 months on treatment while the lean mass percentage was increased from 50.3 +/- 5.4% to 53 +/- 5.8% ($p=0.0001$). None of our subjects showed an ALMI index lower than 7 for men or lower than 5.5 kg/m2 for women that is indicative of sarcopenia duiring the observation period.

Conclusion:

These results suggest that liraglutide effectively reduces body weight and fat mass while preserving muscle mass in subjects aged over 60 years. These findings are consistent with the effects observed in younger adults in previous studies.Given the risk associated with lean mass loss in older people, it is essential to monitor body composition during liraglutide treatment.

IL-1-receptor antagonist during cephalic phase of insulin secretion in health and type 2 diabetes - an interim analysis of the Cephalira study

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Background/Introduction:

The initial insulin response to sensorial stimuli, occuring in the first 10 minutes after contact with food, is called cephalic phase of insulin secretion. Although the amount of insulin secreted is small compared to overall postprandial secretion, it plays a key role in early meal response. In obese and type 2 diabetes (T2DM) patients, this cephalic phase is reduced. One possible reason is the chronic low-grade inflammation in T2DM patients, which might blunt the early insulin response. With our study, we wanted to block this inflammation, in order to restore the cephalic phase insulin secretion.

Methods:

The study had two subgroups, which were processed parallel to each other. Group 1 consisted of healthy, non-obese subjects, while group 2 included obese patients with T2DM (HbA1c 7.0-10.0 %) and a CRP ≥ 2 mg/l. Patients with signs of acute infection or concomitant treatment with insulin, GLP-1 agonists and/or DPP-4 inhibitors were excluded. After inclusion, patients were randomized to receive 100 mg Anakinra (Kineret ®) or matched placebo in a double-blind cross-over fashion on two separate dates. On both visit days, a Mixed Meal Tolerance Test with a standardized meal was conducted. It was ensured that no prior sensorial contact to the food (visual, olfactory or otherwise) was possible. Clinical parameters were monitored and blood analysis was performed throughout the test. For group 2, patients were instructed to self-administer Anakinra subcutaneously for 6 days prior to a third visit. No medication was administered prior to the MMTT on that day.

Results:

This is an interim analysis of the 12 subjects in group 1. We found that acute treatment with anakinra did not significantly impact insulin secretion during the cephalic phase after meal intake in healthy individuals (AUC anakinra: 148.6 pmol/l (130.8 - 182.9); NaCl: 151.9 pmol/l (144.6-181.3), p-value: 0.622). During the cephalic phase, we were able to show a significant increase in insulin secretion compared to baseline. No changes in c-peptide, glucose and glucagon secretion were seen, which was expected.

Conclusion:

We were able to convincingly show a cephalic phase of insulin secretion. This is key for the study continuation with group 2, since we might be able to see a recovery of the cephalic phase in T2DM patients with antiinflammatory therapy. Even though there was a slight trend towards reduced insulin secretion with anakinra, we did not see any significant difference. supporting the notion that acute suppression of inflammation does not have an impact on glucose metabolism in healthy individuals.

81

Management Algorithm of Patients with Concomitant Diabetes Mellitus and Chronic Venous Insufficiency

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Background/Introduction:

Diabetes mellitus (DM) and Chronic Venous Insufficiency (CVI) are significant burden in patient daily life. While the two diseases share common risk factors and pathophysiology, they are often assessed and managed as separate conditions.
The aim of this project was to develop recommendations for the identification and treatment of patients with concomitant DM and CVI.

Methods:

Using a modified Delphi method, a panel of experts developed 38 statements and 2 multiple choice questions. These were used to form an online survey which was disseminated through vascular and diabetes specialists across Europe, Central America, South America, and Middle East. Respondents indicated their level of agreement with each statement. The threshold for consensus was set as ≥75% of agreement.

Results:

A total of 238 responses were received. Most of the statements (27/38) reached >90% agreement, 9/38 attained between 75-90% agreement, and 2 failed to meet the threshold. The awareness around the impact of the two diseases was high and a gap was highlighted in the identification of patients suffering from concomitant DM and CVI. Seventy-seven (77%) respondents consider overweight (BMI >30) and leg oedema as signs for assessment of the presence of DM and diabetic microvascular complications (DmVC) in patients with CVI, while 63% agreed that three parameters (skin changes, leg burden and oedema) would be required to trigger investigation for coexistent CVI in patients with DM. Treatment of patients with DmVC and CVI should be accomplished with a combination approach, including lifestyle change, non-medical and pharmacological treatments. Venoactive drugs indicated in both DmVC and CVI were recognized as treatment option in this patient population.

Conclusion:

These results raised the need to consider DM and CVI as a combined therapy area. As outcome, an algorithm is proposed to help the identification of at-risk patients and to provide recommendation on the management of patients with concomitant diseases.

82

Selective Upregulation of Stress-Response Pathways Nrf2 and Notch in Adipocytes, but Not in Immune Cells, in Subjects with Obesity

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Background/Introduction:

Obesity is typified by elevated levels of Reactive Oxygen Species (ROS) within adipose tissue. Central to the regulation of antioxidant and cytoprotective genes is Nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor. Notch signaling, renowned for its roles in development, cellular differentiation, apoptosis, and proliferation, relies on a family of intermembrane receptors. The Notch Intracellular Domain (NICD) is released, after binding of the extracellular part of the receptor to ligands of neighbor cells, enters the nucleus and stimulates the expression of target genes. Recent studies have revealed that ROS can activate NICD cleavage. Moreover, a bidirectional transcriptional regulation between Nrf2 and Notch has been described. Therefore, both Nrf2 and Notch pathways can be conceptualized as stress-response mechanisms. We hypothesized that both Nrf2 and Notch pathways are upregulated in the adipose tissue of obese subjects in response to increased ROS levels.

