Jahresversammlung
Assemblée annuelle

2018

15. und 16. November 2018
15 et 16 novembre 2018

Inselspital Bern
Hôpital de l' Île, Berne

Schweizerische Gesellschaft für
Endokrinologie und Diabetologie - SGED

Société Suisse d'Endocrinologie
et de Diabétologie - SSED

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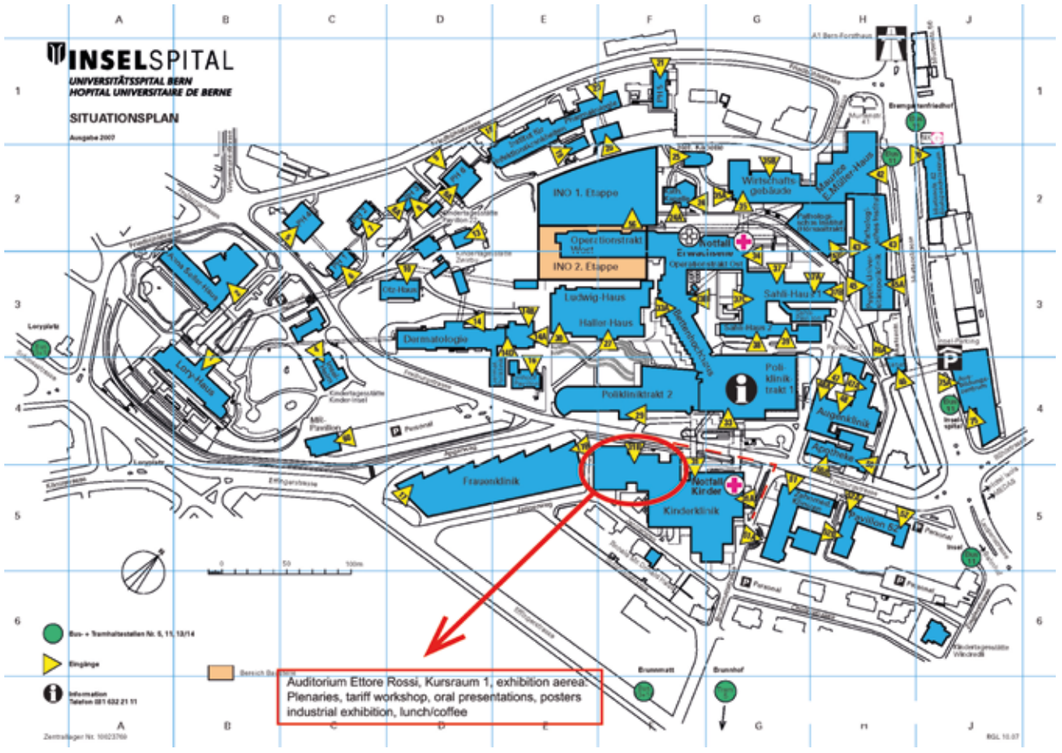

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Schweizerische Gesellschaft für Endokrinologie und Diabetologie
Société Suisse d'Endocrinologie et de Diabétologie
Società Svizzera d'Endocrinologia e Diabetologia
Societad Svizra d'Endocrinologia e Diabetologia

Bern, September 2018

Liebe Kolleginnen und Kollegen

Im Namen des wissenschaftlichen Komitees der Schweizerischen Gesellschaft für Endokrinologie und Diabetologie möchten wir Sie ganz herzlich zu unserer Jahresversammlung am Inselspital willkommen heissen. Hier einige Hinweise zu unserem Programm:

Wie in den Vorjahren trifft sich die ASEMO-SAMO (= Association Suisse pour l'Etude du Métabolisme et de l'Obésité, Schweizerische Arbeitsgruppe Metabolismus und Obesitas) bereits am Donnerstagmorgen (in Kooperation mit dem Fachverband AKJ).

Der Donnerstagnachmittag ist inhaltlich dreigeteilt: zuerst wird Prof. M. Polak (Paris) über die mütterlich-fetalen Wechselwirkungen von Schilddrüsenhormonen in der Schwangerschaft sprechen. Das folgende Minisymposium widmet sich verschiedenen endokrinen Störungen in der Schwangerschaft und in der anschliessenden Pro- und Kontra Debatte wird die Frage diskutiert, ob Diabetes-Typen 1 und 2 eine oder verschiedene Entitäten darstellen. Das Programm runden wir mit der Generalversammlung ab. Mit einem Apéro, welcher unseren jungen Mitgliedern ab 18.30 Uhr offensteht und dem nachfolgenden Galadinner mit der Verleihung der Forschungspreise beenden wir schliesslich den ersten Kongresstag.

Der Freitagmorgen beginnt mit der traditionellen Albert Renold Lecture, welche durch Prof. K. Clément (Paris) gehalten wird. Das vielfältige Tagesprogramm umfasst Vorstellungen neuer klinischer und präklinischer Studienergebnisse, einen Tarifworkshop sowie ein klinisches Update zu den Themen «Diabetes und Bluthochdruck», «Diabetes Typ 1 und Essstörungen» und «Screening bei einem polyglandulären Autoimmunsyndrom, wen und wie». Das Plenar-Referat (F. Beuschlein) widmet sich dieses Jahr den Mechanismen eines Nebennierenrinden-Hormon-Überschusses und deren Konsequenzen.

Abgeschlossen wird unsere Jahresversammlung mit der Preisverleihung: Erneut wird der beste Vortrag und das beste Poster aus den beiden Sparten „clinical" and „basic-experimental" mit einem Preis ausgezeichnet. Es ist uns ein Anliegen, jüngeren Forschenden eine Plattform zur Präsentation ihrer Resultate zu geben. Ein Preis für die beste Präsentation eines/r Studenten/in unterstreicht dies.

Unsere Jahrestagung ist nur möglich dank der Unterstützung unserer Partner der pharmazeutischen und medizinisch-technischen Industrie. An dieser Stelle möchten wir uns im Namen unserer Gesellschaft wiederum ganz herzlich bei unseren Platin-und Goldsponsoren bedanken. In diesem Zusammenhang sei auch auf das Platin-Sponsor-Symposium der Firma Roche (Donnerstag) verwiesen.

Wir freuen uns, Sie im November in Bern zu treffen.

Für das wissenschaftliche Komitee

M. Christ-Crain

Prof. Dr. Mirjam Christ-Crain

Prof. Dr. Christian Meier

Schweizerische Gesellschaft für Endokrinologie und Diabetologie
Société Suisse d'Endocrinologie et de Diabétologie
Società Svizzera d'Endocrinologia e Diabetologia
Societad Svizra d'Endocrinologia e Diabetologia

Berne, septembre 2018

Chères et chers collègues,

Au nom du comité scientifique de la Société Suisse d'Endocrinologie et Diabétologie nous nous réjouissons de vous accueillir à notre réunion annuelle à l'hôpital de l'île. Voici quelques précisions sur notre programme:

Comme les années précédentes, le ASEMO-SAMO (= Association Suisse Pour l'Etude du Métabolisme et de l'Obésité, Schweizerische Arbeitsgruppe Metabolismus und Obesitas) se réunit dès le jeudi matin (en coopération avec l'association AKJ).

Le jeudi après-midi, sera divisé en trois parties: en premier le professeur M. Polak (Paris) donnera une conférence sur les interactions thyroidiennes entre fœtus et mère. Celle ci sera suivi d'un mini symposium consacré aux troubles endocriniens lors de la grossesse. Après nous aurons un débat critique « pro et contra» : Diabètes type 1 et 2 : une seule entité ? Nous terminerons le programme comme d'ahbitude avec l'Assemblée générale qui sera suivi d'un apéritif: De plus cette année, il y aura un autre apéritif spécialement conçu pour nos jeunes membres. Notre dîner annuel avec remise des prix de la recherche concluera cette première journée de congrès.

Vendredi matin a lieu la traditionnelle conférence Albert Renold, qui cette année, sera donné par le professeur K. Clément (Paris). Le programme de ce deuxième jour est diversifié et comprend les présentations de résultats d'études cliniques et précliniques, un atelier tarifaire ainsi qu'une mise à jour clinique sur les thèmes « Diabetes and Hypertension », « Type 1 Diabetes and Eating Disorders » et «Polyglandular Autoimmune Syndrome : Who to Screen and How?». Finalement, cette année le Professeur Beuschlein de l'Hopital universitaire de Zürich consacrera sa conférence plénière au thème du « Mechanisms and Consequences of Adrenocortical Hormone Excess ».

Notre assemblée annuelle s'achèvera avec la traditionnelle cérémonie de remise des prix: la meilleure présentation et le meilleur poster des deux catégories „clinical" and „basic-experimental" seront récompensés par un prix. Il est important de donner aux jeunes chercheurs une plate-forme pour présenter leurs résultats. C'est pour cela qu'un prix sera consacré à la meilleure présentation d'un(e) étudiant(e).

Notre conférence annuelle n'est possible que grâce au soutien de nos partenaires des industries pharmaceutiques et de la technologie médicale. C'est dans ce contexte que nous tenons particulièrement à remercier au nom de notre organisation nos sponsors Platine et Or et nous vous invitons chaleureusement au Symposium Platinum Sponsor de la société Roche qui se déroulera jeudi.

Nous nous réjouissons de vous voir à Berne en novembre.

Pour le Comité scientifique

M. Christ-Crain

Prof. Dr Mirjam Christ-Crain

Prof. Dr Christian Meier

Schweizerische Gesellschaft für Endokrinologie und Diabetologie
Société Suisse d'Endocrinologie et de Diabétologie
Società Svizzera d'Endocrinologia e Diabetologia
Societad Svizra d'Endocrinologia e Diabetologia

Program of the Annual Meeting 2018 – Inselspital Bern

Thursday, 15th November

09:00	Registration
	13 th Annual Meeting ASEMO-SAMO (in cooperation with AKJ) (Room: Ettore Rossi) **Update Lectures and New Issues** Chairs: K. Laederach, D. l'Allemand
09:15 – 09:50	**« Stigmatisation in Health Care Setting »** (D. Durrer, Vevey, CH)
09:50 – 10.25	**« The Overlap between Eating Behaviour and Obesity/Overweight: Developmental Effects »** (N. Micali, Genève, CH)
10.25 – 11:00	**« The Role of Physical Activity and Exercise Training in Weight Management Programs »** (D. Malatesta, Lausanne, CH)
11.00 – 11.20	Coffee Break (exhibition area)
11.20 – 12.10	**Research Communications - 3 oral presentations** (Room: Ettore Rossi) Chair:P. Gerber Abstract 90 Abstract 93 Abstract 106
12.15 – 12.45	**General Assembly (ASEMO Members only)**
12:15 – 12:45	Lunch (exhibition area)
12:45 – 13:45	Platinum Sponsor's Symposium (Room: Kursraum 1) **«Integrated Personalized Diabetes Management: Connecting the Dots to Improve Outcomes…»** Chair: M. Laimer **«Mrs Brönnimann's Digital Transformation»** (J. Holm, Berne, CH) **«App Support in Diabetes Management: Cornerstone or waste of time?»** (M. Laimer, Berne, CH)
14:00	**Welcome** (Room: Ettore Rossi)
14:05 – 14:45	**Opening Plenary Lecture** Chair: D. Konrad **«Thyroid / Fetal - Maternal Interactions etc.»** (M. Polak, Paris, FR)
14:45 – 16:15	**Symposium** (Room: Ettore Rossi) **«Endocrine Disorders in Pregnancy»** Chairs: M. Christ-Crain, Ch. Meier 14.45 – 15.15 **«Thyroid Disorders in Pregnancy»** (P. Kopp, Chicago, US) 15.15 – 15.45 **«Hyperparathyroidism in Pregnancy»** (F. Palazzo, London, UK) 15.45 – 16.15 **«Adrenal Disorders in Pregnancy»** (H. Timmers, Nijmegen, NL)
16:15 – 16:35	Coffee Break (exhibition area)
16:55 – 17:30	**Pro-Con-Debate** (Room: Ettore Rossi) **«Type 1 and Type 2 Diabetes: One Entity»** Chair: P. Schütz 16.55 – 17.10 Pro: M. Donath (Basel, CH) 17.10 – 17.25 Contra: Ch. Stettler (Berne, CH) 17.25 – 17.30 Discussion
17:30	General Assembly SGED/SSED (Room: Ettore Rossi)
18.30	Apéro for Young Endocrinologists
20:00	Galadinner

Friday, 16th November

09:00	Registration
09:15 – 10:00	**Albert Renold Lecture** (Room: Ettore Rossi) Chair: D. Konrad **«Adipose Tissue Remodeling in Obesity and Diabetes: Role of Progenitors»** (K. Clément, Paris, FR)
10:00 – 10:30	Coffee Break (exhibition area)
10:30 – 12:30	**Oral Presentations** **Session Basic / Clinical Endocrinology** Chair: F. Pralong, Ch. Henzen (Room: Ettore Rossi) **Session Basic / Clinical Metabolism / Diabetes** Chairs: Ch. Dibner, G. Gastaldi (Room: Kursraum 1)
12:30 – 13:30	Lunch (exhibition aerea)
12:30 – 13.30	**Poster Session** (Room: Ettore Rossi) **Tarifworkshop** P. Elsässer (Moutier, CH) J. Lareida (Aarau, CH) U. Meinhardt (Dübendorf, CH) (Room: Kursraum 1)
13:30 – 14:15	**Plenary Lecture** (Room: Ettore Rossi) Chair: M. Christ-Crain **«Mechanisms and Consequences of Adrenocortical Hormone Excess»** (F. Beuschlein, Zurich, CH)
14:15 – 16:00	**Clinical Updates** (Room: Ettore Rossi) Chairs: J. Puder, M. Faulenbach 14.15 – 14.40 **«Diabetes and Hypertension»** (T. Burkard, Basel, CH) 14.40 – 14.50 Discussion 14.50 – 15.15 **«Type 1 Diabetes and Eating Disorders»** (B. Isenschmid, Zofingen, CH) 15.15 – 15.25 Discussion 15.25 – 15.50 **«Polyglandular Autoimmune Syndrome: Who to Screen and How?»** (S. Fischli, Luzern, CH) 15.50 – 16.00 Discussion
16:00 – 16:30	Prize Session (Room: Ettore Rossi)
16:30	Apéro (exhibition area)

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Association Suisse pour l'Etude du Métabolisme et de l'Obésité
Schweiz. Arbeitsgruppe Metabolismus und Obesitas

Program of the 13th Annual Meeting ASEMO-SAMO, in cooperation with AKJ

Association Suisse pour l'Etude du Métabolisme et de l'Obésité
Schweiz. Arbeitsgruppe Metabolismus und Obesitas

in cooperation with

Fachverband Adipositas im Kindes- und Jugendalter
Association obésité de l'enfant et de l'adolescent

(preceding the Annual Meeting of SGED)

Thursday, November 15th, 2018, Inselspital Bern, Kinderklinik
Update Lectures and New Issues

Chairs: K. Laederach and D. l'Allemand

09:15 – 09:50 **Stigmatisation in Health Care Setting**
D. Durrer, Vevey, CH

09:50 – 10:25 **The Overlap between Eating Behaviour and Obesity/Overweight: Developmental Effects**
N. Micali, Genève, CH

10:25 – 11:00 **The Role of Physical Activity and Exercise Training in Weight Management Programs**
D. Malatesta, Lausanne, CH

11.00 – 11.20 Coffee Break

Research Communications - 3 Oral Presentations

Chair: P. Gerber

11:20 – 11:35 **Abstract 90 (S) - Reduced skeletal muscle protein turnover and altered local thyroid hormone metabolism in the adaptive thermogenesis that facilitates body fat recovery during weight regain**
Julie Calonne; Laurie Isacco; Jennifer L Miles-Chan; Denis Arsenijevic; Jean-Pierre Montani; Christelle Guillet; Yves Boirie; Abdul G Dulloo (Fribourg, Besançon France, Clermont-Ferrand France)

Association Suisse pour l'Etude du Métabolisme et de l'Obésité
Schweiz. Arbeitsgruppe Metabolismus und Obesitas

11:35 – 11:50 **Abstract 93 - The impact of daily sugar sweetened beverage consumption on lipid metabolism in healthy men - a double-blind, randomized, controlled study** *Bettina Geidl-Flueck, Michel Hochuli, Agota Nemeth, Harald Köfeler, Luc Tappy, Kaspar Berneis†, Giatgen Spinas and Philipp Gerber (Zurich, Lausanne, Graz Austria)*

11:50 – 12:05 **Abstract 106 - Effects of Relaxation on Cortisol and Obesity in Adolescents - a Randomised Controlled Study.**
A. Stasinaki, D. Büchter , C.-H. I. Shih, K. Heldt, C. White, D. Rüegger, A. Filler, P. Gindrat, D. Durrer B. Brogle, N. Farpour-Lambert, T. Kowatsch, D. L'Allemand (St. Gallen, Zurich, Nyon, Vevey, Geneva).

