ORAL PRESENTATIONS «BASIC / CLINICAL» – ENDOCRINOLOGY

Friday, 12th November, 10.30 – 12.30, Room «Ettore Rossi»

Chairs:

10.30 **Abstract 08 – Glucagon-stimulated copeptin measurements: a novel approach for the differential diagnosis of polyuria-polydipsia syndrome**
Cihan Atila, Odile Gaisl, Gabor Szinnai, Mirjam Christ-Crain (Basel)

10.45 **Abstract 19 – 18F-Fluorocholine-PET combined with contrast-enhanced CT for localizing hyperfunctioning parathyroid glands in patients with hyperparathyroidism**
Stefan Fischli, Markus Gass, Corinna Wicke, Caroline Mona, Klaus Strobel, Werner Müller, Jürg Metzger, Isabelle Suter-Widmer, Christoph Henzen (Lucerne)

11.00 **Abstract 49 (S) – Alterations in cortical grey matter volume in adults with early-treated phenylketonuria**
Raphaela Muri, Stephanie Abgottspon, Christian Rummel, Michael Rebsamen, Roland Wiest, Michel Hochuli, Bernadette M. Jansma, Regula Everts, Roman Trepp (Berne, Maastricht NL)

11.15 **Abstract 74 (S) – Essential oil metabolites can regulate adrenal Androgen production**
Katyayani Sharma, Angelo Lanzilotto and Amit V Pandey (Berne)

11.30 **Abstract 77 – Cholesterol deprivation drives DHEA production in human adrenals**
Emanuele Pignatti,, Emre Murat Altinkilic, Idoia Martínez de LaPiscina, Alexander Kanitz, Kostantin Bräutigam, Aurel Perren, Mihaela Zavolan, Christa E. Flück (Berne, Barakaldo Spain, Basel)

11.45 **Abstract 75 (S) – Colonization by the common mouse protozoa *Tritrichomonas* modulates gut innate immunity and impacts glucose tolerance**
Andy J. Y. Low, Angela J. T. Bosch, Lena Keller, Zihan Ding, Claudia Cavelti-Weder (Basel)

12.00 **Abstract 79 – IL-18 binding protein (IL-18BP) deficiency alters gut microbiota composition and exacerbates both type 1 and type 2 inflammation in liver during nutritional stress**
Emmanuel Somm, Elodie Perroud, Vladimir Lazarevic, Jacques Schrenzel, Cem Gabay, François R. Jornayvaz (Geneva)

12.15 **Abstract 78 (S) – Loss of protein stability and function caused by a single point mutation (P228L) in the Cytochrome P450 Oxidoreductase.**
Rojas Velazquez, Maria Natalia; Noebauer, Mathias; Pandey, Amit V. (Berne)

ORAL PRESENTATIONS «BASIC / CLINICAL» – METABOLISM / DIABETES

Friday, 12th November, 10:30 – 12:30, Room «Kursraum 1»

Chairs:

10.30 **Abstract 01 (S) – Neural correlates of working memory in early-treated adult patients with Phenylketonuria**
Stephanie Abgottspon, Raphaela Muri, Shawn Christ, Michel Hochuli, Martin Zbinden, Nicolas Langer, Regula Everts, Roman Trepp (Berne, Columbia USA, Zürich)

10.45 **Abstract 06 – Effectiveness of a real-life group program (DIAfit) to promote physical activity in patients with type 2 diabetes: a pragmatic cluster randomized clinical trial**
Amar Arhab, Nicolas Junod, Jean-Benoit Russel, Olivier Giet, Frederic Sittarame, Sandra Beer5, Daniela Sofra, Dominique Durrer, Humberto Delgado, Montserrat Castellsague, Markus Laimer, Jardena J. Puder (Lausanne, Gland, Sierre, Genève, Berne)

11.00 **Abstract 21 – Perioperative fully closed-loop insulin delivery versus standard insulin therapy in adults undergoing pancreatic surgery**
David Herzig, Simon Suhner, David Studer, Jonathan Roos, Daniel Schürch, Dominik Günsch, Beat Gloor, Andreas Vogt, Lia Bally (Berne)

11.15 **Abstract 69 (S) – Endocrine and metabolic counterregulation to postprandial hypoglycemia in patients with postprandial hypoglycemia after gastric bypass compared to non-affected surgical and non-surgical controls**
A. Tripyla, D. Herzig, A. Müller, A. Gretz, G. Reverter, P. Eugster, E. Grouzmann, J. Pavan, C. Dalla Man, S. Del Favero, J. Zehetner, D. Giachino, P. Nett, A. von Eckarstein, L. Bally (Berne, Lausanne, Padova Italy, Zurich)

11.30 **Abstract 33 (S) – Non-invasive hypoglycemia detection for drivers with diabetes: A machine learning approach using driving and gaze behavior data**
Vera Lehmann MD, Thomas Zueger MD, Martin Maritsch, Mathias Kraus PhD, Caroline Albrecht, Caterina Bérubé, Stefan Feuerriegel PhD, Felix Wortmann PhD, Tobias Kowatsch PhD, Naïma Styger, Sophie Lagger, Markus Laimer MD, Elgar Fleisch PhD, Christoph Stettler MD (Berne, Zurich, Erlangen-Nürnberg D, St. Gallen)

11.45 **Abstract 91 – Bone microarchitecture and strength in patients with long-standing type 1 diabetes**
Lilian Sewing, Laura Potasso, Sandra Baumann, Denis Schenk, Furkan Gazozcu, Kurt Lippuner, Marius Kraenzlin, Philippe Zysset, Christian Meier (Basel, Berne)