Methods:

We utilized publicly available single-cell RNA sequencing datasets from human adipose tissue samples, including individuals with a Body Mass Index (BMI) less than 25 kg/m2 (normal weight) and those with a BMI exceeding 30 kg/m2 (obese). Additionally, we obtained data from C57BL6 mice subjected to either a high-fat diet (comprising 60% kilocalories from fat) or a regular chow diet (consisting of 6.4% kilocalories from fat) over a duration of 13 weeks.The data was analyzed using R studio, specifically employing the 'read RDS' and 'fetchdata' functions. These analyses were conducted on various cell types within adipose tissue, including vascular cells, immune cells, mesothelial cells, and adipocytes.

Results:

We observed a minimum of two-fold increase in the RNA levels of various cytoprotective genes, including NQO1, TXNRD1, GCLC, HMOX1, GSTA4. These genes are known to be regulated by Nrf2, and their upregulation was identified in adipocytes derived from obese humans compared to those from normal-weight individuals. A similar pattern of gene expression was identified in adipocytes from obese mice. Interestingly, these gene sets did not show any significant differences in immune cells from both human and mouse adipose tissue, irrespective of whether the subjects were lean or obese. We also observed an increased expression of Notch 1-3 RNA, at least two-fold, in the human adipocytes derived from obese patients, while only Notch3 RNA was increased in the adipocytes of obese mice. Additionally, we noted increased expression of Hes1, a common target gene of Notch signaling, in both human (two-fold) and murine (four-fold) adipocytes from obese subjects. Similar to the cytoprotective genes regulated by Nrf2, these changes in Notch signaling were not reflected in the immune cells from both human and mouse samples.

Conclusion:

The observed enhancement in Nrf2 and Notch signaling within adipocytes in conditions of obesity necessitates further detailed investigation. It's plausible that these upregulated pathways are integral to the maintenance of adipose tissue homeostasis and its functional capacity under the burden of obesity. Moreover, the interplay of these pathways may significantly contribute to the resultant metabolic phenotype associated with obesity.

IL-1beta promotes formation of new adipocytes by targeting their precursors

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Background/Introduction:

Postprandial IL-1beta surges are predominant in the white adipose tissue (WAT), but its consequences are unknown. Here, we investigated the role of IL-1beta in WAT energy storage.

Methods:

- Adipocyte-specific deletion of IL1R1 in mice
- IL1R1-deficient mice
- In vivo 5-Ethynyl-2′-deoxyuridine (EdU) tracing experiments
- Differentiation of human and murine mesenchymal adipose tissue stem cells

Results:

Deletion of IL-1R1 in mature adipocytes had no metabolic consequences, whereas whole-body IL1R1-KO mice displayed reduced body weight gain, WAT mass, and adipocyte size. Among all major WAT-resident cell types, adipocyte progenitors expressed the highest IL1R1 levels. Direct measurement of new adipocyte formation in vivo by EdU tracing revealed a substantially decreased production of new fat cells in both gWAT and scWAT of IL1R1-KO mice upon HFD-feeding. In vitro, IL-1beta potently promoted adipogenesis in murine and human adipose-derived stem cells. This effect was exclusive to early-differentiation-stage cells, in which the adipogenic transcription factors C/EBPdelta and C/EBPbeta were rapidly upregulated by IL-1beta and enriched near important adipogenic genes. The pro-adipogenic, but not pro-inflammatory effect of IL-1beta was potentiated by acute treatment and blocked by chronic exposure. Thus, we propose that transient postprandial IL-1beta surges regulate WAT remodeling by promoting adipogenesis, whereas this physiological function becomes blunted in obesity by chronically elevated IL-1beta levels.

Conclusion:

We investigated the role of IL-1beta in WAT remodeling and report that this cytokine promotes adipocyte differentiation by directly targeting adipose-derived stem cells.

Selenium Supplementation in Patients with Hashimoto Thyroiditis - A Systematic Review and Meta-Analysis of randomized clinical trials

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Background/Introduction:

Hashimoto thyroiditis (HT) is the most common cause of hypothyroidism in iodine-sufficient areas. Selenium is an essential trace mineral required for thyroid hormone synthesis and exerts anti-oxidative effects. It may therefore be of relevance in the management of HT.

Methods:

We conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) to evaluate the effect of selenium supplementation on thyroid function (e.g. thyroid-stimulating hormones [TSH]), thyroid antibodies (e.g. thyroid peroxidase [TPOAb]), ultrasound findings, immune markers, quality of life, blood levels of selenium, and adverse events in HT. The study protocol was registered on PROSPERO (CRD42022308377). We systematically searched MEDLINE, Embase, CINHAL, Web of Science, Google Scholar, and the CENTRAL Cochrane Library trial registry from inception to January 2023, and searched citation of eligible studies. Two independent authors reviewed and coded the identified literature. The primary outcome was TSH, and the other were considered as secondary outcomes. We synthesized the results as standardized mean differences (SMD), assessed risk of bias, and rated evidence, and followed the PRISMA guidelines throughout the process.

Results:

We screened 606 records and included 35 unique studies. Selenium supplementation achieved the highest effect on TSH levels in euthyroid and subclinical hypothyroid patients without hormone replacement therapy (SMD -0.37, 95% CI -0.71, -0.03; 865 participants; I2 = 62%) and on TPOAb in patients with thyroid hormone replacement therapy (SMD -1.40, 95% CI -2.29, -0.51; 938 participants; I2 = 94%). Adverse effects were comparable between the two groups (OR 0.89, 95% CI 0.46, 1.75; 18 RCTs; 1341 participants; I2 = 0%). No significant change in free triiodothyronine, free thyroxine, and thyroglobulin antibodies was observed. Certainty of evidence was moderate for TSH and low for TPOAb.