12:15 End of the Scientific ASEMO Meeting

12:15 – 12:45 **General Assembly (ASEMO Members only)**

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ORAL PRESENTATIONS «BASIC / CLINICAL» – ENDOCRINOLOGY

Friday, 16th November, 10:30 – 12:30, Room «Ettore Rossi»

Chairs: F. Pralong (Geneva) and Ch. Henzen (Lucerne)

10:30 **Abstract 77 – The GLP-1 receptor agonist liraglutide improves hepatic inflammation and fibrosis in mouse non-alcoholic steatohepatitis.**
Sophie A. Montandon, Emmanuel Somm, Claudio de Vito, François R. Jornayvaz (Geneva)

10:42 **Abstract 89 – Air pollution induced-diabetes is mediated via the gut**
Angela J.T. Bosch, Theresa Rohm, Shefaa Al Asfoor, Thomas Dervos, Claudia Cavelti-Weder (Basel)

10:54 **Abstract 61 – Copeptin after Arginine Stimulation - A new Test for Diabetes Insipidus?**
Bettina Winzeler, Nicole Nigro, Julie Refardt, Cornelia Imber, Benedict Morin, Milica Popovic, Michelle Steinmetz, Clara Sailer, Deborah Vogt, Gabor Szinnai, Irina Chifu, Martin Fassnacht, Mirjam Christ-Crain (Basel, Würzburg Germany)

11:06 **Abstract 111 – Individualized nutritional support in medical inpatients at nutritional risk: a randomized clinical trial**
Philipp Schuetz, Rebecca Fehr, Valerie Baechli, Martina Geiser, Manuela Deiss, Filomena Gomes, Alexander Kutz; Pascal Tribolet, Thomas Bregenzer, Nina Braun, Claus Hoess, Vojtech Pavlicek, Sarah Schmid, Stefan Bilz, Sarah Sigrist, Michael Brändle, Carmen Benz, Christoph Henzen, Silvia Mattmann, Robert Thomann, Claudia Brand, Jonas Rutishauser, Drahomir Aujesky, Nicolas Rodondi, Jacques Donzé, Zeno Stanga, Beat Mueller (Aarau, Lachen, Münsterlingen, St.Gallen, Lucerne, Solothurn, Baselland, Berne)

11:18 **Abstract 56 – Effect of IL1-receptor antagonist on hemodynamics and Renin-Angiotensin-Aldosteron System in obese individuals**
Sandrine Andrea Urwyler MD, Fahim Ebrahimi MD, Thilo Burkard MD, Philipp Schuetz MD, Beat Mueller MD, Marc Y. Donath MD, Mirjam Christ-Crain MD (Basel, Aarau)

11:30 **Abstract 36 – Influence of Free Thyroid Hormone Levels on Thermogenesis in Euthyroid Humans**
Claudia Irene Maushart, Jaël Rut Senn, Rahel Löliger, Gani Gashi, Matthias Johannes Betz (Basel)

11:42 **Abstract 25 (S) – Evaluation of routine molecular testing of fine needle aspirate samples from cytologically indeterminate thyroid nodules using a 7-gene panel**
Ann-Kristin Jochum, Izadora Demmer Buchs, René Schönegg, Wolfram Jochum, Michael Brändle, Stefan Bilz (St. Gallen)

11:54 **Abstract 48 – Thermogenesis in Hyperthyroidism and Effect of Anti-Adrenergic Therapy – The HEAT study**
Jaël Rut Senn, Claudia Irene Maushart, Gani Gashi, Matthias Johannes Betz (Basel)

12:06 **Abstract 14 – Targeted metabolomics analysis in pheochromocytoma patients: towards clarification of the complexity in clinical presentation and morbidity?**
Zoran Erlic, Max Kurlbaum, Susan Richter, Aleksander Prejbisz, Svenja Nölting, Henri Timmers, Martin Reincke, Jacques Lenders, Andrzej Januscewicz, Graeme Eisenhofer, Matthias Kroiss, Felix Beuschlein (Zurich, Würzburg Germany, Dresden Germany, Warsaw Poland, Munich Germany, Nijmegen The Netherlands)

12:18 **Abstract 5 – Application of the EU-TIRADS ultrasound classification system in the work-up of thyroid nodules**
Barbara Bischofberger-Baumann, Joël Capraro, Thomas Clerici, Walter Kolb, Michael Brändle, René Schönegg, Stefan Bilz (St. Gallen, Aarau)

ORAL PRESENTATIONS «BASIC / CLINICAL» – METABOLISM / DIABETES

Friday, 16th November, 10:30 – 12:30, Room «Kursraum 1»

Chairs: Ch. Dibner (Geneva) and G. Gastaldi (Geneva)

10:30 **Abstract 30 – Gestational Diabetes Mellitus as a Potential Risk Factor for Metabolic Syndrome in the Early and Late Postpartum Period – A prospective cohort study**
Dr C Kosinski, Dr T-H Collet, J Gross, C Helbling, DY Quansah, Prof JJ Puder (Lausanne)

10:42 **Abstract 2 – Closing the loop on nutrition support in hospital - a randomised clinical study**
Lia Bally, Charlotte Boughton, David Herzig, Nicole Hunkeler, Sara Hartnell, Malgorzata E Wilinska, Mark L Evans, Anthony P Coll, Roman Hovorka and Christoph Stettler (Bern, Cambridge United Kingdom)

10:54 **Abstract 57 – Association between glycaemic control and fracture risk in diabetic patients: a nested case control study**
Janina Vavanikunnel, Sarah Charlier, Claudia Becker, Cornelia Schneider, Susan S. Jick, Christoph R. Meier, Christian Meier (Basel, Boston USA)

11:06 **Abstract 6 – The landscape of genetic diabetes in Switzerland**
Jean-Louis Blouin, Philippe Klee, Mirjam Dirlewanger, Federico Santoni, Antoine Poncet, Valerie M. Schwitzgebel (Geneva, Lausanne)

11:18 **Abstract 85 (S) – Role of cell type-specific IL-1β overexpression in type 2 diabetes mouse models**
Josua Wehner, Stéphanie P. Häuselmann, Elise Dalmas, Leila Rachid, Daniel T. Meier, Sophia Wiedemann, Friederike Schulze, Marianne Böni-Schnetzler and Marc Y. Donath (Basel)

11:30 **Abstract 98 – Comparative lipidomic analysis of human skeletal muscle and visceral adipose tissue biopsies derived from lean, obese and type 2 diabetic individuals**
Ursula Loizides-Mangold, Stephanie Chanon, Maud Robert, Etienne Lefai and Charna Dibner (Geneva, Lyon France, Saint-Genès Champanelle France)

11:42 **Abstract 88 – Impaired Proinsulin but not Impaired Central POMC Processing Mediates PC1/3-related Obesity**
Daniel T. Meier, Leila Rachid, Sophia J. Wiedemann, Josua Wehner, Marianne Böni-Schnetzler and Marc Y. Donath (Basel)

11:54 **Abstract 86 – A short bout of HFD desynchronizes feeding behaviour in mice thereby affecting glucose and lipid metabolism**
Stephan Wueest, Mara A Dedual, Daniel Konrad (Zurich)

12:06 **Abstract 81 – Regulation of beta-cell function by an intronic insulin circular RNA**
Adriana Rodriguez-Trejo, Lisa Stoll, Sonia Gattesco, Claudiane Guay, Ana Claudia Marques, Morten Trillingsgaard Venø, Kailun Lee, Jørgen Kjems, D. Ross Laybutt, and Romano Regazzi (Lausanne, Aarhus Denmark, Sydney Australia)

12:18 **Abstract 69 (S) – Cystatin C alleviates Obesity-Associated Tissue Inflammation and Insulin Resistance**
Mara A Dedual, Stephan Wueest, Tim RJ Aeppli, Tegnane D Challa, Daniel Konrad (Zurich)

POSTER PRESENTATIONS

Friday, 16th November, 12:30 – 13:30 – Room «Ettore Rossi»

CLINICAL

1 **A case of Cushing's disease responding to dopamine agonist treatment**
Gurpreet Anand, Christoph Schmid, Felix Beuschlein (Zurich)

3 **Poorly Differentiated Thyroid Carcinoma: a Diagnostic Challenge**
S.Bervini, A.Schmitt, M.Dettmer, A.Melmer, C.Stettler, R.Trepp (Berne)

4 **Unusual Sonographical Appearance of a Parathyroid Adenoma**
S.Bervini, A.Schmitt, R.Trepp (Berne)

7 **Differential diagnosis for chronic hypokalemia**
Dr. med. B. Bucher, Dr. med. B. Röthlisberger, Dr. med. J. Capraro (Aarau)

8 **The prevalence of MC4R deficiency and its metabolic consequences in the Swiss population**
Tinh-Hai Collet, James Acierno Jr., Cheng Xu, Michael Hauschild, Pedro Marques-Vidal, Peter Vollenweider, Nelly Pitteloud, Lucie Favre (Lausanne)

9 **Long-Term Efficacy and Safety of Dapagliflozin in Patients with Inadequately Controlled Type 1 Diabetes: The DEPICT-1 Study**
Paresh Dandona, Chantal Mathieu, Moshe Phillip, Lars Hansen, Diethelm Tschoepe, Fredrik A. Thoren, John Xu, Anna Maria Langkilde, the DEPICT-1 Investigators, Williamsville, NY, Leuven, Belgium, Petah Tikva, Isreal, Gaithersburg, MD, Bad Oeynhausen, Germany, Molndal, Sweden, Gothenburg, Sweden; Peter Bretscher (presenting author, Astra Zeneca Switzerland)

10 **Hypophosphatasia - a rare disease meets a less rare carrier**
Tilman Drescher, Karl Heinimann, Ina Krull (St. Gallen, Basel)

11 **Clinical and Genetic Features of Familial Hypercholesterolemia in Eastern Switzerland**
Author/Address of institution:
Andrea Ebert, Yannick Gerth, Karin Jung, Wolfgang Korte, Stefan Bilz (St. Gallen)

12 **Effects of Anti-Inflammatory Treatment on Fibroblast Growth Factor-21 in Obesity and Metabolic Syndrome**
Fahim Ebrahimi, Sandrine Andrea Urwyler Matthias Betz, Emanuel Christ, Philipp Schuetz, Beat Mueller, Marc Y. Donath and Mirjam Christ-Crain (Basel, Aarau)

13 **Effects of the Number of Thyroidectomies per Instuitution on Clinical Outcomes in Switzerland**
Fahim Ebrahimi, Alexander Kutz, Emanuel Christ, Philipp Schuetz and Beat Mueller (Basel, Aarau)

15 **Rare Cause of Pathological 17-OH-Progesteron Response after ACTH-Stimulation. Two case reports.**
Zoran Erlic, Martin Litzel, Christoph Henzen, Stefan Fischli (Lucerne)

16 **How does source matter? Perceptions of Interprofessional Feedback in Workplace-based Assessments in Diabetology**
Katrin Feller, MD, MME; Livia Remund, psychologist; Sibylle Stocker, diabetes nurse; Michelle Müller; nutritionist; Christoph Stettler, Prof.,MD, Head of Department (Berne)

17 **Efficacy and Safety of an Expanded Dulaglutide Dose Range: A Phase 2, Placebo-controlled Trial in T2D Patients on Metformin**
Juan Frias, Alan Wynne, Beata Matyjaszek-Matuszek, Dagmar Bartaskova, David Cox, Brad Woodward, Ying Grace Li, Zvonko Milicevic, Regis Babey (Presenter only Eli Lilly Switzerland), (Los Angeles USA; Topeka USA, Lublin Poland, Prague Czech Republic, Indianapolis, IN, USA)

18 **Follicular thyroid carcinoma manifesting as a solitary intracranial metastasis 19 years after thyroidectomy**
R. Giger, S. Bervini, S. Berezowska, R. Trepp (Berne)

19 **Clinical features of 35 patients with 172 spontaneous vertebral fractures after denosumab discontinuation: a single center observational study**
Elena Gonzalez Rodriguez, Bérengère Aubry-Rozier, Delphine Stoll, Didier Hans, Olivier Lamy (Lausanne)

20 **Identification of a novel THRβ mutation affecting GRIP1 interaction in a patient with resistance to thyroid hormone**
Matthias Hepprich, MD; Pascal Joset, PhD; Emanuel Christ, MD, PhD; Heinrich Sticht, PhD; Matthias J. Betz, MD (Basel, Erlangen-Nuremberg Germany)

21 **The burden of inpatient diabetes at the University Hospital Bern – Insights provided by the Clinical Data Warehouse System**
David Herzig, Franco Martignoni, Philippe Gubler, Alexander Leichtle, Christoph Stettler and Lia Bally (Berne)

22 **Impact of Flash Glucose Monitoring on HbA1c in pediatric type 1 diabetes patients**
Anastasia Hillenbrand, Gabor Szinnai (Basel)

23 **Remission of hypercortisolism after unilateral adrenalectomy in a patient with Carney complex and primary pigmented nodular adrenocortical disease**
Vera Jenni, Gudrun Neises, Udo Schirp, Thomas Clerici, Michael Germer, Stefan Bilz (St. Gallen, Lucerne)

24 **Postpartum isolated IgG4-related hypophysitis, a master of imitation.**
Anders Boisen Jensen, Claudia Hader, Wolfram Jochum, Stefan Aczél, Stefan Bilz (St. Gallen)

26 **Effects Of Once-weekly Treatment With Somapacitan: A Randomised, Double-blind, Placebo-controlled And Open Active-controlled Study In Adult Growth Hormone Deficiency**
Gudmundur Johannsson, University of Göteborg and Sahlgrenska University Hospital, Göteborg, Sweden; Koji Takano, Kitasato University, Tokyo, Japan; Michael Højby Rasmussen, Novo Nordisk A/S, Søborg, Denmark; Ida Holme Håkonsson, Novo Nordisk A/S, Søborg, Denmark; Beverly MK Biller, Neuroendocrine Clinical Center, Massachusetts General Hospital, Boston, MA, USA

27 **Real-world impact of insulin glargine 300 U/mL in patients with type 2 diabetes uncontrolled on oral therapy: glycemic target achievement in Switzerland**
François R Jornayvaz, Stefan Zechmann, Nicola Alexander-David, Robert Thomann (Geneva, Baden, Bellinzona, Solothurn)

28 **Quality of blood glucose control and complications in glycogen storage disease type I: data from the Swiss registry**
Kaiser N, Gautschi M, Bosanska L, Meienberg F, Baumgartner M, Hochuli M (Zurich, Berne, Basel)

29 **Towards an integrated approach for the diagnosis of 46,XY disorder of sex development.**
Zofia Kolesinska, James Acierno Jr, Cheng Xu, S. Faisal Ahmed, Karina Kapczuk, Anna Skorczyk-Werner, Hanna Mikos, Aleksandra Rojek, Maciej Krawczynski, Nelly Pitteloud, Marek Niedziela (Lausanne, Glasgow United Kingdon, Poznan Poland)

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S = contribution of a student

01

A case of Cushing's disease responding to dopamine agonist treatment

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Background/Introduction:
A 47-year-old Swiss male was referred to our clinic for further investigation of a clinically and biochemically confirmed ACTH-dependent Cushing's syndrome. His family physician had screened for endogenous hypercortisolism because of poorly controlled diabetes (HbA1c 11.5%). The patient also reported slow weight gain over the last 10 years, whereby central obesity became prominent in the last 2 years. In addition, he had hypertension and was on CPAP treatment for obstructive sleep apnea which was diagnosed 1 year ago. Detailled questioning revealed other symptoms of hypercortisolism such as proximal muscle weakness in the last 6 months as the patient could no longer climb stairs. The patient described this as " having no juice in his legs". His libido was reduced. He also noticed diffuse hair loss on the scalp. Physical examination revealed abdominal striae rubrae and left temporal hemianopsia.

Methods:
Endocrine evaluation revealed markedly increased 24-h urinary cortisol of 2050 ug (normal <417), late-night salivary cortisol was 33.6 nmol/l (normal <5.7), ACTH was 90 ng/l (Ref. <46) confirming ACTH-dependent Cushing's syndrome. While Overnight 1 mg dexamethasone did not suppress the cortisol value next morning, 8 mg dexamethasone could suppress cortisol down to 84 nmol/l compatible with a pituitary source of ACTH secretion. Surprisingly, prolactin turned out to be very high at 3482 ug/l, testosterone was 1.15 nmol/l, HGH 1.85 ug/l, IGF1 465.7 ug/l, TSH 0.79 mU/l and fT4 6.2 pmol/l. A pituitary tumor producing ACTH, prolactin and GH and causing central hypothyroidism, hypogonadotropic hypogonadism and visual field defects was presumed based on these findings.
Brain MRI revealed a diffusely invasive macroadenoma with suprasellar extension (3,1x2,2x3,8 cm)

Results:
Within 4 weeks of treatment with cabergoline, the patient's ACTH and cortisol excess were controlled and his Cushing phenotype improved (16 kg weight loss, HbA1c improved to 6.1%, no CPAP needed). Prolactin normalised within 9 months of treatment. In the follow-up MRI tumor size decreased as well.

Conclusion:
We describe a case-report of a patient with Cushing's disease convincingly responding to medical treatment with a dopamine agonist normalising ACTH/cortisol and prolactin excess and improving patient's clinical phenotype. Despite missing immune histochemistry of the tumor sample as patient did not undergo surgery, a diagnosis of plurihormonal tumor producing ACTH, prolactin and GH can be strongly suspected.

02

Closing the loop on nutrition support in hospital - a randomised clinical study

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Background/Introduction:
Hyperglycaemia is a frequent complication of enteral and parenteral nutrition in hospital with adverse effects on medical outcomes and nutritional status. Glucose control is challenged by acute illness, high rate of nutrient delivery and interfering medication requiring frequent insulin dose adjustment. An automated system that directs insulin in a glucose-responsive manner (also known as closed-loop) may improve glucose control whilst obviating the need for additional staff input.