12.00 **Abstract 53 – Precision medicine in diabetes: A non-invasive prenatal diagnostic test for the determination of fetal glucokinase mutations**
Thierry Nouspikel, Jean-Louis Blouin, Jardena Puder, Bettina Köhler Ballan, Valerie M. Schwitzgebel (Geneva, Lausanne)

12.15 **Abstract 76 – Human Islet Amyloid Polypeptide Expression Combined with PC1/3 Deficiency Induces Frank Diabetes in Mice**
Daniel T. Meier, Leila Rachid, Marianne Böni-Schnetzler, Marc Y. Donath (Basel)

S = contribution of a student

08

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

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

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

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

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

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

Author/Address of institution:

Stefan Fischli (1, 3), Markus Gass (2, 3), Corinna Wicke (2, 3), Caroline Mona (1), Klaus Strobel (3, 4), Werner Müller (5), Jürg Metzger (2, 3), Isabelle Suter-Widmer (1), Christoph Henzen (1, 3)

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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

49 S

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

Author/Address of institution:

Raphaela Muri[1,2,3], Stephanie Abgottspon[1,3], Christian Rummel[2], Michael Rebsamen[2], Roland Wiest[2], Michel Hochuli[1], Bernadette M. Jansma[4], Regula Everts[1,5] & Roman Trepp[1]
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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

74 S

Essential oil metabolites can regulate adrenal Androgen production.

Author/Address of institution:

Katyayani Sharma, Angelo Lanzilotto and Amit V Pandey
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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

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Cholesterol deprivation drives DHEA production in human adrenals

Author/Address of institution:

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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

75 S

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

Autor/Adress of institution

Andy J. Y. Low[1,2], Angela J. T. Bosch[1,2], Lena Keller[1,2], Zihan Ding[1,2] and Claudia Cavelti-Weder[1,2]

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Background/Introduction:

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

Research Design and Method:

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

Results:

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

Conclusion:

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

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

Emmanuel Somm[1,2], Elodie Perroud[1,2], Vladimir Lazarevic[3], Jacques Schrenzel[3,4], Cem Gabay[5] and François R. Jornayvaz[1,2]

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Background: Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic hepatic disease worldwide. NAFLD can progress to hepatic inflammation [nonalcoholic steatohepatitis (NASH)] and to fibrosis. Interleukin-18 (IL-18) is a prototypic pro-inflammatory cytokine, the activity of which is regulated by IL-18 binding protein (IL-18BP), a secreted protein that binds to IL-18 to prevent its signaling, thus acting as a natural inhibitor. Our goal is to delineate the role of the IL-18/IL-18BP balance in hepatic metabolism and the gut-liver axis, in particular during nutritional stress inducing NAFLD/NASH.
Methods: Wild-type (WT) or IL-18BP$^{-/-}$ C57BL/6J mice aged 2 months were fed with 1) regular chow diet; 2) high fat diet (HFD) for 10 weeks (60 kcal% from fat); 3) methionine- and choline-deficient (MCD) diet for 8 weeks; or 4) atherogenic (ATH) diet for 14 weeks (1.25% cholesterol/0.5% cholate). Gene expression was assessed by RT-quantitative PCR using a LightCycler Detection System (Roche Diagnostics). Gut microbiota composition was determined by metataxonomics, based on bacterial 16S rRNA gene sequencing and analysis using various bioinformatics tools (Trimmomatic/PEAR/USEARCH/MOTHUR). Immunohistochemistry was performed using classical protocols and images were taken using Axio Scan.Z1.
Results: We previously showed that on HFD, MCD and ATH diet, circulating levels of transaminases (reflecting hepatocyte damage), as well as gene expression of classic pro-inflammatory markers, were exacerbated in the liver of IL-18BP$^{-/-}$ compared to WT mice. Surprisingly, we now show that diet-induced over-inflammation observed in the liver of IL-18BP$^{-/-}$ mice concerns not only type 1 (IFN-γ driven) immunity, but also type 2 immune response (as reflected by an upregulation of IL-5, IL-10, IL-13 expression). Concomitant elevation in type 1 and type 2 immune responses could respectively explain increased hepatocyte damage and fibrosis observed in IL-18BP$^{-/-}$ mice. In the principal coordinates analysis, overall gut microbiota clustering pattern suggested an interaction between diet and genotype. Analysis of microbiota composition at the family level revealed consistently increased proportion of Enterobacteriaceae in IL-18BP$^{-/-}$ compared to WT mice, regardless of the diet.
Conclusion: Derepression of IL-18 signaling, through genetic deletion of its negative regulator IL-18BP, induces gut microbiota dysbiosis and an exacerbated upregulation of both type1/2 immunity in the liver during nutritional stress. Elucidation of underlying mechanisms, especially concerning the role of gut enrichment in Enterobacteriaceae on liver inflammation could lead to therapeutic perspectives in NAFLD/NASH.

78 S

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

Author/Address of institution:

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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

S = contribution of a student

01 S

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

Author/Address of institution:

Stephanie Abgottspon[1,2], Raphaela Muri[1,2,3], Shawn Christ[4], Michel Hochuli[1], Martin Zbinden[3], Nicolas Langer[5], Regula Everts[1,6] & Roman Trepp[1]

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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

06

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

Author/Address of institution:

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

Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

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

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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

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

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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

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

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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

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

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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

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

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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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

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

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Background/Introduction:

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

Methods:

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

Results:

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

Conclusion:

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