Conclusion:

In people with HT without hormonal replacement therapy, selenium was effective and safe in lowering TSH and TPOAb levels in HT. Indications for lower antiTPO was found independent of thyroid hormone replacement.

85

Association of an unfavourable body composition with educational status - data from the Zurich Obesity Cohort

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Background/Introduction:

While different novel treatment options for the treatment of obesity are available today, personalized treatment strategies are still rarely used. In this regard, it is most important to identify patients who may profit from specific treatment strategies.
Patients with an unfavourable body composition are particularly at risk of developing metabolic sequelae of obesity. Existing data provides evidence for an unfavourable body composition being associated with socio-economic disadvantages and lower educational status. However, there is no data about such an association in obese adults in Switzerland, where social inequality is generally low.

Methods:

Body composition measurements performed by bioelectrical impedance analysis (BIA) from patients participating in the Zurich Obesity Cohort, a longitudinal, prospective cohort study, were analysed and a possible correlation with the educational status was assessed. Educational status was defined as final education being one of the following: compulsory school, an apprenticeship, university of applied sciences or university.
A generalized linear model was applied to separate the effect of educational status on body composition from effects of age, gender and weight.

Results:

BIA measurements as well as information regarding education was available in 183 (out of 319; 57.4%) patients included in the cohort study, all of them suffering from overweight or obesity.
The mean age ± SD of this group was 44.5 ± 13.4 years, BMI was 39.1 ± 6.3 kg/m2. 124 patients (67.8%) were female.
The educational status in this cohort subgroup was distributed as follows: Compulsory school: 27 (14.8%), Apprenticeship: 93 (50.8%), university of applied sciences: 36 (19.7%), university: 27 (14.8%).
The ratio of fat to lean body tissue differed between groups, with the highest ratio (0.94 ± 0.21) seen in compulsory school graduates, followed by apprenticeship graduates (0.89 ± 0.23), university of applied science graduates (0.82 ± 0.17), and university graduates (0.77 ± 0.17). This difference proved to be of statistical significance after correcting for gender, age and total body weight ($p<0.001$).

Conclusion:

In a cohort of overweight and obese patients, lower educational status was associated with an unfavourable body composition (fat-to-lean ratio), which may lead to a higher burden of metabolic diseases in these patients.
Reasons for this difference may include differences in the knowledge and affordability of a healthy diet or differences in physical activity.
Thus, it seems highly important to focus on this issues during obesity treatment in particular in patients with a low educational status.

Inhibin *α* (*INHA*) and steroidogenic factor 1 (*NR5A1/*SF-1) collaborate in regulating human sex development.

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Background:
Inhibin consists of two homologous subunits, the α (*INHA)* and the βA or βB subunits (*INHBA/INHBB*). Both inhibins play an important role in the hypothalamic-pituitary-gonadal axis by regulating the follicle stimulating hormone levels. *INHA* knockout mice develop mixed or incompletely differentiated gonadal stromal tumours. In females, some *INHA* variants have been associated with primary ovarian failure (POF), while in males, homozygous *INHA* variants were recently described causing decreased prenatal and postnatal testosterone production and infertility. Similarly, variants in *NR5A1/SF-1* may cause a very broad phenotype of variation of sexual development. This study aimed at understanding the combined effect of heterozygous variants in *INHA* [c.675T>G, Ser225Arg] and *NR5A1*/SF-1 [c.58G>C, Val20Leu] found in a 46,XY individual with severe undervirilization.

Methods:
Genetic family analysis was performed. Different *in silico* tools predicted the possible impact of *NR5A1/*SF- 1 and *INHA* variants on protein structure and function to classify them according to the ACMG guidelines for pathogenicity. We searched for human *INHA* variants in literature and in databases (ClinVar, HGMD, UniProt and Ensembl), and for interaction between *NR5A1*/SF-1 and *INHA* in different species. Using bioinformatic tools, binding sites for *NR5A1/*SF-1 in the 5′ flanking region of *INHA* were searched and used as templates to generate promoter-reporter constructs in pGL3. Functional studies assessed the transcriptional activation of the *INHA* promoter-reporter constructs by WT and/or mutant *NR5A1*/SF-1 in two different cells lines (NCI-H295R and HEK293T).

Results:
The healthy father of the index patient carried only the *NR5A1/*SF-1 variant. But *in silico* analyses suggested that both *NR5A1/*SF-1 and *INHA* variants were pathogenic. Multiple sequence alignment showed conservative amino acids affected. We found no reported interactions between the two proteins. However, 26 *INHA* variants with suggested pathogenicity were reported in different databases, majority missense variants (18/26, 69%), 12 (66%) with unknown significance (VUS), although associated with adrenocortical or ovarian tumours, POF and male infertility. Two *-2050* and *-520_INHA* promoter reporter constructs containing *NR5A1*/SF-1 binding sites were activated by transfected or endogenous WT *NR5A1*/SF-1 in non- steroidogenic HEK293T or adrenal NCI-H295T cells, respectively. By contrast, mutant *NR5A1*/SF-1 [c.58G>C, Val20Leu] revealed impaired activity on both *INHA* promoter constructs in HEK293T cells. These results clearly indicate that *NR5A1*/SF-1 regulates *INHA* transcription.

Conclusions:
The exact role of *INHA* in human sex development remains largely unknown. We found that *NR5A1*/SF-1 regulates *INHA* promoter activity and that the digenic variants in *NR5A1*/SF-1 and *INHA* together most likely explain the 46,XY DSD phenotype in our index patient. Further studies are ongoing to show an additional likely regulation of activin/inhibin in collaboration with *NR5A1*/SF-1 on the GnRH regulated gonadal axis.