Methods:
Fully automated fully closed-loop (CL) insulin delivery system was evaluated in non-critical care (medical and surgical) patients receiving parenteral and/or enteral nutrition. Seventeen partients were randomised to either CL-directed s/c insulin delivery (n=9) or conventional s/c insulin therapy as per local practice with masked continuous glucose monitoring (n=8) for up to 15-days or until hospital discharge. Randomisation was stratified according to pre-study total daily insulin dose and nutrition regime. The study did not interefere with the nutrition support provided. Non-insulin therapies (if prescribed) were continued with the exception of sulfonylureas in the CL arm.The primary end point was the percentage of time with sensor glucose measurements in target range between 5.6 to 10.0mmol/l. Analyses were performed by intention to treat.

Results:
Study groups were comparable in terms of age (70(6) vs. 70(4)yrs; CL vs. control), HbA1c (6.6(0.9) vs. 6.4(0.9)%; CL vs. control) and pre study insulin dose (0.5(0.4) vs. 0.6(0.4)U/kg; CL vs. control). The proportion of time when sensor glucose was in target range was 51.6 percentage points (95% confidence interval [CI] 37.9 to 65.9; p<0.001; primary end point) greater during CL compared to control. CL significantly decreased time spent above target by 52.8 percentage points (95% CI 69.1 to 36.4; p<0.001) without increasing total daily insulin delivered (41.3(24.2) vs. 52.8(41.1) U/24h, p=0.49). Mean glucose and standard deviation of sensor glucose were significantly reduced by 4.0(0.9) mmol/l (p=0.001) and 1.9(0.5) mmol/l (p<0.01) during CL compared to control, whilst proportion of time and area under the curve below 3.0mmol/l was not significantly different (p=0.60 and 0.61, respectively). Daily carbohydrate supply (parenteral, enteral and oral route) was comparable between groups (p=0.25). Mean study follow-up was 8 and 10 days in the CL and control group, respectively (p=0.54). No severe hypoglycaemia or or hyperglycaemia with ketonaemia occurred in either group

Conclusion:
Fully automated CL in patients receiving parenteral and/or enteral nutrition resulted in significantly better glycaemic control compared to conventional treatment without increasing the risk of hypoglycaemia. CL may therefore be a promising tool to optimise nutrition support in hospital.

05

Application of the EU-TIRADS ultrasound classification system in the work-up of thyroid nodules

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Background/Introduction:
Several professional societies have adopted risk stratification systems that serve to assign thyroid nodules to different risk categories according to their echographic appearance rather that size and identify those which require further work-up by fine needle aspiration biopsy (FNAB). The EU-TIRADS system has been developed from the previously released TIRADS system and endorsed by the European Thyroid Association.

Methods:
All patients referred for the workup of thyroid nodules between May 2015 and March 2018 that underwent FNAB were prospectively investigated and clinical, echographic, cytological and if available histological data were collected. Echographic benign (EU-TIRADS 2) nodules were not routinely biopsied. Isoechoic nodules (EU-TIRADS 3, low-risk category) and mildly hypoechoic nodules (EU-TIRADS 4, intermediate risk category) underwent FNAB if the largest diameter exceeded 2 cm and 1-1.5 cm, respectivley. Nodules with any high-risk feature, i.e. irregular (taller-than-wide or taller-than-long) shape, spiculated or lobulated margins, marked hypoechogenicity or microcalcifications (EU-TIRADS 5) were biopsied if larger than 1 cm. Cytological results were reported according the Bethesda system. Lobectomy or follow-up within 6 months was suggested for BIII nodules and immediate lobectomy or thyroidectomy for Bethesda IV-VI nodules. A final diagnosis of malignancy was made if the work-up resulted in a diagnosis of thyroid cancer. Descriptive statistics, chi-square and fisher's exact tests were used as appropriate and a p<0.05 considered significant.

Results:
365 nodules were investigated in 317 patients (244 females, 73 males). The malignancy risk was 4% (95% CI 0-13%) in the EU-TIRADS 2, 2% (95% CI 0-5%) in the EU-TIRADS 3, 10% (5-15%) in the EU-TIRADS 4 and 22% (95% CI 14-31%) in the EU-TIRADS 5 category. A highly significant association was found between the EU-TIRADS category and both the Bethesda class (chi-square 37.9, p=0.001) and the rate of malignancy (chi-square 22.5, p=0.0001). The sensitivity, specificity and positive predictive value of a EU-TIRADS 5 pattern to predict malignancy was 53 % (95% CI 36-69%), 79% (95% CI 74-83%) and 22% (14-31%). The sensitivity, specificity and positive predictive value of the combined EU-TIRADS 2 and 3 patterns to predict a benign nodule was 38% (95% CI 33 44%), 92% (95% CI 78-98%) and 98% (95% CI 95-100%). If the EU-TIRADS classification was retrospectively applied to the non-diagnostic cytological categories Bethesda III, IV and V, a benign or low risk ultrasound pattern (EU-TIRADS 2 and 3) retained its high positive predictive value for a benign nodule (94%, 95% CI 85-100%). Within the Bethesda III category, none of the nodules with a benign or low risk ultrasound pattern fulfilled the criteria for malignancy.

Conclusion:
Nodules with benign (EU-TIRADS 2) and low risk (EU-TIRADS 3) ultrasound patterns carry a low risk of malignancy. Nodules with a non-conclusive cytological (Bethesda III) but benign ultrasound (EU-TIRADS 2 and 3) pattern may be safely followed without an immediate need for diagnostic surgery.

06

The landscape of genetic diabetes in Switzerland

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Background/Introduction: Monogenic diabetes is thought to affect 1-5% of the diabetes population. Diabetes-related gene alterations may lead to either a reduction in the function or number of beta cells or to a postnatal progressive destruction of beta cells. Monogenic diabetes causes neonatal diabetes (ND), maturity-onset diabetes of the young (MODY), and syndromic diabetes. It is estimated that these forms of diabetes remain undiagnosed in 90% of patients or more. The aim of the study was to identify mutations causing monogenic diabetes in Switzerland.

Methods: Inclusion criteria were ND, autoantibody negative type 1 diabetes (T1D), presumed MODY, type 2 diabetes (T2D) diagnosed before the age of forty-five without metabolic features and syndromic diabetes regardless of treatment. Haloplex technology was used to perform targeted next-generation sequencing (NGS) for 323 to 483 genes known to be involved in diabetes, glucose homeostasis and pancreas development, for identifying pathogenic DNA variants, all confirmed by Sanger sequencing.

Results: We have analyzed 234 probands (137 females, 97 males) living in Switzerland by NGS. The mean age at diabetes diagnosis was 27.7 ±15.4 years, including four probands with neonatal diabetes diagnosed < 6 months of age. We identified variants in the MODY genes 1-13 (*HNF4A, GCK, HNF1A, PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8, KCNJ11*) in 41% (95/234) of the patients, of which 7 had variants in two, and one in three genes. The most frequent variants involved *GCK* in 58% (55/95), followed by *HNF1A* 19%, *HNF4A* 7%, *ABCC8* 6%, *HNF1B/KCNJ11/KLF11* 3%, *NEUROD1* 2% and *PAX4* 1%. We identified 27 different mutations in *GCK*, of which 35% (19/55) carried the p.Val203Ala mutation. When mapped to age at diabetes onset, MODY variants were most frequent in the neonatal group (50%, 2/4), and declined with age to reach 36% (13/36) in the >45 year group. In the group with other variants (n=111) onset was 30 ±16 years, contrasting with the group where no variant was found (n=28), where the mean age at onset was 25 ±14 years.

Conclusion: We provide proof of feasibility for the diagnosis of monogenic diabetes by NGS. In our Swiss population, 58% of the MODY patients had *GCK* related diabetes; the p.Val203Ala missense mutation was the most prevalent. Diagnosis rate of MODY diabetes was above 35% in all age groups.

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03

Poorly Differentiated Thyroid Carcinoma: a Diagnostic Challenge

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Background/Introduction:
Poorly differentiated thyroid carcinomas (PDTC) account for 3-5% of all thyroid carcinomas. The prognosis is generally poor. Despite the development of defined pathological criteria in 2006 (Turin Criteria), the cytological diagnosis is often problematic.

Methods:
By applying the Turin Criteria, we identified 39 patients with PDTC at the University Hospital of Bern between January 2007 and October 2017. A pathological review was performed for all cases (blinded to clinical data and outcome).

Results:
Mean age at diagnosis was 66.7 years (range 38-90), 56% were men. 20 out of 39 patients (51%) had a fine needle aspiration (FNA) prior to surgery: only 4 nodules (20%) were classified as Bethesda V, 10 nodules (50%) were classified as Bethesda IV, 4 nodules (20%) as Bethesda III and 2 as Bethesda II (10%). Surgery was performed on all patients: 21 patients (53%) underwent total thyroidectomy, while 18 patients (46%) initially had a hemithyroidectomy and needed completion surgery. Intraoperative frozen section was performed in 24 cases (60%): of these, only 10 (42%) were reported as suspicious for malignancy, 7 (29%) as uncertain, 7 (29%) as probably benign.

Conclusion:
Our data suggest that, due to the lack of cytological criteria, the diagnosis of PDTC is rarely suspected based on the result of FNA. We found that only a minority of intraoperative frozen sections were reported as suspicious for malignancy. This often resulted in a less extensive initial procedure and in the need for an additional surgery. Hence, the cytological diagnosis of PDTC remains a challenge. Future studies should investigate molecular markers which could improve cytological accuracy.

04

Unusual Sonographical Appearance of a Parathyroid Adenoma

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Background/Introduction:
Parathyroid adenomas are most often hypoechoic on sonography. Hereby, we describe the case of a patient with primary hyperparathyroidism harbouring a left parathyroid adenoma which appeared strongly hyperechoic on ultrasound examination.

Case report:
A 52-year old postmenopausal woman was accidentally diagnosed with primary hyperparathyroidism during a routine check-up. She showed no symptoms or clinical signs of hypercalcemia. Laboratory exams showed an albumin-corrected calcium of 2.91 mmol/L (N 2.15-2.5), an iPTH of 128 pg/ml (N 15-65), a severe 25-OH-Vitamin D-deficiency (< 25 nmol/L) and a preserved kidney function. DXA scan revealed osteoporosis. In this setting, parathyroidectomy was recommended and preoperative localization was performed. On ultrasound examination, we observed a strongly hyperechoic, large, oval, homogeneous, vascularized structure adjacent to the left thyroid lobe. On scintigraphy, the structure showed increased Tc-99 uptake, compatible with a parathyroid adenoma. No other lesion compatible with a parathyroid adenoma was detected either on sonography or on scintigraphy. Due to the atypical aspect of the lesion, we performed an FNA: Cytopathology showed a macrofollicular pattern of epithelial cells; immunohistochemistry for TTF-1 and PTH was inconclusive, but iPTH in the aspirate fluid was very high (> 5000 pg/ml), confirming the presence of parathyroid tissue. During surgery, the lesion was macroscopically suggestive of a parathyroid adenoma and was resected. iPTH intraoperatively fell from 170 to 27 pg/ml. Histopathological examination showed a hyperplastic parathyroid gland without increased fibrosis or sclerosis. The patient had an uneventful postoperative recovery and, 6 weeks later, her blood exams showed normalized calcium and iPTH levels.

Discussion:
Although typically hypoechoic to cystic, about 25% of all parathyroid adenomas are isoechoic and 1% are hyperechoic on ultrasound examination. The increase in echogenicity mostly correlates with hyalinisation, fibrosis, haemorrhage or fat deposition. In our case, surprisingly, no such changes were detected on histopathology: the parathyroid gland, though hyperplastic, was of normal appearance.

Conclusion:
Atypical ultrasound features of parathyroid lesions represent a diagnostic challenge. Awareness of these features would help improve lesion detection.

07

Differential diagnosis for chronic hypokalemia

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Background/Introduction:
Gitelman syndrome (GS) is a seldom reason for hypokalemia and its complications and should be diagnosed after having excluded other reasons for the patients conditions. Treatment is guided by potassium levels of the patient and symptoms (hypotension).

Methods:
Case:The young Patient presented himself on the emergency department with recurrent dizziness and falls. He reported recurrent similar episodes with palpitation and syncopation. A hypokalemia is known since teenage years. Family history was remarkable for consanguinity in the family (parents are cousins). Clinical findings were normal. Laboratory results revealed a hypokalemia, with renal salt loss, a low urin calcium excretion and a normal magnesium. The arterial blood gas analysis showed a metabolic alkalosis. Primary aldosteronism was excluded by an elevated renin activity. The clinical suspicion of GS was genetically confirmed. We found a homozygote pathogenic mutation in the SLC12A3 gene (SLC12A3:c.1928C>T / p.Pro643eLeu).

Results:
GS also referred to as familial hypokalemia-hypomagnesemia, is a salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria. With a prevalence about 1-10 per 40'000, GS is arguably the most frequent inherited tubulopathy. The disease is caused by biallelic inactivating mutation in the SLC12A3 gene encoding the thiazide-sensitive NaCl cotransporter (NCC) in the distal tubule. The estimated prevalence of heterozygotes is at least 1% in Western countries. Reduced NCC activity will mimic the effect of persistent thiazide diuretic action. To date, more than 450 different mutations in SLC12A3 have been identified. In most patients, symptoms occur in adulthood, but some can present in childhood. Bartter or Gitelman syndrome is often suspected in patients with unexplained hypokalemia, metabolic alkalosis and a normal or low blood pressure. The presence of BS or GS can be diagnosed after more common causes have been excluded. Measurement of urinary calcium excretion can help differentiate between BS and GS. Treatment, which must be lifelong, is aimed at minimizing the effects of secondary increases in renin and aldosterone, as well as correcting the volume deficit and electrolyte abnormalitis, potassium values should targeted 3mmol/l.

Conclusion:
NSAIDs may effectively raise the serum potassium in such patients. Drugs that block distal tubule sodium-potassium exchange, such as spironolactone, eplerenon or amiloride, can raise the serum potassium, reverse the metabolic alkalosis and partially correct hypomagnesemia.

In patients with hypokalemia and normal blood pressure, in which other reasons for hypokalemia are excluded, we suggest to confirm the diagnosis of GS molecular genetically to guide therapy and make an adequqate conselling.

08

The prevalence of MC4R deficiency and its metabolic consequences in the Swiss population

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Background/Introduction:
The global obesity epidemic seems largely driven by increased caloric intake and reduced energy expenditure. However, the variance in body mass index (BMI) is also genetically determined with heritability estimates from 40 to 70%. The hypothalamic leptin-melanocortin pathway is central to energy homeostasis and mutation of the melanocortin 4 receptor (MC4R) is the most frequent genetic form of obesity. This condition called MC4R deficiency has a co-dominant transmission and a prevalence of 0.1-1.0% in the general population (reaching up to 5% in cohorts with severe obesity) and leads to obesity, tall stature, but paradoxically normal blood pressure and lipid profile. We studied the prevalence of MC4R deficiency in Switzerland, its metabolic consequences and checked for potential genotype-phenotype correlations.

Methods:
Whole exome sequencing was performed on 406 participants (34% women, aged 35-75) with BMI > 25 kg/m2 from the community-based CoLaus cohort in Lausanne. We evaluated rare variants in the obesity-related genes (i.e. LEP, LEPR, POMC, PCSK1, MC4R, MRAP2) for pathogenicity. We assessed weight history, adult obesity and other metabolic phenotypes in gene variant carriers. We finally checked gene variants and their potential dysfunction following a classification based on in vitro assays, testing for genotype-phenotype correlations while adjusting for age and sex.

Results:
Of the 406 participants, 60 individuals (14.8%) were carriers of obesity-related gene variants. Rare variants in the MC4R gene were found in 26 individuals (6.4%), while no pathogenic mutations were found in the other obesity-related genes.
MC4R variant carriers were older (mean 64.4 years ± SD 6.5) than wildtype individuals (60.8 ± 8.5; p = 0.04), but the sex distribution was similar (42% women among MC4R variant carriers, 33% women in wildtypes, p = 0.23).
While the BMI was comparable between MC4R variant carriers and wildtypes (30.8 ± 3.8 kg/m2, p = 0.24), their self-reported weight history differed. Among the 268 individuals with known weights at different ages, a larger proportion reported being overweight before age 20 among women with MC4R variants compared to wildtypes (44% vs 14% resp.; OR 4.92, 95%CI 1.17-20.8). All MC4R variant carriers reported being overweight after age 50, compared to 77% wildtypes (p = 0.02).
There was no difference in height, blood pressure, lipid profile and glucose metabolism between groups. We did not show any genotype-phenotype correlation with in vitro functional assays of MC4R, possibly due to the small number of variants with known in vitro effect.

Conclusion:
In this community-based population of Switzerland, the prevalence of MC4R variants was 6.4% among overweight/obese individuals, while the number of functionally relevant mutations was much lower, thus preventing us from detailed comparison of genotype-phenotype correlations. The high prevalence of self-reported overweight before age 20 is an argument for screening for obesity-related genes in patients who are obese in early childhood, but also early adulthood.

09

Long-Term Efficacy and Safety of Dapagliflozin in Patients with Inadequately Controlled Type 1 Diabetes: The DEPICT-1 Study

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This study was supported by AstraZeneca

Background/Introduction:
In this short term (24-week) period of the Phase 3 study DEPICT-1, treatment with the SGLT2 inhibitor dapagliflozin (DAPA) as adjunct to adjustable insulin (INS) improved glycemic control and was well-tolerated in patients with inadequately controlled T1D (HbA1c 7.5-10.5%) (Lancet Diabetes Endocrinol. 2017;5:864-76).