89

Data-driven algorithms for real-time hypoglycaemia event forecasting in individuals after Roux-en-Y gastric bypass using standalone continuous glucose monitoring

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Background/Introduction:

Post bariatric hypoglycaemia (PBH) is a late metabolic complication of Roux-en-Y gastric bypass (RYBG) characterised by critical blood glucose levels (i.e., BG<3.0 mmol/L) following meal-induced glycaemic excursions. Due to the potentially debilitating consequences of hypoglycaemia, forecasting hypoglycaemic events and generating alerts (e.g., 20/30 minutes ahead in time) could assist in improving patients' safety by allowing for preventive or mitigating actions (e.g., ingestion of carbohydrates). The objective of this study was to develop various prediction algorithms for the real-time forecasting of PBH events on the basis of continuous glucose monitoring (CGM) and select the one with superior performance.

Methods:

Autoregressive Integrated Moving Average (ARIMA), recursive Autoregressive (rAR) and a feed forward neural network (NN) were used to build a forecasting model that best represents PBH episodes and to raise hypoglycaemic alarms at different prediction horizon (PH = 15, 20, 30 minutes) ahead in time. The proposed algorithms have been tested on a dataset generated by 50 individuals, with a diagnosis of PBH, monitored for 36 days (on average) in daily life conditions using the Dexcom G6 CGM sensor. The dataset yielded a total of 802 PBH episodes, defined as sensor glucose <3.0mmol/L for at least 15 minutes, with an average duration of 25 minutes: almost 4 episodes every 10 days per subject. Performance of algorithms were assessed by measuring Recall (R), i.e., the ratio of correctly predicted PBH episodes over the total number of events, False Alarms per day (FA/day) and the time gain (TG), i.e., the time distance between a true alarm and the onset of the event.

Results:

Overall, the numerical results indicate that NN tends to overestimate critically low BG levels. As a consequence, only a few alarms are triggered and the majority of the PBH episodes are not predicted, as indicated by low values of recall (R = 44%, 37%, 29%, for PH = 15, 20 and 30 minutes, respectively). Compared to NN, ARIMA better describes the PBH dynamics and improves the performance in terms of recall (R= 76%, 70% and 50%) and TG (10 minutes) with less than one FA every two days. Finally, although a larger FA/day than ARIMA (about one every 2 days), the rAR model provides the best performance in terms of recall and TG by granting: R = 95%, 94%, 95% and TG = 5, 10, 15 minutes, for PH = 15, 20 and 30 minutes, respectively. Hence, the rAR model provides accurate forecasts of (almost) all the PBH events with an actionable lead time.

Conclusion:

The real-time forecasting of PBH episodes is challenged by noise affecting CGM data and the rapid postprandial glucose dynamics, allowing minimal time for the algorithms to raise timely alerts. Our findings suggest that the rAR approach with a PH of 20 minutes provides the best solution by achieving sufficient time anticipation and accurate prediction capabilities.

90

Quantifying objective eating behavior measures using Auracle™; a novel behind-the-ear wearable digital tool

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Background/Introduction:

Eating behaviors can influence diet quality, obesity, and overall mortality. A device with the capacity to provide objective measures can help to personalize interventions to support regulated eating behaviors. Real-time chewing detection can be a first step to measure objective eating behavior. This study evaluated the potential of Auracle™, a behind-the-ear wearable device, to detect periods of chewing and chewing counts in healthy volunteers.

Methods:

We included five (5) healthy volunteers to perform series of eating activities while wearing an Auracle™. Bone vibrations transmitted through the mandible to the mastoid were recorded through the ear-mounted pick-up microphone and data acquisition module of Auracle™ to classify chewing duration and counts while eating. Experimental conditions for subjects included five specific conditions were biting, chewing, and pause conditions including 1) bite, chewing fast for 10 seconds, 2) bite, chewing slow for 15 seconds, 3) bite, chewing fast for 10 seconds, pause for 5 seconds, 4) bite, chewing slow for 10 seconds, pause for 10 seconds, and 5) bite, chewing slow 10 seconds, talk for 10 seconds. Each experimental condition was repeated over a period of 60 seconds. The number of chews were counted and recorded manually by an observer to serve as ground truth. All participants ate carrots during the experiment.

Results:

The ground truth total chewing duration was 60, 60, 40, 30, and 30 seconds for the fast, slow, fast pause, slow pause, slow talk experimental conditions, respectively. Subject-averaged automatically detected chewing duration for each experimental condition was 60.3±9.2, 60.7±2.4, 41.7±3.4, 31.7±0.8, and 38.2±9.1 seconds for the five experimental conditions. Average discrepancies between ground truth and automatic detection were less than 10% for the four non-talking patterns (9.4%, 3.3%, 7.5%, and 5.6%) and extended to an average of 32% (range: 0-60%) when the subjects spoke during the pause period. Standard-deviation-based automated chewing count correlated (r=0.3) with manual chew counts.

Conclusion:

The Auracle™ device accurately identified periods of chewing during an eating event. Auracle™ will be further developed and has the potential to objectively assess eating behavior measures such as chewing duration and counts as opposed to subjective report. This could in the future help to develop personalized eating behavior interventions.

91

Comparative differences in the metabolic and mental health outcomes of women with gestational diabetes in Ghana and Switzerland

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Background/Introduction:

The prevalence of gestational diabetes mellitus (GDM) in Ghana and Switzerland are similar, i.e., around 9-15%. This is interesting because Ghana and Switzerland are different in lifestyle and healthcare systems. There is a complete lack of data on the metabolic and mental health outcomes of GDM during pregnancy in Ghana. As prevalence of obesity and GDM are similar and eating behaviour represent an important GDM risk factor, we investigated and compared the metabolic, mental health, and eating behaviour outcomes of GDM in Ghana and Switzerland.