Methods:
Here we describe the 28-week extension of DEPICT-1, assessing the 52-week efficacy and safety of DAPA in patients who completed the 24-week period.

Results:
747 patients in the DAPA 5 mg (n=250), 10 mg (n=270), or placebo (PBO; n=227) plus INS group entered the long-term period (90% of the randomized patients); 85% competed the study. Reductions in HbA1c and body weight were maintained in the DAPA groups vs PBP over 52 weeks. The moderate decrease in HbA1c with DAPA was accompanied by a more substantial dose-dependent reduction in body weight. Total events of adjudicated definite DKA increased in the long-term period, with more in the DAPA groups vs PBO at Week 52. Most were mild to moderate, with the primary cause related to missed insulin doses or pump failure. Adverse events (AEs), serious AEs, and hypoglycemic events were balanced betweed groups.

Conclusion:
In conclusion, DAPA plus INS provided a sustained reduction in HbA1c and body weight, and was well-tolerated, but increased events of DKA over 52 weeks in patients with inadequately controlled T1D.

10

Hypophosphatasia - a rare disease meets a less rare carrier

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Background/Introduction:
Hypophosphatasia is a rare disorder of bone and teeth mineralization caused by deficient activity of the tissue nonspecific Alkaline Phosphatase (AP). More than 300 mutations in the encoding ALPL gene have been described with recessive or dominant inheritance. The clinical features range from lethal perinatal to mild adult forms reflecting the genetic heterogeneity. The prevalence of severe disease in Europe is estimated at 1/300.000, corresponding to a carrier frequency of 1/270. Mild forms of the disease are more frequent and calculated at 1/6370.

Methods:
Case description: A 33 year old man was referred to our clinic for re-evaluation of a known hypophosphatasia. The disease was diagnosed as a 15 months old child revealing clinical signs of rachitis, loose teeth and the characteristic reduced activity of serum-AP. His clinical course was basically uneventful, no fracture events occurred. He has been under pediatric surveillance until the age of 18. The patient was accompanied by his spouse, both expressed the desire to have children and raised the question of inheritance and possible consequences for their offspring.

Results:
We initiated a genetic analysis of the patients ALPL gene. Two heterozygous variants in exon 6 and 11 have been detected, being consistent with the clinical diagnosis of childhood HPP. The characteristic low activity of AP in the patient`s serum could be confirmed. In the light of the low disease frequency we initially resigned genetic testing of the spouse who is clinically unconspicuous for HPP. However, we screened her serum AP, being unexpectedly clearly below the normal range. Therefore we decided to perform a genetic analysis of the wife`s ALPL gene, revealing exactly the same heterozygous mutation in exon 6, as been detected in her husband.
Consanguinity was therefore suspected; furthermore, the couple shares the same date of birth and area of origin. However, no common relatives could be identified within the two families. The fact, that the mutation found in both persons (p.Glu191Lys) represents the most frequent mutation of ALPL gene in Europe, also argues against consanguinity. Under the assumption of compound heterocygous mutation with recessive inheritance in our patient and the carrier status of the wife, risk of having clinically affected children exists. Genetic counselling currently is in progress.

Conclusion:
Genetic counselling of couples with one partner clinically suffering from HPP can be challanging. Screeening for decreased serum AP activity and potentially additional genetic testing should also be performed in the clinically non affected partner due to the wide spectrum of HPP, ranging from relatively frequent clinically inapparent gene carriers to rare mild- and very rare severe clinical manifestation.

13

Effects of the Number of Thyroidectomies per Instuitution on Clinical Outcomes in Switzerland

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Background/Introduction:
Epidemiologocal data suggest an continuous increase in thyroid carcinoma diagnosis. Therefore, thyroidectomy rates are projected to increase world-wide in exponential scale. In Switzerland, the institutional number of thyroidectomies varies, however there is no data yet on the association between institutional thyroidectomy volume and clinical outcome.

Methods:
Cross-sectional analysis of adult inpatients in Swiss hospitals using a nation-wide inpatient database covering the years 2011-2015. The study population consisted of adult (≥18 years) inpatients who underwent total thyroidectomy or hemithyroidectomy as the primary procedure. Hospitals were stratified into very low (<20 thyroidectomies per year), low (20-100 thyroidectomies per year), intermediate (101-200 thyroidectomies per year) and high (>200 thyroidectomies per year) thyroidectomy volume institutions. Multivariate regression models were used to determine complications, length of hospital stay (LOS), intensive care unit admission (ICU), 30-day readmission rates, and mortality in relation to hospital volume.

Results:
A total of 17`410 patients were included whereof two-thirds (11`613; 66.7%) of thyroidectomies were performed at very low and low volume hospitals and one-third (5`797, 33.3%) at intermediate and high-volume hospitals, respectively. Operations of malignant thyroid diseases were more frequent among high-volume hospitals compared to low-volume hospitals (27.7% vs. 17.4%; p<0.001). Rates of hypocalcemia following thyroidectomy were lowest in high-volume hospitals (very low 6.7%, low 9.5%, intermediate 9.7%, and high 3.7%) with an overall adjusted odds ratio of 0.34 (95%CI, 0.29-0.42; p<0.001). Rates of recurrent laryngeal nerve paralysis were overall low at 2.1% (SD 14.5) for both total and hemithyroidectomies, just as mortality rates which did not show significant differences in relation to institutional number of thyreoidectomies (overall 8 deaths (0.05%). Length of stay revealed a bell-shaped curve and was lowest among high-volume hospitals when compared to other hospital volume with a mean difference of 0.61 days (95%CI; (-0.72)-(-0.50); p<0.001).

Conclusion:
Despite higher rates of malignant thyroid diseases, high-volume hospitals had less or comparable complications and shorter length of stay following thyroidectomy when compared to hospitals with low thyroidectomy volume. Mortality rate was low and independent of institutional thyroidectomy volume.

14

Targeted metabolomics analysis in pheochromocytoma patients: towards clarification of the complexity in clinical presentation and morbidity?

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Background/Introduction:
Pheochromocytoma and paraganglioma (PPGL) are tumors associated with distinct clinical manifestations and increased morbidity and mortality, the underlying mechanisms of which are not completely elucidated. Mass spectrometry based metabolomic profiling is a relatively new technique for high-throughput parallel identification and quantification of many hundreds of low molecular weight molecules (metabolites) within one biological sample. This approach has been widely used for risk profiling of patients with cardiovascular and tumor diseases, identifying a variety of diagnostic markers and contributing to the understanding of pathophysiological mechanism of diseases. Within the current study, we screened for specific metabolite alterations in blood samples of PPGL patients using a targeted metabolomic approach with the aim to identify metabolic patterns that might aid in the diagnostics, risk stratification and follow-up of patients.

Methods:
A subgroup of 61 patients from the Prospective Monoamine-producing Tumor (PMT) Study with diagnosed hormonally active PPGL who underwent surgery was included in the current protocol. Targeted metabolic analysis (LC/MS, AbsoluteIDQ-p180 Kit, Biocrates) of blood specimens from PPGL patients before and after surgery was performed. First, metabolic profiles from PPGL patients prior to surgery were compared according to sex, tumor localization, malignancy and secretory phenotype. Further, we investigated the preoperative and postoperative metabolite values for patients with confirmed post-surgical biochemical remission, either combined or separate for male and female patients, as well as for adrenergic and noradrenergic tumors. To test whether the identified metabolic changes were related to surgery-induced changes in catecholamine levels we performed a correlation analysis with urinary catecholamine values.

Results:
No significant correlations were identified between metabolite patterns and tumor localization, malignancy or catecholamine phenotype after correction for multiple testing. Comparing samples before and after surgery revealed 19 significantly altered metabolites (7 amino acids/biogenic amines, 9 glycerophospholipids, 2 sphingomyelins and hexose). In the separate analysis of female and patients with a noradrenergic tumor phenotype, significantly altered metabolites could be identified, in contrast to the male and patients with an adrenergic tumor phenotype, where no alteration could be found. Weak correlations for 12 of these 19 metabolites with urine catecholamine levels were identified.

Conclusion:
Using a targeted metabolomics approach, we could identify for the first time significant metabolic changes in blood from patients with PPGL after successful tumor removal. Our results widen the knowledge on the spectrum of metabolic changes in PPGL patients, which are not explained solely by catecholamine excess. The observed metabolic changes share similarities with published data on diseases associated with increased cardiovascular risk.

11

Clinical and Genetic Features of Familial Hypercholesterolemia in Eastern Switzerland

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Background/Introduction:
Familial hypercholesterolemia (FH) has been considered a classical monogenic disease following an autosomal dominant pattern of inheritance. However, it has been recognized within the last years that the hypercholesterolemia has a polygenic background in a substantial portion of patients with a clinical diagnosis of FH. Since the genetic background of FH may be well relevant to both family screening and treatment of individual patients we characterized both the clinical and genetic features of patients referred to our lipid clinic for suspected FH.

Methods:
Patients with an LDL-cholesterol (LDL-C) > 4.9 mmol/l and/or a Dutch Lipid Network Criteria (DLNC) Score > 2, indicating possible (3-5 pts.), likely (6-8 pts.) or definite (>8 pts.) FH , were offered molecular testing using a next-generation-sequencing technique for the presence of mutations in the LDL-receptor (LDLR, all exons)-, APOB (exon 26)- and PCSK9-gene (all exons). Patients with a pathogenic mutation (mut +) were considered having monogenic FH whereas those with a clinical diagnosis but no mutation (mut -) were considered having polygenic FH. Data are given as median and range. Descriptive statistics, Mann-Whitney and Chi-square tests are used as appropriate and a p<0.05 was considered significant.

Results:
62 patients were included. A pathogenic mutation in one of the candidate genes was found in 47% (LDLR 35%, APOB 10%, PCSK9 2%). Mut + patients had higher DLNC scores (7 pts. (2-16) vs 5 pts. (3-12), p=0.04) and LDL-C concentrations (6.9 mmol/l (4.9-10.6) vs. 5.8 mmol/l (4.6-13.0), p=0.01). Clinical cardiovascular disease (CVD) was present in 55% (95% CI 42-67) of the cohort and diagnosed at a median age of 46.5 years (34-64). In those with CVD, FH had not been recognized before the first cardiovascular event in 67% and only 21% had received primary preventive lipid lowering therapy with statins. Mutational status was not associated with the presence of CVD (mut + 55%, 95% CI 37-73, mut - 55%, 95% CI 38-72). 97% of the patients were on lipid lowering therapy including statins (95%), ezetimibe (61%) and PCSK9 inhibitors (24%) and a median 61% (26-89) reduction of LDL-C when compared to untreated baseline levels was observed at the last follow-up. Nevertheless, currently recommended LDL-C targets of < 2.6 and < 1.8 mmol/l for patients without and with CVD were achieved in 18 % (95% CI 4-32) and 35% (95% CI 19-51%) of the patients only.

Conclusion:
Since hypercholesterolemia has a polygenic background in a substantial portion of patients with a clinical diagnosis of FH both genetic and clinical screening is required to identify affected subjects. The optimal screening strategy for polygenic FH remains to be defined. Despite the availability of effective medical therapies a premature clinical cardiovascular event preceded the diagnosis of FH in more than 50% of the patients, indicating that a majority of patients with FH is still unrecognized and untreated. Although LDL-C reductions of up to 90 % may be achieved with combination lipid-lowering therapy, current LDL-C targets are met by a minority of FH patients. In summary, patients with FH are at very high cardiovascular disease risk and strategies to identify and appropriately treat affected patients need to be improved.

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Effects of Anti-Inflammatory Treatment on Fibroblast Growth Factor-21 in Obesity and Metabolic Syndrome

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Background/Introduction:
Fibroblast growth factor-21 (FGF21), which has recently been identified as a central regulator of metabolism, is known to be increased in conditions of obesity, insulin resistance, and fatty liver. Likewise, there is evidence that FGF21 increases with systemic inflammation. The aim of this study was to evaluate whether chronic low-grade inflammation might be the underlying mechanism and whether an anti-inflammatory treatment decreases FGF21 levels in metabolic disorders.

Methods:
This is a secondary analysis of two interventional studies of treatment with an Interleukin-1 (IL-1)-receptor antagonist anakinra (Kineret®) in patients with obesity and features of the metabolic syndrome. The CortIL trial was a prospective interventional trial (n= 61) investigating short-term effects of anakinra and dexamethasone in metabolic syndrome. The TestIL trial was a placebo controlled, double-blinded interventional trial (n=67) investigating longer-term effects of anakinra in metabolic syndrome versus placebo. FGF21 was measured at baseline, at day2 and at 4 weeks of treatment with anakinra. Furthermore, FGF21 levels were measured after dexamethasone suppression test.

Results:
Mean age of all includes patients (n=140) was 54 years (SD 12.1), 26% were female and the mean body mass index (BMI) was 37 kg/m2 (SD 4.8). Almost half of the patients were diabetic (45%) and had slightly increased c-reactive protein levels of 4.7 mg/L (SD 5.4), mirroring a state of chronic low-grade inflammation. FGF21 levels highly positively correlated with fasting glucose levels, HOMA-index, c-peptide levels, HbA1c and BMI.
Treatment with anakinra led to a short-term reduction of FGF21 levels by 49.0 pg/mL (95%CI, (-205.9) - 107.9); p=0.064; however, this effect was no longer visible at 4 weeks (between-group difference: -8.8 pg/mL (95%CI, (-130.9) - 113.3); p=0.89.
Short-term treatment with dexamethasone was associated with profound reduction of FGF21 by 174.5 pg/mL (95%CI, (-235.8) - (-113.2)); p<0.001.

Conclusion:
Anti-inflammatory treatment led to a reduction of FGF21 levels in individuals with obesity and features of the meatolic syndrome. Chronic low-grade inflammation may be one of the key mediators for increased FGF21 in metabolic disorders.

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Rare Cause of Pathological 17-OH-Progesteron Response after ACTH-Stimulation. Two case reports.

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Background/Introduction:
In the cortisol and aldosterone biosynthesis pathway 17-OH-Progesteron (17-OH-P) is the product of progesteron hydroxylation, which in further hydroxylation steps builds either cortisol or androstenedione within the adrenal glands. Enzymatic deficiencies in the downstream hydroxylation processes of 17-OH-P are mainly congenital (e.g. 21-hydroxylase deficiency causing congenital adrenal hyperplasia [CAH]), with subsequent elevation of the upstream steroids, where in less severe deficiencies levels of 17-OH-P are increased only after ACTH stimulation. Bilateral adrenal hyperplasia can occur in CAH over the years, mainly in undiagnosed and untreated patients with mild forms. However, enzymatic defects with increased 17-OH-P levels basal and after ACTH stimulation have been described in non-functioning adrenal adenomas and in primary bilateral macronodular hyperplasia [PBMAH].

Case Reports:
Two patients had incidentally discovered bilateral adrenal masses. A 44-year-old female patient with bilateral adrenal incidentaloma (3 and 5.4cm in diameter) had no findings of autonomous hormone secretion except of increased 17-OH-P level (basal 8.7 nmol/l, after ACTH stimulation 54.7 nmol/l) at the first endocrine visit. The findings were interpreted as adrenal hyperplasia due to late-onset CAH. After 8 years the patient was hospitalized with neurological deficits due to pseudotumor cerebri, where a slight increase of the adrenal nodules size was described. The endocrine work-up revealed a slight cortisol excess (inadequate cortisol suppression after dexamethasone, increased midnight salivary cortisol and repeatedly normal 24-hours cortisoluria). Within the 8 years she gained 5 kg (6.3% of her initial body weight) and developed mild depression. The patient was lost from follow-up and no further evaluations could be done. The second patient is a 60-year-old male with adrenal incidentalomas of 3.4 cm left and 8.3 cm right maximal diameter. At the same imaging a papillary renal cell carcinoma has been incidentally diagnosed and subsequently surgically removed. The endocrine work up showed a pathological 17-OH-P response (basal 4.5 nmol/l, stimulated 156.7 nmol/l) and mild hypercortisolism (normal midnight salivary cortisol, inadequate cortisol suppression after dexamethasone, slightly elevated 24-hours cortisoluria). The ACTH was found repeatedly to be suppressed and further work-up found aberrant excessive cortisol response to orthostatic test, as well as to vasopressin- and metoclopramide-stimulation suggesting aberrant presence of vasopressin and prolactin receptors. The diagnosis of mild hypercortisolism due to PBMAH was made. Germline mutation analysis of *ARMC5* and *FH* genes are pending.

Conclusion:
The clinical picture of PBMAH is that of bilateral adrenal incidentalomas, as it was in our cases. Increased basal and stimulated levels of 17-OH-P are very common, but in contrast to CAH, ACTH levels are generally suppressed and PBMAH may cause subclinical, cyclic and overt hypercortisolism over time, rather than hypocortisolism. Screening for hypercortisolism at baseline and during follow up is mandatory. Surgery is the main treatment option for hypercortisolism, with in few cases necessitating subsequent bilateral adrenalectomy over time. Specific pharmacological options (beta-blocker, somatostatin analogues) for patients with aberrant stimuli response have been addressed. The pathophysiological processes leading to PBMAH and cortisol hypersecretion are incompletely elucidated. Intra-adrenal ACTH production, defects in intracellular regulation of cAMP, as well as presence of aberrant receptor causing cortisol hypersecretion after distinct, non-physiological stimuli has been in part described, the latter found also in our patient. Hereditary forms associated with germline mutations in *ARMC5* and *FH* genes, have been acknowledged.