Methods:

We included 147 women with GDM from two cohorts (n=88 from Switzerland, n=59 from Ghana). All women were diagnosed with GDM between 24-28 weeks gestational age using the International Association of the Diabetes and Pregnancy Study Groups criteria and were followed up between 01.03.2022 to 08.08.2022. Outcomes were assessed at diagnosis, the end of pregnancy, and after childbirth. Primary outcomes were metabolic (HbA1c, gestational weight gain), lifestyle, and mental health variables (Well-being (WHO-5 questionnaire), symptoms of depression (Edinburgh Postnatal Depression Scale), timing of food intake, and intuitive eating scores: physical rather than emotional reasons (EPR) and reliance on hunger and satiety (RHSC) of the intuitive eating scale-2) during pregnancy. Secondary outcomes were obstetric and neonatal outcomes.

Results:

The weight at GDM diagnosis was similar in both cohorts. The Ghana cohort (GC) had lower total gestational weight gain (GWG) compared to the Swiss cohort (SC) (4.5±5.3 vs 11.3±5.8, $p<0.001$). More women in the SC had excessive GWG compared to GC (17% vs 5%, $p=0.03$). Both, fasting glucose (6.8±1.9 vs 5.1±0.7) and HbA1c at GDM diagnosis (5.6±0.9 vs 5.3±0.3; both $p\leq0.019$) were higher in the GC. Compared to SC, more women in the GC received metformin for GDM treatment (80% vs 1.1%, $p<0.001$). The GC had increased well-being scores (74.1±18.7 vs 59.8±18.3, $p<0.001$), whereas the SC had a tendency for more depressive symptoms during pregnancy. We observed a higher EPR subscale score (4.6±0.5 vs 3.6±0.7) in the GC, whereas the SC had higher (3.5±0.7 vs 3.04±1.0) RHSC subscale score (both $p\leq0.01$). The timing of first and last meal intake were earlier in the GC (both $p\leq0.02$). Compared to the SC, the prevalence of macrosomia (13% vs 5%), caesarean delivery (61% vs 40%), and neonatal hospitalizations (39% vs 15%), were higher in the GC (all $p\leq 0.044$).

Conclusion:

Compared to Switzerland, mental health in women with GDM in Ghana was better. Despite the lower weight gain during pregnancy in the GC, they had elevated glucose control and increased rates of macrosomia compared to the SC.

92

Real-world evidence supporting the use of advanced hybrid closed loop in poorly con-trolled type 1 diabetic patients

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Background/Introduction:

The advanced hybrid closed loop (a-HCL) algorithm of the MiniMed 780G includes automated basal and correction bolus insulin and offers the possibility to choose between three glucose targets. The aim was to evaluate the effectiveness of the a-HCL compared to its predecessors, the predictive low glucose suspension (PLGS, MiniMedTM 640G) and the standard hybrid closed loop (s-HCL, MiniMedTM 670G), and to assess which group of patients benefitted the most from the implementation of the a-HCL.

Methods:

Type 1 diabetes patients >18 years of age followed at the University Hospital Zurich (USZ), who initially used a PLGS or a s-HCL and were subsequently switched to the a-HCL until December 2021, were included in the study. Glucose metric data regarding HbA1c, time in range (TIR), time above range (TAR), time below range (TBR), average sensor glucose (SG), and variation coefficient (VC) was retrospectively analyzed before and after the conversion to the a-HCL.

Results:

88 patients were screened, and 71 patients were included in the analyzes. After the implementation of the a-HCL, there was a significant decrease in HbA1c (pre 7.3±0.7% to post a-HCL 6.8±0.5%, $p<0.001$), SG (8.8±1.2 mmol/L to 7.9±0.8 mmol/L, $p<0.001$) and a significant increase in TIR (73.5% to 81%, $p<0.001$). Additionally, a significant decrease in TAR (23% to 17%, $p<0.001$) was observed, while TBR (1.5% to 1%, $p=0.573$) and the VC did not significantly change (33±6.6% to 32.4±5.8%, $p=0.313$). The changes in glycemic control were most pronounced in patients with a higher baseline HbA1c, a higher baseline SG, a lower baseline TIR, and a higher VC, all measures of poor glycemic control. Furthermore, patients with a body-mass index (BMI) >30kg/m2 achieved the greatest changes in HbA1c and TIR.

Conclusion:

In conclusion, our data support the use of a-HCL in all patients, but especially in poorly controlled type 1 diabetic patients with a high BMI.

Weight categories, trajectories, eating behavior and metabolic consequences during pregnancy and postpartum in women with GDM

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Background/Introduction:

The increasing prevalence of obesity is a global health concern. In healthy rodents and humans, rapid weight gain followed by weight loss does not seem to impact on long-term weight or metabolic health, but this has not been studied in pregnancy. Pregnant women with overweight (OW, 25.0-29.9kg/m2) or obesity (OB, ≥30kg/m2) or excess gestational weight gain (EGWG) have more metabolic complications, such as gestational diabetes mellitus (GDM). GWG influences postpartum weight retention (PPWR), which is the main predictor of future diabetes. Eating behavior can also influence weight gain during pregnancy. Based on pre-pregnancy BMI categories, we investigated the weight trajectories, eating behaviors, and metabolic consequences during pregnancy and postpartum in women with GDM.

Methods:

We included 461 women diagnosed with GDM followed at our tertiary hospital with weight data at 24-32 weeks gestational age, end of pregnancy, 6-8 weeks and 1 year postpartum. Intuitive eating (IE) was assessed with the Intuitive Eating Scale 2 questionnaire. Pre-pregnancy weight was obtained from the medical charts. We calculated EGWG based on the IOM recommendations and PPWR was defined as the difference in weight between weight at 6-8 weeks or 1-year postpartum and pre-pregnancy weight (>0.1kg). Glucose intolerance (GI, prediabetes and diabetes) was assessed at 1-year postpartum based on the American Diabetes Association criteria.

Results:

Mean pre-pregnancy BMI was 26.3±5.7 kg/m2. Of the 459 women, 228 women had a normal pre-pregnancy BMI (NW, <25 kg/m2, including <4% underweight), 136 women were OW and 95 were OB. GWG was lower in women with OB (8.3±7.6 kg, p≤0.0001) compared to the others. However, PPWR at 1 year did not differ between BMI categories (overall 3.5±6.5 kg, p=0.65). Between 6-8 weeks and 1 year postpartum, women with NW lost a mean of 2.3 kg, OW of 0.6 kg and OB gained a mean of 3.4 kg (overall p≤0.0001). Within the NW category, women in the lowest tertile lost more postpartum weight than the other two tertiles (p=0.02). IE was significantly related to BMI categories, but not to GWG or postpartum weight changes. Independent of BMI, women with PPWR at 1 year had a 2.4-fold (95%CI 1.5-3.9, p≤0.0001), increased risk of GI at 1 year postpartum, especially in those with OB (OR 8.7, 95%CI 2.8-26.4, p≤0.0001). Weight increases between the early and late postpartum were associated with a 1.8-fold (95%CI 1.23-2.62, p=0.003) increased risk for GI.

Conclusion:

Women with OB had the lowest GWG, but weight increase in the postpartum. For them, PPWR had the highest impact on their adverse metabolic health. Postpartum weight decrease was most pronounced in NW women and within this category, in their lowest tertile. These results suggest that there is an adaptive capacity/plasticity to relatively rapid weight changes in the perinatal period, that is more pronounced with lower BMI.

Role of Astrocytic MPC1 in Systemic Energy Metabolism

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Background/Introduction:

Astrocytes recently evolved as active players in central energy and glucose homeostasis control, specifically by regulating brain glucose uptake and by acting as gatekeepers of neuronal energy supply. Timper K et al. previously demonstrated that a slight impairment in astrocyte mitochondrial glucose oxidation upon ablation of the glucagon like peptide (GLP)-1 receptor improves central and systemic glucose homeostasis as well as learning and memory formation. Thus, directly targeting astrocyte metabolism might represent a novel therapeutic strategy to improve energy and glucose homeostasis. Glucose-derived pyruvate is shuttled into mitochondria via the mitochondrial pyruvate carrier-1 (MPC-1) to serve as a major substrate for ATP production via the tricarboxylic acid (TCA) cycle and mitochondrial oxidative phosphorylation (OXPHOS). Here, we investigated cellular and systemic metabolic effects of astrocyte-specific depletion of mitochondrial pyruvate carrier-1 (MPC-1).

Methods:

Postnatal ablation of MPC-1 in glial fibrillary acidic protein (GFAP)-expressing astrocytes in the adult mice wa achievd using the inducible Cre-lox system. Metaboolic phenotyping was conducted upon control and high-fat diet (HFD) feeding. For mechanistic studies, MPC-1 was ablated using siRNA in isolated and cultured primary hypothalamic mouse astrocytes.

Results:

Astrocyte-specific MPC-1 depletion results in reduced body weight gain due to reduced food intake and slightly improved systemic glucose tolerance in lean normal diet-fed but not in high-fat diet-fed obese mice. Upon 16 h fasting, astrocyte-specific MPC-1 depleted mice showed increased mRNA expression of gluconeogenic and ketogenic markers at the level of the liver in line with increased systemic levels of ketone bodies, overall indicating an amplified hepatic starvation signal. To the contrary, upon random feeding, gluconeogenic and ketogenic marker expression at the level of the liver was reduced in mice with astrocyte-specific MPC-1 depletion compard to control mice in line with reduced systemic levels of ketone bodies, indicating an amplified hepatic fed signal. In vitro we could demonstrate that depletion of MPC-1 in primary hypothalamic astrocytes impaired mitochondrial OXPHOS and increased glycolytic capacity as well as dependency on fatty acid oxidation in vitro. Along the same line, metabolomics of the hypothalamus of random fed lean mice with astrocyte-specific MPC-1 depletion showed alterations in the abundance of free fatty acids and tricarboxylic acid cycle (TCA) intermediates such as malate, aspartate and fumarate, pointing towards a switch in substrate utilization

Conclusion:

We unraveled a crucial role of astrocyte MPC-1 in food intake, systemic glucose regulation and in directing the hepatic fasting and fed state in the physiologic control-diet setting, all of which was ablated in the high-fat diet-induced state.

Inflammation in the exocrine pancreas impairs insulin release.

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Background
In patients with type 2 diabetes, there is increasing evidence of pathological changes not only in the endocrine but also in the exocrine pancreas. In particular, the number of immune cells is increased in both, the endocrine and exocrine pancreas. Furthermore, patients with chronic pancreatitis have an increased risk of developing diabetes. Nevertheless, the causal relationship between exocrine immune cell infiltration and impaired insulin secretion has not been explored.

Methods
We established a mouse model that mimics exocrine and endocrine inflammation. Exocrine inflammation was induced by multiple injections of caerulein for 3 weeks combined with a high fat diet to induce insulin resistance and subsequent islet inflammation. Due to the anorexic effect of caerulein, body weight differences were avoided by pair feeding of saline-treated mice. We assessed insulin secretion and glucose metabolism by a glucose tolerance test in vivo, followed ex vivo by glucose stimulated insulin secretion in isolated islets. Pancreata were immunohistochemically stained with the pan immune cell marker CD45.