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How does source matter?
Perceptions of Interprofessional Feedback in Workplace-based Assessments in Diabetology

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Background/Introduction:
Diabetes care is inherently interprofessional, and interprofessional collaboration is recognized as essential for quality patient care. Interprofessional teamwork should include interprofessional feedback, but literature on receptiveness to interprofessional feedback in the context of workplace-based assessment is sparse.

Methods:
From 2016 to 2017, all health care professional of our Department of Diabetology participated in interprofessional education sessions about diabetes-specific topics as well as about feedback in medical education. During the period from September 2017 to January 2018, all residents conducted four workplace-based assessments under direct observation of a senior physician and a team member from anonther healthcare profession (diabetes nurse, nutritionist, psychologist). An assessment form that specifially adresses the needs of interprofessional feedback in Diabetology has been developed.Immediately after the patient encounter the residents received written and oral feedback from both observers.From February to March 2018 three focus group interviews were conducted, audiorecorded and transcribed.

Results:
Using a constructivist grounded theory approach, the data was analized qualitatively against the background of social identity theory to unravel receptivity to interprofessional feedback, the perceived benefit on performance improvement and its impact on interprofessional collaboration. Despite attaining a firm professional identity, residents in our postgraduate subspecialty training in Diabetology maintain a positive attitude towards interprofessional feedback. Among the several factors modifying the complex relationship between feedback and performance improvement, the trustworthiness and the perceived competence of the feedback source are more important than professional affiliation. All participant of the study perceived a benefit on interprofessional collaboration and patient care after participating in interprofessional workplace-based assessments.

Conclusion:
This qualitative research study in medical education adds to our understanding about receptivity to interprofessional feedback and collaboration in a postgraduate subspecialty training.

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Efficacy and Safety of an Expanded Dulaglutide Dose Range: A Phase 2, Placebo-controlled Trial in T2D Patients on Metformin

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Background/Introduction: Dulaglutide is approved at two doses (0.75 and 1.5 mg) for treatment of T2D. There has been limited assessment of higher doses. We hypothesized that higher doses of dulaglutide may provide further improvement in glucose and body weight control. In this study, 3 and 4.5 mg doses were evaluated for safety/efficacy after 18 weeks (wks) of treatment, including a 6-wk dose escalation.

Methods: Patients (N=318) on ≥1500 mg metformin, were randomized (1:1:1:1) to placebo (n=82), dulaglutide 1.5 mg (n=81), dulaglutide 3 mg (n=79), dulaglutide 4.5 mg (n=76). The primary objective was superiority of dulaglutide doses over placebo in HbA1c reduction at 18 wks.
Results: Table 1 presents the primary and selected secondary efficacy data. Reductions in HbA1c and body weight were significant for each dose vs placebo. Incidence of gastrointestinal events (mostly mild to moderate) were dose-dependent for nausea (placebo, 4.9%; dulaglutide 1.5 mg, 22.2%; dulaglutide 3 mg, 24.1%; dulaglutide 4.5 mg, 30.3%) but not for vomiting (placebo 4.9%; dulaglutide 1.5 mg, 11.1%; dulaglutide 3 mg, 10.1%; dulaglutide 4.5 mg, 13.2%). No patients experienced severe hypoglycemia.

Conclusions: The results of this trial show that 3 mg and 4.5 mg doses, compared to the 1.5 mg dose, may provide additional glycemic benefit and weight reduction with an acceptable safety profile in treatment of T2D patients, providing support for further phase 3 development.
Table 1: Summary of HbA1c and body weight data

Parameters	Placebo (n=82)	Dulaglutide 1.5 mg (n=81)	Dulaglutide 3 mg (n=79)	Dulaglutide 4.5 mg (n=76)
HbA1c (%)[a]				
Baseline, mean (SD)	8.10 (0.80)	8.02 (0.81)	8.20 (0.93)	8.13 (0.81)
Week 18, LS mean (SE)	7.67 (0.10)	6.85 (0.09)	6.63 (0.10)	6.59 (0.10)
LS mean (SE) change from baseline	-0.42 (0.10)	-1.24** (0.09)	-1.47** (0.10)	-1.50** (0.10)
LS mean change difference vs placebo	-	-0.82	-1.04	-1.08
Body weight (kg)[a]				
Baseline, mean (SD)	94.5 (22.9)	87.5 (17.0)	96.4 (22.6)	89.3 (18.8)
Week 18, LS mean (SE)	90.8 (0.41)	89.5 (0.40)	88.2 (0.41)	88.0 (0.43)
LS mean (SE) change from baseline	-1.6 (0.41)	-2.9** (0.40)	-4.2**(0.41)	-4.4** (0.43)
LS mean change difference vs placebo	-	-1.3	-2.6	-2.8

HbA1c=glycated hemoglobin; LS=least-squares; SE=standard error; a=mixed-model repeated measures analysis, intent-to-treat population on treatment without postrescue data; **=p<0.001 for dulaglutide compared to placebo

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Follicular thyroid carcinoma manifesting as a solitary intracranial metastasis 19 years after thyroidectomy

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Background/Introduction:
Intracranial metastases of differentiated thyroid cancers are rare, with an incidence of 0.7-1.3%. Hereby, we report the case of a patient with a solitary skull base metastasis manifesting 19 years after initial treatment by thyroidectomy.

Case report:
A 72 year old woman presented with a two week history of right-sided peripheral facial nerve palsy. MRI showed an intracranial, contrast enhancing lesion on the apex of the right petrosus bone (2.8 x 2.9 x 2.2 cm), infiltrating the facial nerve and the internal meatus acusticus, and extending into the posterior fossa. An atypical meningeoma was initially suspected. The patient underwent tumor debulking via retrosigmoidal craniotomy. Histopathological examination surprisingly revealed metastasis of follicular thyroid carcinoma.
On review of her medical records, the patient had undergone left-sided hemithyroidectomy in 1999 for treatment of hyperthyroidism due to a scintigraphically "hot" nodule. On histopathology, a follicular thyroid carcinoma with papillary nuclear features (pT2b, max 3.5 cm) was described. The patient underwent completion thyroidectomy and no additional malignancy was found. She did not receive treatment with radioactive iodine and did not have follow-up thyroglobulin measurements. Current thyroglobulin was elevated (3587 ng/ml) with slighlty positive Anti-Thyroglobulin-Antibodies (139 U/ml); cervical ultrasound showed minimal residual thyroid tissue (ca. 0.8 ml) of normal appearance and no suspicious lymph nodes.
After surgical debulking of the intracranial metastasis, the patient received adjuvant radiation therapy of the residual metastatic tissue (5x7 Gy). She then underwent treatment with radioactive iodine (7.522 GBq I-131) after administration of recombinant human TSH (rhTSH). Post-therapy whole-body scan showed a highly increased uptake of the intracerebral metastasis and an increased uptake of the residual thyroid tissue with no other sites affected.

Conclusion:
Recurrence of follicular thyroid carcinoma can occur even many years after thyroidectomy. Rarely, it manifests as a solitary intracranial metastasis. It is therefore important to consider the possibility of a metastatic lesion in any patient with focal neurological signs and a personal history of thyroid carcinoma.

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The burden of inpatient diabetes at the University Hospital Bern – Insights provided by the Clinical Data Warehouse System

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Background/Introduction:
The proportion of persons with diabetes is rapidly increasing, as is the proportion of inpatients with the disease. Given the strong association between dysglycaemia and adverse medical outcomes, insight into the prevalence of diabetes in hospital, patient characteristics and indicators of diabetes care is required to ensure adequate glycaemic management. For this purpose, integrated data platforms such as the Clinical Data Warehouse System (CDWH) of the University Hospital Bern have been implemented with required IT capabilities to extract, analyse and summarize large-scale inpatient data within pre-defined time periods in a standardised manner.

Methods:
Data were obtained from the CDWH of the University Hospital Bern via the Insel Data Coordination Lab. Cases with diabetes in hospital were identified based on ICD10 codes, laboratory values (HbA1C≥6.5%, random glucose>11mM) and prescribed glucose-lowering medication between 1st March 2017 and 1st March 2018. Annual inpatient diabetes prevalence was calculated as the percentage of identified patients with diabetes in hospital relative to all admitted patients within that year, overall as well as for age classes ≥18yrs (adult) and >65yrs (elderly). Patient-specific blood glucose (BG) values during hospitalization were stratified into the following glycaemic ranges: 5.6-10.0mM (target range), <3.9mM (hypoglycaemia) and >16.7mM (significant hyperglycaemia).

Results:
Amongst 47,089 patients admitted to the University Hospital Bern within the analysed 12 months, diabetes was identified in 8,522 persons, translating into a prevalence of 18.1%. The prevalence was 21.4% for the adult (≥18yrs) and 31.4% for the elderly (>65yrs) population. The proportion of women in the diabetic cohort was 39%, mean age was 66.2(17.4)yrs and mean BMI 28.1(6.6)kg/m2. Of the 8,522 patients, 58.3% had type 2 diabetes and 2.9% had type 1 diabetes according to ICD10 codes. In 33% of patients, the diabetic status in hospital was not recorded. Regarding diabetes treatment, 52.0% received insulin therapy and 39.9% non-insulin agents (of whom 62% concomitantly treated with insulin). Metformin (23.7%) was the most commonly prescribed non-insulin medication, followed by DPP4-inhibitors (9.6%). Mean HbA1c across all patients with diabetes in hospital was 6.9%. Mean frequency of BG testing was 2.1 times daily, amongst insulin-treated patients 2.2 times daily. Patient-day weighted mean BG was 8.6mM. The mean proportion of BG measurements in target range (5.6-10.0mM) was 67%, while 10.3% of the measurements per patient were <3.9mM and 20.1% >16.7mM. Occurrence of BG events <3.9mM and >16.7mM were inversely correlated with frequency of blood glucose monitoring (both p<0.001).

Conclusion:
The burden of diabetes in hospital is remarkable with major impact on patient health and health care expenditure. Knowing about the prevalence of inpatient diabetes and glucose control during hospitalisation helps identifying areas requiring optimisation of diabetes care. Adequate glucose monitoring on site and centralised surveillance systems using novel data infrastructure may lead to better diabetes care in hospital.

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Impact of Flash Glucose Monitoring on HbA1c in pediatric type 1 diabetes patients

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Background/Introduction:
Flash glucose monitoring (FGM) offers rapid information on interstitial glucose levels and trends. Data on safety and effect on glycemic control in children is scarce. We evaluated the impact of FGM use on HbA1c in a pediatric population.

Methods:
We analyzed retrospectively data from 21 patients with type 1 diabetes using the FGM system routinely as part of their treatment at the University Children's Hospital Basel. Inclusion criteria were 1) diagnosis of type 1 diabetes >12 months, 2) continuous 18 months follow-up divided into a complete 9 months pre-FGM observation period without CGM use and a 9 month observation period starting with the first day of FGM use. HbA1c data were retrieved from the patient files and parameters of FGM use (scans per day and 24 hour coverage (%)) were downloaded from the FGM system. The primary outcome was change of HbA1c after start of FGM. HbA1c was documented for each patient at three time points during the pre-FGM period and at three time points after initiation of FGM.

Results:
The observational period was 18 months for each patient with 6 HbA1c measurements in total (31.5 patient years). Mean age of the study population was 13 years and 3 months, mean duration of diabetes was 6 years and 3 months. Twelve patients were using intensified conventional insulin therapy (ICT) and 9 insulin pumps (CSII). Use of FGM had no impact on glycaemic control measured as mean HbA1c over the 9 months of FGM use compared to the pre-FGM 9 months observational period. However, HbA1c was correlated with number of scans/day (r square 0.13, p<0.05), and with 24 hour coverage (r square 0.27, p <0.001). Piecewise linear regression analysis revealed that correlation was significant between HbA1c and <10 scans/day (r square 0.17, p<0.05), while HbA1c was not correlated to number of scans if the number of scan was >10/day (r square 0.02, p 0.51).

Conclusion:
FGM use over 9 months did not improve glycaemic control in the pediatric study population. However, HbA1c was correlated with number of scans per day, this effect being most pronounced with less than 10 daily scans.

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Clinical features of 35 patients with 172 spontaneous vertebral fractures after denosumab discontinuation: a single center observational study

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Background/Introduction:
In the absence of bisphosphonate treatment, denosumab discontinuation (DD) induces an increase of B-crosslaps above baseline values for two years, and a complete or partial loss of the BMD gain after one year. This rebound effect is associated with spontaneous clinical vertebral fractures (SCVF) in 1 to 10% of patients. We report the clinical characteristics of 35 patients with SCVF after DD evaluated at our center from July 2015 to March 2018.

Methods:
We report the cases of 35 patients who received denosumab 60mg every 6 months for 2 to 11 doses. All were on calcium and vitamin D during and after DD. VF have been documented by MRI. A wide biological assessment, performed at the time of fracture, was strictly normal. A secondary cause of osteoporosis was excluded. Patients did not received any osteoporosis treatment between DD and the onset of SCVF.

Results:
Thirty-four women and one man, 66.3±9.6 years, experienced 172 SCVF (median 5) in the 11.6±2.8 months (median 11; min 7, max 20) following the last denosumab injection. Eight women received a bisphosphonate before Denosumab, and nine women received aromatase-inhibitors (AI) with denosumab. Eleven women had prevalent osteoporotic fracture. Twelve women had vertebroplasties with 58 new SCVF in the following days. The mean B-crosslaps value at the time of SCVF was 1523±588 ng/l; B-crosslaps values increase with the number of denosumab doses (R2=0.28). The number of SCVF was inversely associated with age: 5.4±2.0 vs 2.8±1.3, < vs > 65 years (p<0.001). The delay between DD and the occurrence of SCVF increases with age: 10.4±1.3 vs 12.7±2.6 months, < vs > 65 years (p=0.008). The mean reasons for DD were end of AI or no more osteoporosis (15), omission (7), patient's wish (5), atypical femoral fracture or dental intervention (4).

Conclusion:
After denosumab discontinuation, women < 65 years have a higher number of SCVF and in a shorter period than women over 65 years. SCVF are a very severe and frequent clinical complication after DD. A close follow-up for 2 years after DD is necessary. Bisphosphonates may decrease the rebound effect at DD. Studies are urgently needed to better define who and when to treat with denosumab, as well as strategies to avoid SCVF after denosumab discontinuation.

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Identification of a novel THRβ mutation affecting GRIP1 interaction in a patient with resistance to thyroid hormone

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Background/Introduction: Resistance to thyroid hormone (RTH) is a rare but important condition characterized by elevated free thyroid hormones (TH) in the presence of inadequately normal or even increased TSH levels. Patients most often have only mild or no symptoms. We describe a clinically euthyroid female patient with multinodular goiter who presented with elevated TH and normal TSH.

Methods:
Resting energy expenditure as assessed by indirect calorimetry was mildly elevated suggesting resistance to TH. In order to confirm the diagnosis we sequenced the *THRB* gene and found a novel mutation in exon 10 affecting a highly conserved amino acid (L456F). In silico analysis was performed based on the crystal structure of THRβ in complex with GRIP1 revealing a structural change in the binding-site of the receptor. Modeling of the L456F variant was performed with SwissModel, and RASMOL was used for structure analysis and visualization

Results: Exchange of leucine to phenylalanine (L456F) leads to steric clashes, which are expected to cause a conformational rearrangement of the C-terminus. This will result in a loss of interaction between the TH receptor and GRIP1and consequently leading to weaker coactivator binding.

Conclusion: This is the first report of a mutation of *THRB* leading to an impaired GRIP1-coactivator binding as the most likely reason for RTH observed in our patient.

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Remission of hypercortisolism after unilateral adrenalectomy in a patient with Carney complex and primary pigmented nodular adrenocortical disease

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Background/:
Primary pigmented nodular adrenocortical disease (PPNAD) is the rarest form of ACTH-independent cushing syndrome (CS) and can be associated with endocrine and non-endocrine tumors, forming the Carney complex (CNC). CNC is a multiple neoplasia syndrome with autosomal dominant inheritance, associated with germline mutations in PRKAR1A, the protein kinase A regulatory subunit type 1 alpha gene. CNC is characterized by the presence of myxomas, spotty skin pigmentation and endocrine overactivity.

Case presentation:
The endocrine workup in a 26 year old previously healthy male referred because of newly diagnosed grade III hypertension led to the diagnosis of ACTH-independent hypercortisolism. Subsequent MR-imaging showed a 5 mm left-adrenal nodule and a normal right gland. Since the clinical exam, in addition to very subtle cushingoid features, was remarkable for facial lentiginosis primary pigmented nodular adrenal disease associated with Carney complex was suspected despite a negative family history. The further extensive workup demonstrated no further manifestations of the syndrome. Genetic testing revealed a not yet described variant of unknown significance in the gene encoding the regulatory subunit of protein kinase A (PRKAR1A). Since we failed to confirm the diagnosis of PPNAD associated with CNC both clinically and by genetic testing and a NP-59 scintigraphy showed exclusively left-sided tracer uptake, the patient underwent unilateral left adrenalectomy. Intraoperatively, the right adrenal appeared brownish discolored and histopathological analysis confirmed pigmented micronodular disease, thereby establishing the diagnosis of CNC. Postoperatively, a full clinical and biochemical remission of hypercortisolism was observed and hydrocortisone replacement was discontinued within 3 months after surgery..

Conclusion:
Despite the final diagnosis of PPNAD and hence CNC, a full clinical and biochemical remission was achieved and the patient currently has a normal adrenal function with no need for hormone replacement therapy one year after left adrenalectomy. Therefore, unilateral surgery and close follow-up may be appropriate in selected patients with PPNAD associated with CNC and imaging results pointing to predominantely unilateral disease. This view is compatible with case reports describing long-lasting remissions of cushing's syndrome associated with PPNAD for up to 27 years following unilateral adrenalectomy. This approach may spare patients from hypoadrenalism and its sequelae for extended time periods.

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Postpartum isolated IgG4-related hypophysitis, a master of imitation.

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Background:
IgG4-related hypophysitis is a very rare condition with <100 cases described to date. IgG4-related disease is an immune-mediated tumor-like multiorgan disease characterized by dense lymphoplasmacytic infiltrates with abundant IgG4 positive polyclonal plasma cells in varying tissues and often elevated IgG4 serum levels, occurring primarily in elderly males.

Case presentation:
We present the case of a 33-year-old female who suffered sudden diplopia and headaches two weeks after the delivery of her first child. Clinical exam upon admission revealed a paresis of the right abducens nerve with normal peripheral vision. Brain magnetic resonance imaging (MRI) showed a largely cystic intra- and suprasellar lesion compatible with a partially necrotic macroadenoma. An endocrine workup was unremarkable with no evidence for hypopituitarism or diabetes insipidus. Selective endoscopic transsphenoidal decompression resulted in immediate recovery of the diplopia. The subsequent histological workup of the intraoperative biopsy was indicative of a Rathke's cleft cyst. Postoperatively desmopressin was begun because of new-onset partial diabetes insipidus with no evidence for anterior pituitary impairment. About two years after the initial presentation the headaches and diplopia recurred and a repeat MRI demonstrated a mostly solid, inhomogenously contrast enhancing sellar mass with bilateral cavernous sinus involvement. Repeat transsphenoidal decompression resulted in recovery from the diplopia. At this time the histological exam revealed granulation tissue with necrosis, lymphoplasmacytic infiltration and IgG4-immunoreactivity of an elevated number of plasma cells in the infiltrate. Serum IgG4 concentrations were increased (177 mg/dl, normal <135 mg/dl) and a diagnosis of isolated IgG4-related hypophysitis was established after further organ involvement had been excluded by MR imaging. Shortly thereafter, the course was complicated by repeat diplopia, new-onset thyrotroph and corticotroph insufficiency and a course of high-dose oral prednisone was started leading to rapid recovery of the diplopia and partial shrinkage of the sellar mass. However, clinical signs recurred whenever the prednisone dose was tapered below 15 mg/day and azathioprine 150 mg/day was added as an alternative immunosuppressant. Thereafter, the course was favorable with resolution of the clinical signs, impressive shrinkage of the intra- and parasellar mass and partial recovery of the corticotroph axis after prednisone had been discontinued.

Conclusion:
This case demonstrates the protean nature of IgG4-related hypophysitis, mimicking radiologically a macroadenoma and histologically a Rathke's cleft cyst in a young female patient, not at all fitting the typical demographic presentation of this disease. Azathioprine may be an effective alternative immunosuppressant if glucocorticoids fail to achieve clinical and structural remission.

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Evaluation of routine molecular testing of fine needle aspirate samples from cytologically indeterminate thyroid nodules using a 7-gene panel

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Background/Introduction:
Fine-needle aspiration (FNA) is the single most important diagnostic tool in the work-up of thyroid nodules (TN). The majority of those nodules are found to be benign upon cytological analysis, whereas 5 – 15% are malignant. The remaining TN (20 – 30%) are classified as indeterminate (Bethesda category III, IV or V). Only 15 – 35% of indeterminate TN prove to be malignant on subsequent histological examination, which results in uncertainties regarding their management. Many thyroid tumors harbor characteristic genetic alterations, such as mutations in the BRAF and RAS genes, and translocations of the RET and PAX8 genes, which may be used as diagnostic markers. We aimed to evaluate the performance of a previously described 7-gene panel to preoperatively diagnose thyroid malignancy on FNA samples of cytologically indeterminate TN.

Methods:
Patients with indeterminate TN (Bethesda III, IV or V) from a single institution (Kantonsspital St.Gallen) were included. Molecular testing was performed using the Thyroid Cancer Mutation Analysis Kit (EntroGen) and the Thyroid Cancer Fusion Gene Detection Kit (EntroGen), which can detect hotspot mutations in the BRAF, KRAS, NRAS and HRAS genes, and RET/PTC1, RET/PTC3 and PAX8/PPARG fusion gene variants, respectively. Detection of a mutation or fusion gene variant was considered a positive test result. Patients with subsequent partial or total thyroidectomy were identified and histopathology reports were retrieved. Sensitivity, specificity, negative (NPV) and positive predictive values (PPV) were estimated using the histological diagnosis as the gold standard.

Results:
A total of 145 patients with 157 indeterminate TN (Bethesda III: 71; IV: 66; V: 20) were included in the study (mean age, 55 years; 105 females [72%]). Molecular testing was conclusive in 152 TN and revealed a mutation or translocation in 34 cases (22%). Positive test results included 33 point mutations (BRAF: 12, KRAS: 1, NRAS: 15, HRAS: 5) and one fusion gene variant (PAX8/PPARG). Partial or total thyroidectomy was performed on 104/157 (66%) TN, for which histological evaluation revealed 75 benign lesions (hyperplastic nodule: 28; follicular adenoma: 46; NIFTP: 1) and 29 malignant tumors (papillary carcinoma: 22; follicular carcinoma: 4; medullary carcinoma: 1; anaplastic carcinoma: 1; malignant teratoma: 1). A positive 7-gene panel test result had a sensitivity of 41% and a specificity of 81% to identify thyroid malignancy. The NPV and PPV were 77% and 46%, respectively. For the individual genetic alterations, the PPV varied between 0% and 100%.

Conclusion:
Our results demonstrate that molecular testing using a 7-gene panel can improve the diagnostic outcome of cytologically indeterminate TN, however largely depending on the genetic alteration found.

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Effects Of Once-weekly Treatment With Somapacitan: A Randomised, Double-blind, Placebo-controlled And Open Active-controlled Study In Adult Growth Hormone Deficiency

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Background/Introduction:
Daily injection of growth hormone (GH) replacement represents a barrier to treatment for some adult growth hormone deficiency (AGHD) patients. Somapacitan is a reversible albumin-binding GH derivative developed for once-weekly administration. In somapacitan, fatty acids with noncovalent albumin-binding properties have been conjugated by alkylation to GH in order to bind endogenous albumin, resulting in an extended half-life of the molecule. The primary objective of this trial (NCT02229851) was to demonstrate the efficacy of once-weekly dosing of somapacitan versus placebo after 34 weeks' treatment in patients with AGHD. The secondary objective was to evaluate the clinical safety of once-weekly dosing of somapacitan.

Methods:
Patients with AGHD (n=301) were randomised 2:2:1 to one of three treatment arms: once-weekly somapacitan, once-daily somatropin (Norditropin® FlexPro®, Novo Nordisk A/S, Denmark), or once-weekly placebo for 34 weeks. Body composition was measured using dual-energy X-ray absorptiometry; the primary endpoint was change from baseline to week 34 in truncal fat percentage. Insulin-like growth factor I (IGF-I) was assessed at each study visit and IGF-I standard deviation scores (SDS) calculated. Safety was assessed from reporting of adverse events (AEs), glucose homeostasis, and antibody development. A comparison between somapacitan and once-daily somatropin was included to help judge the clinical relevance of any differences between somapacitan and placebo.

Results:
Serum IGF-I SDS increased significantly with weekly somapacitan versus placebo. Change in IGF-I SDS from baseline to week 34 did not differ between somapacitan and somatropin. The change in truncal fat percentage was significantly greater with somapacitan than with placebo, confirming superiority of somapacitan over placebo (estimated difference: –1.53% [–2.68; –0.38]; p=0.0090). Somapacitan also showed statistically significant beneficial effects compared with placebo on: visceral adipose tissue, android fat mass, lean body mass, truncal lean body mass and appendicular skeletal muscle mass.
The incidence and severity of AEs in patients treated with somapacitan were similar to those observed in the study patients who were randomised to somatropin. The majority of AEs were of mild/moderate severity and reported as unlikely to be related to trial products. All injection site reactions were evaluated as mild or moderate. No anti-somapacitan antibodies or anti-human GH antibodies were detected.

Conclusion:
In patients with AGHD, somapacitan administered once weekly significantly reduced truncal fat percentage and improved other body composition parameters versus placebo, and tolerability was similar to that with daily injections. These findings indicate that somapacitan may provide a weekly treatment alternative for patients with AGHD.

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Towards an integrated approach for the diagnosis of 46,XY disorder of sex development.

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Background/Introduction:
46, XY disorders of sex development (DSD) are rare clinical and genetically heterogenous conditions. Although complete androgen insensitivity syndrome (CAIS) has a strong genotype-phenotype correlation, the other subtypes of 46, XY DSD are less well-defined and thus the precise diagnosis is challenging. Targeted gene panels are now used in the diagnostic algorithms of DSD on a routine basis. This study focused on identifying the relationship between clinical assessment and genetic findings in a pediatric cohort of 33 well-phenotyped patients.

Methods:
The study group consisted of 35 patients (33 probands) with 46,XY DSD who were referred to a single specialist paediatric endocrinology centre due to atypical genitalia or improper puberty. The appearance of external genitalia was described using external masculinisation score (EMS), and endocrine profiling included serum sex steroids, gonadotrpins, AMH and Inhibin B levels. Transabdominal ultrasound examination was used to visualize internal genitalia. Targeted gene panel sequencing consisting of 37 genes known to underly 46,XY DSD was performed.

Results:
Based on clinical findings including EMS, the cohort was classified into (i) disorder of gonadal development (n=9); (ii) disorder of androgen synthesis (n=4); (iii) disorder of androgen action (n=14); and (iv) syndromic DSD (n=8). Using an integrated approach, the genetic findings in 12 children confirmed our clinical assessment (34%). However, in 13 children (37%), a variant of uncertain significance (VUS) was identified, mainly due to a discrepancy between the genetic results and the phenotype.
The correlation between clinical and genetic findings was higher in patients with a more severe phenotype (low EMS). In 3 patients (9%), the genetic studies guided further clinical assessment which resulted in a refined diagnosis. Furthermore, we identified 7 patients (20%) harboring rare variants in more than one DSD genes.

Conclusion:
Using an integrated approach, our study shows a clinical and genetic correlation in > 30% of the patients, especially in the most affected patients (low EMS). The identification of a subset of patients with more than one rare variant in the known DSD genes is intriguing and suggests the possibility of oligogenicity in DSD.

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Gestational Diabetes Mellitus as a Potential Risk Factor for Metabolic Syndrome in the Early and Late Postpartum Period – A prospective cohort study

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Background/Introduction:
Gestational diabetes mellitus (GDM) is associated with an increased risk of future diabetes mellitus, however little is known about the development of other cardiovascular risk factors in women with GDM. The aim of this study was to assess the changes in prevalence of the metabolic syndrome (MetS) and its components in a cohort of women with GDM followed during pregnancy to 1 year postpartum (PP). We also assessed possible predictors of the MetS.

Methods:
We prospectively evaluated 622 women with GDM followed at the CHUV between June 2011 and December 2017 who completed the 6-8 weeks PP follow-up visit. A subgroup analysis of patients at 1 year PP (n = 162) visit was also conducted. The International Diabetes Federation's definition of MetS and its components were used. MetS was defined with either waist circumference (WC) > 80 cm (MetS-WC) or body mass index (BMI) > 30 kg/m2 (MetS-BMI). We used both criteria, as WC can change in the early PP period.

Results:
At the first GDM visit (24-28 weeks of gestational age), the mean age was 33.2 ± SD 5.4 years, the mean weight 79.8 ± 15.1 kg (i.e. a weight gain of 10.4 ± 5.5 kg from the pre-pregnancy, $p < 0.001$) and the mean BMI before pregnancy was 25.9 ± 5.3 kg/m2. At 6-8 weeks PP, MetS-BMI was found in 10% and MetS-WC in 24% of patients. The prevalence of other MetS components were: 30% for low HDL-cholesterol, 23% for high triglycerides, 16% for elevated blood pressure and 13% for increased fasting glucose. The mean HbA1c was 5.4 ± 0.4%.

In the subgroup analysis, the prevalence of MetS-BMI increased from 8% to 34% and MetS-WC from 22% to 32% between 6-8 weeks and 1 year PP (both $p \leq 0.001$). Specifically, fasting glucose increased by 0.5 ± 0.6 mmol/l, while WC decreased by 2.6 ± 7.6 cm, triglycerides by 0.1 ± 0.6 mmol/l and HDL-cholesterol by 0.1 ± 0.3 mmol/l (all $p \leq 0.005$). BMI and blood pressure did not change significantly. The prevalence of obesity increased from 20% before pregnancy to 32% at 1 year PP ($p \leq 0.001$).

Predictors of MetS at 6-8 weeks PP were BMI before pregnancy, BMI at first visit, HbA1c at first visit and diastolic blood pressure at first visit (all $p \leq 0.05$). At 1 year PP, only BMI before pregnancy or at first visit predicted the development of MetS ($p \leq 0.003$).

Conclusion:
GDM may be a potential risk factor for MetS after pregnancy. The prevalence of MetS increased after 1 year PP, mainly due to a marked increase in obesity prevalence and fasting glucose. Exploring additional predictors of MetS during and before pregnancy would be beneficial for targeted interventions.

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Real-world impact of insulin glargine 300 U/mL in patients with type 2 diabetes uncontrolled on oral therapy: glycemic target achievement in Switzerland

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Background/Introduction:
Insulin glargine 300 U/ml (Gla-300) is a second-generation once-daily basal insulin with a flatter pharmacodynamic and pharmacokinetic profile with a longer duration of action as compared to insulin glargine 100 U/ml (Gla-100). These properties have been shown to translate into clinical advantages in terms of an effective HbA1c reduction with a lower rate of hypoglycemia in randomized controlled trials of Gla-300 vs Gla-100. In this study we assessed the real-world effectiveness and safety of Gla-300 in Switzerland.

Methods:
Toujeo-1 was a prospective, observational multicenter study that explored the real-world effectiveness of Gla-300 in adult patients with type 2 diabetes (T2D) uncontrolled (HbA1c 7.5-10%) on oral therapy in Germany and Switzerland. Primary endpoint (EP) was the rate of patients achieving individual HbA1c targets after 6 and 12 months, respectively. Secondary EPs included changes in HbA1c, fasting plasma glucose (FPG), body weight (BW) and insulin dose as well as hypoglycemia incidence and safety. Here we report the results for the Swiss patient cohort at 12 months.

Results:
The documented 47 Patients (14 women) had a mean age of 64 years, a mean diabetes duration of 8 years, a mean body mass index (BMI) of 32kg/m2 and were predominantly treated with metformin monotherapy (64%) or a combination of metformin and DPP-4 inhibitors (32%). The mean individual HbA1c target selected by the investigators was 7.4%. Effectiveness and hypoglycemia EPs are shown in the table below. After 12 months of therapy Gla-300 significantly reduced HbA1c by 1.5% ($p<0.0001$) reaching a mean final HbA1c of 7.2%. Likewise, Gla-300 significantly reduced FPG by 3.3 mmol/L ($p<0.0001$) reaching a mean final FPG of 7.1 mmol/L. After one year 70% of patients achieved their individual HbA1c target, 15% achieved FPG ≤ 6.1 mmol/L and 47% achieved FPG ≤ 7.2 mmol/L. Gla-300 was uptitrated to a mean dose of 31 units/day after one year. BW remained stable throughout the study and only one confirmed symptomatic hypoglycemic event was documented. No case of severe hypoglycemia was reported.

Conclusion:
Gla-300 significantly improved glycemic control and allowed the majority of patients with uncontrolled T2D to effectively achieve their individual HbA1c targets with a very low rate of hypoglycemia under real-world conditions in Switzerland.

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Quality of blood glucose control and complications in glycogen storage disease type I: data from the Swiss registry

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Background/Introduction:
Regular carbohydrate intake to avoid hypoglycemia is the mainstay of dietary treatment in glycogen storage disease type 1 (GSDI). The aim of this study was to evaluate the quality of dietary treatment and glucose control in a Swiss cohort of GSDI patients, in relation to the presence of long-term complications.

Methods:
Data of 25 patients (22 GSDIa, 3 GSDIb, median age 20y) from the Swiss hepatic glycogen storage disease registry were analyzed cross-sectionally. Frequency and type of hypoglycemia symptoms were assessed prospectively using a structured questionnaire. Continuous glucose monitoring (CGMS) was performed as part of usual clinical care to assess metabolic control in 14 patients.

Results:
Although maintenance of euglycemia is the primary goal of dietary treatment, few patients (n=3, 13%) performed capillary blood glucose measurements regularly. Symptoms of hypoglycemia were present in 13 patients (57 %), but CGMS revealed periods of low glucose (< 4mmol/l) in all patients, irrespective of the presence of symptoms. GSDIa patients with liver adenomas showed a higher frequency and area under the curve (AUC) of low blood glucose than patients without adenomas (frequency 2.7±0.8 vs 1.5±0.7 per day, AUC 0.11±0.08 vs 0.03±0.02 mM/d; $p< 0.05$). The presence of microalbuminuria was also related to the frequency of low blood glucose. Z-scores of bone density correlated negatively with lactate levels.

Conclusion:
The quality of glucose control is related to the presence of typical long-term complications in GSDI. Many patients experience episodes of asymptomatic low blood glucose. Regular assessment of glucose control is an essential element to evaluate the quality of treatment, and increasing the frequency of glucose self-monitoring remains an important goal of patient education and motivation. CGMS devices may support patients to detect fluctuations of serum glucose in everyday life and to optimize dietary therapy.