Results
Treatment with caerulein and a high-fat diet severely impaired insulin secretion and resulted in hyperglycemia compared to the saline-treated mice on high-fat diet alone. Islets isolated from caerulein-treated mice showed reduced insulin content and glucose-stimulated insulin secretion, but no difference in insulin fold secretion. CD45+ immune cells were elevated in the exocrine but not in the endocrine pancreas of caerulein-treated mice.

Conclusion
Inflammation in the exocrine pancreas impairs insulin release.

96

Extensive Polyostotic Fibrous Dysplasia in a Patient with McCune-Albright Syndrome: a Case Report

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Background/ Introduction:
McCune-Albright syndrome (MAS) is the combination of the rare bone disease fibrous dysplasia (FD), skin hyperpigmentation (Café-au-lait macules) and endocrine disorders. MAS/ FD arises from missense mutations in the GNAS gene locus. Typically, the skeletal manifestation becomes apparent in the first few years of life and progresses until the early adulthood. This results in forming discrete, expansive fibrotic lesions, which may be painful and may lead to skeletal deformity or even pathologic fracture. Given the uniquely broad clinical spectrum of the syndrome, there is a need to identify strategies to improve the clinical outcome for the affected individuals.

Methods:
We describe the clinical course including imaging and laboratory follow-up of polyostotic FD in a 58-year-old woman with MAS in our outpatient clinic.

Results:
In our patient, MAS presented with skeletal pain due to FD at the age of 5 years, precocious puberty at 7 years, and Café-au-lait spots. Due to recurrent pain she had undergone several orthopedic surgeries at the femur and the tibia bilaterally, and the pelvis during childhood. Clinically striking is the right accentuated skull deformity with involvement of the calvaria and different bone of the skull base.
In 2022 the latest whole-body imaging study by EOS showed height reductions of several vertebral bodies, dysmorphia of humerus, scapula/ glenoid right, rib-thorax bilaterally, pelvis, distal femur, tibia and fibula right, and tibial diaphysis left with inhomogeneous bone matrix including osteolytic as well as sclerosing changes and consolidated fractures besides the involvement of the skull.
After receiving long-term bisphosphonate treatment with zoledronate from 2003 to 2010, beyond vitamin D her current treatment is pro re nata medication for pain, mainly due to symptomatic calcium pyrophosphate crystal deposition disease.
Beyond the annual clinical follow-up, the activity of FD is estimated by the bone-related laboratory testing including the bone specific alkaline phosphatase, osteocalcin, β-Crosslaps, and procollagen type 1 amino-terminal propeptide.
Complementary to imaging, regular screenings (gynecological including mammography, thyroid sonography) are performed in view of the increased risk for malignancy in the context of MAS, without abnormal findings until now.

Conclusion:
FD/MAS is a rare, non-hereditary disorder of striking complexity. FD lesions appear in the first few years of life and expand during linear growth. The diagnosis is established clinically after a complete evaluation for skeletal, endocrine, soft tissue and dermatologic features. Nowadays, adolescents suffering from pain from FD are treated early with highly potent antiresorptive drugs to reduce the need of surgical interventions. Clinicians should take a systematic approach to evaluate the extent of disease involvement and initiate treatment according to international consensus statements.

Associations between Chronotype, Sleep, and Mental Health in Women with Gestational Diabetes Mellitus: A prospective Cohort Study

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Background/Introduction:

Chronotype refers to an individual's preference of entrainment and sleep-wake timing under idealized conditions in a 24-hour day and ranges from early to late chronotypes. The evening chronotype is associated with poorer mental health and unhealthy lifestyle habits in the general population. In pregnancy, short sleep duration is linked to obesity and associated with an increased risk of gestational diabetes mellitus (GDM) and mental health problems. However, little is known about chronotype in women with GDM who have an increased risk for adverse mental and metabolic health outcomes. We aimed to evaluate the associations between chronotype, sleep, and mental health in women with GDM, during pregnancy and in the early post-partum period (PP).

Methods:

This prospective cohort included 244 women with GDM followed in 2021-2022 during pregnancy (gestational age 30±3 weeks) up to 6-8 weeks PP. Well-being was assessed with the World Health Organization-5 Well-Being Index during pregnancy and the chronotype using the Morning-Eveningness Questionnaire (MEQ) in the PP. Self-reported sleep quality and timing (Pittsburgh Sleep Quality Index, i.e., sleep times, duration, and quality), depressive symptoms (Edinburgh Postnatal Depression Scale; EPDS), and intuitive eating behavior (Intuitive Eating Scale-2) were assessed at both time points. We examined the relationships between MEQ, sleep, and mental health outcomes with linear regressions adjusting for age, pre-pregnancy BMI, and lifestyle habits (smoking, alcohol, or drug use) during pregnancy.

Results:

The mean age and pre-pregnancy BMI of participants were 33.8±4.8 years, and 26.3±5.5 kg/m2. Self-reported sleep duration and efficiency decreased between pregnancy and 6-8 weeks PP ($p<0.001$). Morningness was associated with earlier bedtime and earlier wake-up time ($p<0.001$), but not with sleep duration or efficiency at either time points. Earlier chronotype was also associated with improved well-being and eating behavior (eating for physical rather than emotional reasons) during pregnancy and less depression in PP. During pregnancy, reduced sleep duration and efficiency were associated with higher EPDS and worsened well-being (all $p \leq 0.03$). Sleeping at a later time was related to eating for more emotional rather than physical reasons, and to lower well-being (both $p \leq 0.04$) in pregnancy, and predicted a higher EPDS total score ($p<0.001$) at 6-8 weeks PP. At 6-8 weeks PP, shorter sleep duration was associated with higher EPDS ($p=0.009$).