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Combined checkpoint inhibitor therapy nivolumab and ipilimumab causes Type 1 diabetes mellitus: two case reports

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Background/Introduction:
The use of checkpoint inhibitor (CI) therapy is becoming a standard of care for several cancers. Monoclonal antibodies targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death-protein 1 (PD-1) or its ligand (PD-L1) all activate the immune system but also cause a broad spectrum of autoimmune adverse events including endocrine toxicities. This latter occurs in nearly 20% of patients and are drug-specific. The most common endocrinopathies are anti-PD-1/PD-L1 induced-thyroid disorders and anti-CTLA-4-induced hypophysitis. Autoimmune diabetes mellitus were reported mainly in the setting of single agent anti-PD-1 therapy. Recently an immunotherapy-combined protocol with an anti-CTLA-4 agent (nivolumab) and an anti-PD-1 agent (ipilimumab) (NIV-IPI) has been validated. This combination of drugs is very efficient but potentially increases the incidence of autoimmune adverse events.

Methods:
Herein, we present one case of new-onset type 1 diabetes mellitus (T1DM) and one case of conversion from type 2 diabetes mellitus (T2DM) to a T1DM following combination CI therapy

Results:
Case 1: A 60 year-old man with a history of T2DM for seven years, well controlled on two oral antidiabetic medications, was diagnosed with metastatic melanoma. Combined immunotherapy with NIV-IPI was initiated in June 2017. Two weeks after the first therapy cycle, he was admitted in the emergency room for severe symptomatic diabetic ketoacidosis (DKA): blood glucose >41.6 mmol/l, serum bicarbonate 5.9 mmol/l, anion gap 33.1 mmol/l. Positive anti-glutamic acid decarboxylase (GAD) and islet cell (ICA) antibodies is consistent with the occurrence of new T1DM. Intravenous insulin treatment lead to a quick recovery and subcutaneous basal-bolus injection regimen was initiated thereafter.

Case 2: A 80 year-old woman without a history of diabetes was diagnosed with metastatic melanoma. Combined immunotherapy with NIV-IPI was started in October 2017. Three weeks after the first treatment cycle, she presented with autoimmune thyroiditis. Shortly thereafter, she was admitted in the emergency room with delirium and severe DKA: blood glucose >41.6 mmol/l, serum bicarbonate 5 mmol/l, anion gap 39.1 mmol/l. Further blood analysis revealed positive GAD and ICA consistent with T1DM. After intravenous insulin treatment, a subcutaneous basal-bolus injection regimen was initiated.

Conclusion:
Among adverse events of immunotherapy related to the endocrine system, T1DM remains uncommon (0.2%). In comparison with the rare reported patients with T1DM following NIV-IPI, our two cases are different as DKA occurs close to the end of the first cycle of CI therapy, both GAD and IA2 antibodies were positive, and there was no prior steroid therapy. Further, this is the first description of the development of T1DM arising from a pre-existing T2DM.

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Gender-specific variations of clinical outcomes after thyroidectomy in Switzerland

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Background/Introduction:
Incidence of thyroidectomies and awareness to postoperative quality measures have both increased in the last decade. Gender-specific indications and variations in clinical outcomes of patients undergoing thyroidectomy in Switzerland are of interest.

Methods:
We cross-sectionally compared administrative patient-level data for length of hospital stay (LOS), intensive care unit (ICU) admission, 30-day readmissions rates, and other quality measures among hospitalized female and male patients from January 2011 through December 2015. Multivariate regression models were used to determine gender-specific variations.

Results:
A total of 17`410 patients were included whereof 8`629 underwent a unilateral thyroidectomy and 8`721 a total thyroidectomy. 13`732 (78.9%) were female and the median age was 52 (IQR 41-63) and 54 (IQR 44-65) for females and males, respectively. The overall mean LOS was lower in female compared to male patients (3.3 [SD 2.8] vs. 3.6 [SD 4.0] days, $p<0.001$). Male patients had a higher risk for postoperative ICU admission compared with female patients (4.8% vs. 7.9%; OR, 1.59 [95%CI, 1.38-1.84], $p<0.001$). 30-day overall readmission rate was increased by about 40% in male patients compared to females (5.5% vs. 9.3%; OR, 1.42 [95%CI, 1.23-1.63], $p<0.001$). In contrast, less postoperative hypocalcemia were documented in male patients (6.0% vs. 8.5%; OR, 0.66 [95%CI, 0.57-0.76], $p<0.001$). The rate of recurrent laryngeal nerve palsy was similar between females and males (2.1% vs. 2.4%; OR, 1.05 [95%CI, 0.84-1.33], $p=0.67$).

Conclusion:
In Switzerland, the rate of thyroidectomies is more than four times higher in females than in males. Female patients undergoing unilateral- or total thyroidectomy had more favourable clinical outcomes compared with male patients. Importantly, these findings are not explained by the common complications of thyroidectomy (i.e. hypoparathyroidism and laryngeal nerve palsy) The underlying reasons remain to be elucidated.

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Severe course of a glycogen storage disease type 1a in an adult patient with psychiatric comorbidities and the impact of interdisciplinary treatment approach

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Background/Introduction:
Glycogen storage disease type 1a (GSD1a; glucose-6-phosphatase deficiency) is characterized by recurrent hypoglycemic episodes due to a glycogen breakdown defect as well as a glycogen accumulation. Frequent intake of carbohydrates is necessary to maintain euglycemic levels and prevent long-term complications. Due to an improved medical as well as consequent parental care, many patients survive to adulthood and are expected to take responsibility for their therapy. Psychiatric comorbidities such as eating or stress disorders may have detrimental consequences in adults with GSD1a.

Methods:
We report on a 23-year-old female patient with a glycogen storage disease type 1a. The therapy adherence in adolescence and adulthood has been negatively influenced by a restrictive eating disorder as well as an instable psychosocial situation and drug abuse. Since the age of 15 years 2-7 severe metabolic decompensations per year with blood glucose as low as 0.8 mmol/l accompanied by a severe lactic acidosis (pH 7.2, lactate 18 mmol/l), hepatopathy (liver enzymes > 2-14 times the upper reference range) and hypertriglyceridaemia (up to 40 mmol/l) occured. Additionally, progression of hepatic adenomas and nephropathy with microalbuminuria may further increase morbidity in the following years.

Results:
To optimize the metabolic control, the patient agreed to take part in a multimodal therapy including psychotherapy, ergotherapy and nutritional therapy in a psychosomatic department. Despite occasional mild hypoglycemia, metabolic parameters improved dramatically within the first 10 days and were maintained up to several weeks after discharge. Especially the triglycerides and liver enzymes, reflecting the chronic metabolic control in GSD1a, decreased by 50% or more (triglycerides 7.7 mmol/l). The patient reported significant improvement of fatigue and nausea as well as cognitive abilities. While the nutritional recommendations did not differ to prior treatment, the structured daily routine, providing the patient with adequate meals as well as psychological support may have contributed to a prompt metabolic improvement. No emergency treatment was required for the following seven months.

Conclusion:
We present a severe course of a glycogen storage disease type 1 in adulthood due to psychiatric comorbidities including disordered eating and the effectiveness of an interdisciplinary approach on the metabolic compensation.

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Truncated AR in a complete androgen insensitivity syndrome patient with recovery of libido after testosterone treatment

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Background/Introduction:
Androgen-insensitivity syndrome (AIS), a disorder of sex development (46 XY DSD) is caused mainly by mutations in the androgen receptor (AR). Gonadectomy is recommended due to the increased risk of gonadoblastoma. A 16-year-old patient with primary amenorrhea and female sexual characteristics was diagnosed with complete AIS (CAIS) based on 46 XY caryotype, a short pouch vagina, no müllerian structures, and an increased serum testosterone (T) level of 8 mmol/l. Laparascopy was unsuccessful to identifying gonads and the patient was lost in follow-up for 12 years. She presented at age 28 for gonadectomy and subsequent estrogen therapy was initiated. After the surgery, the patient experienced a loss of libido, therefore we hypothesized that low serum T levels following gonadectomy were the cause.

Methods:
Assessment of the sexual function using the Female Sexual Function Index (FSFI) 4 years after gonadectomy under different hormonal regimen: (1) after discontinuing estrogen treatment, (2) under testosterone treatment (Testogel® 50 mg for 2 months), and (3) under estrogen treatment only (Estradiol 2 mg daily for 2 months). Molecular characterization of AR by Sanger sequencing of DNA and RNA, and histological analysis of the gonads were performed.

Results:
Based on the FSFI, testosterone treatment (T levels of 24 nmol/l) led to significant improvement in sexual function, especially on desire/arousal and orgasm. In contrast, estradiol therapy (E2 level of 0.10 nmol/l) had no effect.

Genetic testing identified a novel AR mutation in the start methionine, p.Met1Thr (c.2T>C), which is absent in controls and results in a putative downstream start Methionine 190 amino-acids downstream. Mutant AR mRNA was detected in lymphocytes and the presence of a truncated AR protein was confirmed in testicular tissue using region specific antibodies. Notably, the mutant AR lacks the N-terminal domain known to be essential for the transcriptional activation of AR-target genes

Conclusion:
We report the case of a patient with CAIS exhibiting decreased libido following gonadectomy which was successfully treated by testosterone but not by estrogen. This patient harbors a mutation in the start methionine leading to a truncated AR. In vitro studies are ongoing to confirm the functionality of mutant AR. This case suggest a non-genomic effects of T for libido.

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Differences in insulin dosing and glycemic control in type 1 diabetic women before and after the menopause.

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Background/Introduction:
The menopause has substantial impact on glycemic control in women with type 1 diabetes, albeit there are no studies available focusing on insulin requirements in the postmenopausal state. The present study aimed to compare insulin requirements of premenopausal with postmenopausal women with type 1 diabetes using continuous subcutaneous insulin infusion.

Methods:
Data from 1230 adult women registered in the Diabetes-Patienten-Verlaufsdokumentation-database were analyzed. Inclusion criteria were diagnosis of type 1 diabetes, age >40 years and use of CSII for 24 hours per day with plausible and complete documentation of basal rates. Postmenopausal state was defined as age >50 years. Using this definition, 514 women were premenopausal and 716 women postmenopausal.

Results:
Doses of total daily insulin, daily insulin per kg body weight, total prandial insulin, total basal insulin, basal insulin per kg body weight, and body weight were significantly lower in postmenopausal compared to premenopausal women. Total cholesterol and high-density lipoprotein-cholesterol increased following menopause.

Conclusion:
Insulin requirements and body weight were lower in postmenopausal women, while glycemic control was comparable with premenopausal women. It is unknown whether body weight determined or resulted from changes in insulin requirements. Lower insulin resistance during the luteal phase and nutritional changes may have enabled weight loss and reductions of daily insulin doses. However, further research is necessary in order to verify this hypothesis.

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Dulaglutide has Higher Adherence and Persistence than Liraglutide and Exenatide QW: 1-year Follow-up from US Real-World Data

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Background/Introduction: The objective of this retrospective real-world observational study was to compare 1-year adherence and persistence among patients initiating GLP-1 receptor agonists (GLP-1RA), dulaglutide (DULA) vs. liraglutide (LIRA) or DULA vs. exenatide QW (EQW) in the US, using claims data between November 2014 and May 2016 (index date=earliest GLP-1RA fill date) from the HealthCore Integrated Research Database (HIRD®).

Methods: Patients ≥18 years old, with T2DM, no claim for index drug in the 6 months pre-index period, and continuous enrollment 6 months pre- and 1-year post-index were included. DULA users were propensity-matched 1:1 to LIRA (2,427 pairs) or EQW (1,808 pairs) users. Matched cohorts were balanced in baseline characteristics and the mean age was 54 years with around 52% males.

Results: The key adherence and persistence outcomes are included in the table. At 1-year, DULA users were more likely to be adherent [Proportion of Days Covered (PDC)≥80%] than LIRA (odds ratio [OR]=1.76, 95% CI=[1.56, 1.99]) or EQW users (OR=2.31, 95% CI=[2.00, 2.66]). Cox regression showed that DULA users were less likely to discontinue therapy than LIRA (hazard ratio [HR]=0.75, 95% CI=[0.69, 0.81]) or EQW users (HR=0.58, 95% CI=[0.53, 0.63]).

Conclusions: At 1-year follow-up, patients initiating DULA had higher medication adherence, and were more persistent to their treatment compared to patients initiating either LIRA or EQW.

Table: 1-Year Follow-up Adherence and Persistence Outcomes Among GLP-1 RA Initiators

	Matched DULA vs. LIRA Cohorts			Matched DULA vs. EQW[1] Cohorts		
	DULA	LIRA	p-value[2]	DULA	EQW[1]	p-value[2]
	N=2,427	N=2,427		N=1,808	N=1,808	
Proportion of Days Covered (PDC), mean (SD) in %	67.3% (32.1)	59.5% (32.6)	<0.001	66.8% (32.2)	51.3% (34.6)	<0.001
Adherence (PDC ≥ 80%), %	51.2%	38.2%	<0.001	50.7%	31.9%	<0.001
Patients who discontinued therapy, %	51.1%	62.0%	<0.001	51.1%	70.9%	<0.001
Persistence[3], mean (SD) days	251.9 (135.7)	217.3 (143.0)	<0.001	250.5 (136.8)	191.6 (139.3)	<0.001

[1] The study included only exenatide QW pen users
[2]P-values for categorical variables were obtained using Chi-square tests; p-values for continuous variables were obtained using Wilcoxon rank sum tests.
[3]The number of days of continuous index GLP-1 RA therapy since initiation, allowing for a maximum gap (between fills) of 45 days. Patients who were censored at the end of the 1-year follow-up period were included.

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Glucose Variables in T1D studies with Dapagliflozin: Pooled Analysis of Continuous Glucose Monitoring Data from DEPICT-1 and 2

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This study was supported by AstraZeneca

Background/Introduction:
Improved glycemic control and weight loss, without increased hypoglycemia, were demonstrated in two short-term, 24-week, Phase 3 studies of the SGLT2 inhibitor dapagliflozin (DAPA) as adjunt to adjustable insulin in patients with inadequately controlled T1D (DEPICT-1 and 2).

Methods:
In this post-hoc analysis we pooled continuous glucose monitoring (CGM) data at baseline and Week 24 from both studies.

Results:
In total, 1591 patients were included (DAPA 5 mg N=530; DAPA 10 mg N=529; placebo N=532). Baseline characteristics were comparable between the study groups. DAPA treatment significantly reduced mean interstitial gluose, mean amplitude of glucose excursions (MAGE), and postprandial gluocse, while expanding the time in glycemic target range (>70 mg/dL to ≤180 mg/dL). In addition, DAPA treatment did not increase the percent of glucose readings ≤70 mg/dL or ≤54 mg/dL, or the percent of readings ≤70 mg/dL in the nocturnal period (00:00 to 05:59).

Conclusion:
These results demonstrate that DAPA as adjunct to insulin in patients with T1D reduced glycemic variability without increasing time in the hypoglycemia range.

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Influence of Free Thyroid Hormone Levels on Thermogenesis in Euthyroid Humans

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Background/Introduction:
Thyroid hormones influence the metabolic activity of all human tissues and play an important role for thermogenesis. In patients thyroid hormone status is routinely assessed by measuring thyroid stimulating hormone (TSH) and thus the pituitary feedback loop. However, in populations of euthyroid patients with TSH levels within the normal range levels of free thyroid hormone (fT4) can vary greatly. The implications for metabolism and thermogenesis of these differences in fT4 status are largely unknown.

Methods:
We measured energy expenditure (EE) by indirect calorimetry in healthy volunteers (n=56) and patients with hypothyroidism who had been substituted with thyroid hormone in a dose sufficient to attain euthyroidism (TSH within the normal range) for at least three months (n=33). EE was measured during warm conditions (EEwarm) and after a standardized mild cold stimulus of 90 min duration (EEcold). The difference in EE in response to cold exposure is called cold induced thermogenesis (CIT). Thyroid hormone levels (fT4, fT3) and TSH were measured by ECLIA. Data were analyzed by simple and multiple linear regression.

Results:
The median TSH level in the group of healthy volunteers was 1.7 mIU/l, fT4 was 16.4 pM and fT3 5.3 pM. In T4 substituted patients median TSH was also 1.7 mIU/l, fT4 was 19.0 pM and fT3 4.4 pM. In healthy, euthyroid volunteers EEcold and CIT were significantly associated with levels of fT4 (R2=0.125, p=0.0078 and R2=0.125, p=0.0076, respectively), while EEwarm was not. Levels of fT3 were not associated with CIT or EEcold. The effect of fT4 was still significant after multivariate linear regression with height, weight and age as well as outdoor temperature prior to the study visit.
In patients with hypothyroidism who were euthyroid for at least three months CIT and EEcold were not associated with levels of fT4.

Conclusion:
In healthy, euthyroid volunteers levels of fT4 are associated with energy expenditure in response to mild cold exposure. This suggests a role for fT4 in the adaption of humans to cold exposure. Further new methods to evaluate thyroid hormone status beyond assessment of the pituitary feedback loop should be evaluated.