Conclusion:

In women with GDM, chronotype is related to the actual sleep schedule, mental health, and eating behavior. Shorter sleep was associated with higher depression scores in pregnancy and in the PP. These results highlight the need to better understand and target sleep to alleviate the risk of mental health problems in the perinatal period in women with GDM.

98

Metabolic effects of a low carbohydrate versus energy-matched balanced diet in morbidly obese individuals with prediabetes – a randomized controlled trial

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Background/Introduction:

Calorie restriction is the cornerstone treatment of obesity and obesity-related comorbidities, but the ideal macronutrient distribution, particularly in the presence of impaired glycemia, remains inconclusive. This study aimed to explore the metabolic effects of a short-term low carbohydrate (LCD) vs. energy-matched balanced diet (BD) in patients with morbid obesity and prediabetes.

Methods:

Adults with body mass index (BMI) >35kg/m2 and glycated hemoglobin (HbA1c): 5.7-6.4% were randomly assigned to 2 weeks of 30% calorie restriction with either a LCD (10% carbohydrates, 70% fat, 20% protein) or isocaloric BD (50% carbohydrates, 30% fat, 20% protein). Diets were prescribed using individualized meal plans. Adherence to the prescribed carbohydrates was verified using an app-based meal photo-documentation and daily capillary β-hydroxybutyrate (β-OHB) testing. Primary outcome was the relative change of intrahepatocellular lipid (IHCL) as quantified using magnetic resonance spectroscopy. Further outcomes were changes in body weight and metrics of glucose-insulin homeostasis using a 3-hour oral glucose tolerance test (OGTT, 75g of glucose). Data are presented as median [interquartile range]. Within and between group differences were assessed using non-parametric tests.

Results:

Twenty patients (48 [43-56]yrs, 6 male, BMI: 41.4 [37.8-48.4]kg/m2, HbA1c: 6.1 [5.9-6.2]%) were included. Daily calorie content was 1549.1 [1463.0-1628.2]kcal in the LCD and 1677.9 [1567.0-1964.9]kcal in the BD, p=0.29. β-OHB levels were 0.3 [0.3-0.5]mM and 0.1 [0.1-0.1]mM in the LCD and BD groups, p<0.001. Self-reported adherence was high in both groups (LCD: 98.8 [97.5-99.9] % vs BD: 96.0 [85.8-98.7]%, p=0.31). LCD led to more weight loss (5.9 [4.1-6.5]kg vs 2.6 [2.1-4.0] kg, p=0.03). Pre-diet IHCL was 22.4 [15.6-29.5]% in the LCD group and fell to 18.3 [13.8-21.7]% post-diet, p=0.01. IHCL in the BD group was 9.3 [6.9-16.7]% pre-diet and dropped to 7.0 [5.6-15.5] % post-diet, p=0.01. IHCL relative change pre- and post-diet did not differ significantly between groups (LCD: 16.4 [6.2-24.7]% vs BD: 13.1 [3.9-24.1]%, p=0.97). Similarly, the reduction in fasting glucose (LCD: 0.4 [0.2-1.1]mM vs BD: 0.4 [0.2-0.6]mM, p=0.77) and insulin (LCD: 21.6 [5.4-51.6] pM vs BD: 31.2 [18.6-58.5]pM, p=0.65) did not differ between groups. Insulin sensitivity during the OGTT increased in both groups (LCD: 18 [-28-73]ml/min/m2 vs BD: 47 [26-61]ml/min/m2, p=0.65). No diet-related safety events occurred. Acceptability and tolerance of the diets were comparable.

Conclusion:

Two weeks of moderate (30%) calorie restriction in adults with class II/III obesity and prediabetes reduced IHCL without noticeable impact of macronutrient distribution. Weight loss was, however, more pronounced after a LCD vs. BD.

99

Screening of natural compounds for antioxidant transcriptional activity and effects on the thyroid

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Background/Introduction:

Recent studies have identified pleiotropic roles for the Nrf2 antioxidant response in the physiology of the thyroid gland and in the pathophysiology of various thyroid diseases. Various natural compounds have antioxidant properties and/or thyroi- dal effects, but it is not well known whether and how the two are related. The aim of the present study was to characterize in a systematic manner the thyroidal and antioxidant effects of natural compounds.

Methods:

We performed a low-throughput manual chemical screen of >400 natural compounds in thyroid follicular cell lines stably transfected with reporter constructs. We used the rat PCCL3 cell line in its wild-type form as well as a PCCL3 Nrf2-knockout clone generated via CRISPR/Cas9 mutagenesis. The following read-outs were assessed: Nrf2 transcriptional activity (ARE-luciferase); Nrf1 protein stabilization (Nrf1-delta-luciferase); cell viability (CellTiter-Glo); reporter gene expres- sion of the thyroid hormone precursor thyroglobulin (TG-luciferase); reporter gene expression of the sodium-iodide symporter (NIS-luciferase); and iodine uptake by the cells. For compounds showing activity in the respective assays, the mRNA and protein levels of NIS, TG and the antioxidant gene Nqo1 were assayed by qRT-PCR and West- ern blot, respectively.

Results:

Among other findings, we observed that certain compounds paradoxically induced higher transcriptional activation of the ARE in Nrf2-knockout cells than in wild-type cells. Further studies showed that these compounds were potent activators of Nrf1, which is highly expressed in the thyroid in vivo. As a further example, the flavonoid compound bavachin was found to increased iodine uptake by the cells in an Nrf2-independent manner. Importantly, bavachin was also able to reverse the decrease in iodine uptake that is induced by exposure to lithium, a drug used in the treatment of bipolar disorder.

Conclusion:

In conclusion, screening of natural compounds in thyroid cell lines can yield relevant hits with potential therapeutic relevance in thyroid diseases.