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The effect of chronic AVP-deprivation on haemoglobin and prevalence of anaemia- The DIANA study

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Background/Introduction:
The antidiuretic hormone arginine vasopressin (AVP) is released upon varies stimuli, e.g. hypovolemia and is therefore elevated after acute haemorrhage. A recent study suggests that AVP plays a role in haematopoiesis by stimulating red blood cell precursors. This might have implications in patients with AVP deficiency (central diabetes insipidus (cDI)) or chronic AVP suppression (primary polydipsia (PP)). The aim of this study was to explore the possible effect of chronic AVP-deprivation on haemoglobin values and prevalence of anaemia in patients with cDI and PP compared to healthy volunteers (HV).

Methods:
We analysed blood samples of 163 patients with either cDI or PP and of 30 HV collected in the context of two prospective diagnostic studies. A standardized work-up was performed in all participants including assessment of medical history, drugs, clinical parameters and lab values (e.g. haemoglobin, haematocrit). Anaemia was defined according to WHO criteria (haemoglobin values of <120 g/L in women and<130 g/L in men).

Results:
Patients with cDI (n=70, 61% female, mean age: 45.6 years (±13.9)) were older than patients with PP (n=93, 69% female, mean age: 35.6 years (±12.6)) and HV (n=30, 57% female, mean age: 31.3 years (±11.4)), p<0.001. The most frequent comorbidity in cDI patients was anterior pituitary deficiency (62.9%), whereas PP patients most commonly suffered from psychiatric disease (26.9%). Mean haemoglobin values were similar in all groups: 139g/L (±15.85) in cDI patients, 140g/L (±13.16) in PP patients and 139g/L (±13.05) in HV (p=0.92) as were mean haematocrit values with 0.41 % in all three groups (p=0.850). The prevalence of anaemia was low in all participants and not higher in cDI patients (n=5 (7.1%)) than in PP patients (n=2 (2.2%)) or in HV (n=3 (10%)), p=0.157.

Conclusion:
Chronic AVP-deprivation in cDI and PP patients shows no clinical relevant effect on haemoglobin values and prevalence of anaemia.

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Dynamics and regulation of copeptin upon exercise

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Background/Introduction:
Interleukin-1 (IL-1) increases during exercise and was shown to induce arginine vasopressin (AVP) in animal models. We here therefore investigate whether copeptin (a surrogate marker for AVP) increases upon exercise in young and healthy males, and whether this increase is regulated by IL-1.

Methods:
This is a post-hoc analysis of a randomized, placebo-controlled, double-blind, crossover trial in 17 healthy male volunteers. The effect of the IL-1 receptor antagonist anakinra on exercise-induced copeptin was compared with placebo. Participants exercised for one hour at 75% of VO2max and were not allowed to drink or eat 6 hours before and during the study. Participants received either 100 mg of anakinra or placebo one hour before exercise. Blood was drawn at certain time intervals before, during, and after exercise.

Results:
In both groups, copeptin levels were induced by 2.5-fold upon exercise (p<0.001), from 4.5–10.6 pmol/l in the placebo, and 4.3-11.3 pmol/l in the anakinra group, (p for group difference =0.38). One hour after exercise, copeptin levels dropped to 7.7 and 7.9 pmol/l in the placebo and anakinra group, respectively (p=0.58). The increase of copeptin levels was not explained by sodium concentrations.

Conclusion:
Exercise induces a continuous rise of plasma copeptin levels in healthy male volunteers independently of sodium levels and fluid intake. This increase is not regulated by the IL-1 pathway.

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Associations between intuitive eating and metabolic health in women with gestational diabetes during pregnancy and in the post-partum period: A prospective cohort study

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Background/Introduction:
High pre-pregnancy weight and body mass index (BMI) increase the odds of developing gestational diabetes mellitus (GDM). Furthermore, increased pre-pregnancy and postpartum weight also augment the risk of future diabetes mellitus after GDM. In GDM, several dietary habits and patterns have been studied to manage or control weight and glycaemia levels. Although eating behavior and intuitive eating is also a determinant of obesity, few studies have investigated the relationship between eating behavior and metabolic health. Outside of pregnancy, a higher adherence to intuitive eating is associated with lower BMI and improved glycemic control. However, there are no studies investigating the relationship between intuitive eating and metabolic health in pregnant women. This study is the first to investigate the relationship between intuitive eating and weight, as well as glucose control in pregnancy and in the post-partum period among women with GDM.

Methods:
Two-hundred and fourteen consecutive women aged ≥18, diagnosed with GDM at 24-32 weeks of gestation between 2015 and 2017 who completed questions on two subscales of the Intuitive Eating Questionnaire: “Eating for Physical rather than Emotional Reasons (PER)” and “Reliance on Hunger and Satiety cues (RHS)” were included in this study. Linear regression models were used to determine the cross-sectional and longitudinal associations between the intuitive eating subscales and BMI, weight and glycemic control during pregnancy and at post-partum.

Results:
Participants’ mean age was 33.32±5.20 years, their weight and BMI before pregnancy were 68.18±14.83kg and 25.30±5.19kg/m2, respectively and their weight and HbA1c at first GDM visit were 79.16±14.87kg and 5.36±0.39%, respectively. Cross-sectional analyses revealed an inverse relationship between the scores of both intuitive eating subscales at first GDM visit with weight before pregnancy, fasting plasma glucose at GDM diagnosis, weight and HbA1c at first GDM visit (β=-0.171 to -0.222, all P≤ 0.013) except for a lack of association between the RHS subscale and HbA1c. In the longitudinal analyses, the scores of both intuitive eating subscales at first GDM visit were inversely correlated with weight at the end of pregnancy, and weight and fasting plasma glucose at 6-8 weeks post-partum (β=-0.139 to -0.242, all P≤ 0.046). The association between intuitive eating and fasting glucose was partially mediated by weight.

Conclusion:
Intuitive eating is associated with weight and glycemic control in pregnancy and the post-partum period in women with GDM. Increased adherence to intuitive eating could represent an interesting and novel approach for weight management during and after pregnancy in women with GDM.

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FGF21-levels in Polyuria-Polydipsia Syndrome

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Introduction:
Fibroblast growth factor 21 (FGF21) is a peptide hormone which has been described as a metabolic stress marker. Recent data in mice reported a connection between FGF21 levels and elevated fluid intake independently of the hormone arginine-vasopressin (AVP) and osmotic stimulation, suggesting an alternate fluid regulation pathway. To further evaluate this observation, we compared FGF21 levels in patients with AVP-deficiency (central diabetes insipidus) and increased fluid intake despite adequate AVP-release (primary polydipsia) before and after osmotic stimulation.

Material and Methods:
FGF21 levels of patients with complete central diabetes insipidus or primary polydipsia as well as healthy volunteers were analysed before and after stimulation with hypertonic saline infusion targeting a plasma sodium level of 150mmol/l. The primary outcome was the difference in FGF21 levels after osmotic stimulation.

Results:
20 patients with complete central diabetes insipidus (75% females; 20% smokers; BMI 29.0 kg/m^2 (23.2, 30.9); age 43.5 years (28.5, 49), 20 patients with primary polydipsia (65% females; 25% smokers; BMI 24.5 kg/m2 (22.5, 26.1); age 31.5 years (23.3, 47.3)) and 20 healthy volunteers (60% females; 20% smokers; BMI 24.7 kg/m^2 (22.5, 26.1); age 30 years (23.3, 43.8) were included.
Although FGF21 levels appeared to be higher in patients with diabetes insipidus at baseline (306 pg/ml (114, 484)) compared to primary polydipsia (122 pg/ml (52, 277)) and healthy volunteers (193 pg/ml (48, 301); p=0.037), this effect could not be confirmed after correcting for BMI and smoking in a multivariate linear regression analysis.
Consistent with the mice data, osmotic stimulation did not affect FGF21 levels in either group (difference to baseline: diabetes insipidus 17 pg/ml (-76, 88); primary polydipsia -23 pg/ml (-43, 22); healthy volunteers -6 pg/ml (-68, 22); p=0.45). No correlations of FGF21 levels with plasma sodium, -osmolality or copeptin levels were found.

Conclusion:
This first evaluation of FGF21 in patients with central diabetes insipidus or primary polydipsia and healthy volunteers showed no difference between the groups and no change upon osmotic stimulation. Further studies are needed to evaluate if exogenous FGF21 administration also stimulates water intake in men, which would confirm the alternate fluid regulation pathway proposed in the mouse model.

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Inferior petrosal or cavernous sinus sampling in ACTH-dependent Cushing’s syndrome: a single center experience

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Background/Introduction:
Most patients with ACTH-dependent Cushing’s syndrome have Cushing’s disease, i.e. a pituitary corticotroph adenoma, but the presence of another tumor secreting ACTH (although the prevalence of ectopic ACTH syndrome is lower) needs to be considered in the differential diagnosis. Distinguishing between these two etiologies can be difficult despite biochemical and radiological examinations. Previous research showed that inferior petrosal/cavernous sinus sampling (IPSS/CSS) has the highest diagnostic accuracy in this differential diagnosis. The aim of this study was to determine the accuracy of IPSS/CSS in predicting the source of ACTH-dependent Cushing syndrome in a tertiary center in Switzerland.

Methods:
Retrospective, single center study of 21 patients (7 male, 14 female; age 40.4±16.8y) with ACTH-dependent Cushing’s syndrome who underwent a selective bilateral inferior petrosal sinus (n=6) or superselective bilateral cavernous sinus (n=15) sampling at the University Hospital Zurich between 2000 to 2017 and provided written informed consent. ACTH levels were measured before and within 20 minutes after corticotropin-releasing hormone (CRH) administration, and the ratios of central-to-peripheral plus interpetrosal ACTH levels were calculated. A central-to-peripheral ratio ≥2 before and ≥3 after CRH is diagnostic of an orthotopic source of ACTH. A ratio ≥1.4 between the two sinuses predicted the tumor lateralization.

Results:
IPSS/CSS confirmed orthotopic (pituitary) source of ACTH in 19 patients with Cushing’s disease and correctly identified 2 patients with ectopic disease. A central-to-peripheral plasma ACTH ratio was diagnostic for Cushing’s disease in 19 patients before CRH and in 19 patients after CRH-administration. Interpetrosal ratios for ACTH lateralization were found in 17 (pre-CRH) and 17 (post-CRH) patients. The IPSS/CSS pre- and post-CRH ACTH ratio was negative (close to 1) in both patients with ectopic Cushing’s syndrome. There was no adverse event in the context of the catheterization procedure.
Perioperative MRI (n=18) showed 1 macroadenoma, 12 microadenomas and no visible lesion in 5 patients. In patients with visible pituitary lesions, IPSS/CSS predicted correctly the localization to the left, right or paramedian side in 7 cases. Judged by surgery, the IPSS/CSS predicted correctly the lateralization of the pituitary tumor in 14 of 19 patients. Pituitary surgery was successful in 14 patients; 5 had persistent cortisol excess.

Conclusion:
Our results confirm previous reports that IPSS/CSS is an effective intervention to locate the source of ACTH production. IPSS/CSS was safe and useful in planning the surgical therapy in patients with Cushing disease.

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Interaction of genetic variation in NFE2L2 and SEPS1 modulates the risk of Hashimoto’s thyroiditis

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Background/Introduction:
The genetic and molecular pathogenesis of Hashimoto’s thyroiditis (HT) is not fully elucidated. Several single-nucleotide polymorphisms (SNPs) are known to increase the risk of HT; such SNPs reside in thyroid-specific genes or in genes related to autoimmunity, inflammation and/or cellular defense to stress. Moreover, HT has been associated with increased levels of systemic oxidative stress. The transcription factor Nrf2, encoded by NFE2L2, is a master regulator of the cellular antioxidant response and was recently shown to control thyroglobulin expression and iodination, but its involvement in autoimmune thyroid disease has not been investigated. This study aimed to evaluate the impact of genetic variation in NFE2L2 on the risk of developing HT. Functional SNPs in the NFE2L2 promoter (rs35652124, rs6706649 and rs6721961) were examined either as independent risk factors or in combination with a previously characterized HT risk allele (rs28665122) in the selenoprotein S gene (SEPS1).

Methods:
This was a case-control candidate gene association study. Participants were recruited in the North of Portugal (Porto) in the period 2007-2013. A total of 997 individuals comprising 481 HT patients and 516 unrelated healthy controls were enrolled. SEPS1 and NFE2L2 SNPs were genotyped using TaqMan® assays. Odds ratios were calculated using logistic regression, adjusting for sex and age.

Results:
Individually, none of the NFE2L2 SNPs was associated with increased risk of HT. When all three SNPs were considered together, the presence of one or more minor alleles was associated with a near-significant increased risk (OR 1.43, p=0.072). Individually, none of the three SNPs abolished or increased the HT risk associated with the known SEPS1 risk allele. When all three NFE2L2 SNPs were considered together, then among subjects harboring only major NFE2L2 alleles, there was no increased HT risk associated with heterozygosity or homozygosity for the SEPS1 minor allele (p-value = 0.708). Conversely, in subjects heterozygous or homozygous for the SEPS1 risk allele, the presence of NFE2L2 minor alleles significantly increased HT risk by 2.5-fold (p-value = 0.003).

Conclusion:
The NFE2L2 promoter genotype interacts with the SEPS1 promoter genotype to modulate the risk of HT.

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Differences in Plasma and Whole Blood Sodium Measurements

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Introduction:
Hypo- and hypernatremia are the most common electrolyte disorders. Precise and reliable sodium measurements are crucial, as dysnatremia can lead to life-threatening complications if not treated correctly. Routinely used sodium measurements are the indirect (plasma) and direct (whole blood) ion selective electrode (ISE) method. Current data suggests the direct method to be more reliable, as the indirect method is affected by changes in albumin levels. No data concerning measurement differences in patients with normal albumin concentration exist.

Material and Methods:
We analysed data of 53 healthy volunteers, 81 patients with primary polydipsia and 57 patients with diabetes insipidus undergoing a hypertonic saline infusion test. Sodium levels were measured simultaneously by indirect and direct ISE before and at different time points during osmotic stimulation up to a threshold of >150 mmol/l. The primary outcome was the difference in sodium levels between the indirect and direct ISE measurement.

Results:
In total, 966 sodium measurements ranging from 132 to 160 mmol/l of 191 participants were analysed. All participants were in a stable condition and had normal albumin concentration. Median baseline sodium values were 141 mmol/l (139, 143) by the indirect ISE vs 139 mmol/l (138, 141) by the direct ISE. Median maximally stimulated sodium values were 152 mmol/l (150, 153) by the indirect ISE and 149 mmol/l (148, 150) by the direct ISE. In general measurements by the indirect ISE were 1.86 mmol/l (±2.56) higher than by the direct ISE (p<0.001); however differences ranged from +14 mmol/l to -7 mmol/l between the two methods, irrespective of the measurement time point.

Conclusion:
Intra-individual sodium levels differ significantly between the indirect and direct ISE measurement method despite normal albumin concentration. It is therefore crucial to adhere to the same method in critical situations to avoid wrong decisions due to measurement differences.

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Tinnitus with unexpected Spanish roots: Head and neck paragangliomas caused by SDHAF2 mutation

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Background/Introduction:
Head and neck paragangliomas (HNPGL) are a subtype of pheochromocytoma/paraganglioma (Pheo/PGL) that originate from the autonomuos nervous system. In contrast to abdominal and thoracic Pheo/PGL, HNPGL are usually non-secretory, of parasympathetic origin and metastasize only rarely. Although HNPGL may occur as sporadic tumors, it is estimated that up to 40% of all cases may have a hereditary background that impacts therapeutic strategies, follow-up of affected patients and diagnostic approaches of family members. The most common mutations are found in the succinate dehydrogenase (SDH) genes with the highest prevalence of mutations in SDH-D, followed by SDH-B and SDH-C.

Methods:
Case report of a rare mutation within the SDH complex and review of the literature.

Results:
A 15 year old male patient presented with tinnitus and hearing loss of the left ear. Imaging revealed a left sided jugulotympanic tumor (33x34mm) and a tumor of the right carotid body (12x15mm). The patient was normotensive, did not report on spells and plasma free metanephrine/catecholamine were not elevated. The morphological suspicion of a paraganglioma was confirmed histologically following resection of the jugulotympanic lesion. Immunohistochemistry showed a loss of SDHB-expression and genetic testing (somatic and germline) revealed a mutation in the SDH assembly factor 2 (SDHAF2) gene (c.232G>A). The patient's father is of Spanish descent. There was no family history for tumors.
The hereditary paraglioma syndrome 2 (PGL2) has first been described in 1982 in a Dutch and later in a Spanish family and was found to be caused by a mutation in the SDHAF2 gene. SDHAF2 is a conserved co-factor involved in the flavination of the SDH-A subunit. The inheritence is autosomal dominant with maternal imprinting, leading to tumorigenesis only by paternal transmission. This may explain the seemingly negative family history. As in our case, patients with PGL2 usually present at young age with multiple, benign and non-secretory HNPGL. The penetrance reaches 88-100% by the age of 50 years.

Conclusion:
Our findings emphasize the relevance of genetic testing in patients with HNPGL, also with negative family history, especially when the patients present at young age and with multiple lesions.

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Improved or comparable efficacy without increased hypoglycaemia with self- vs physician-led titration of insulin glargine 300 U/mL in age groups <65 or ≥65 years: TAKE CONTROL

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Background/Introduction:
TAKE CONTROL, a 24-week, multicentre, randomized, open-label, parallel-group study, aimed to evaluate self- vs physician-led titration of insulin glargine 300 U/mL (Gla-300) in people with T2DM.

Methods:
Efficacy and safety outcomes in people <65 years vs ≥65 years were assessed.

Results:
In each age subgroup, baseline HbA1c and fasting SMPG were comparable between self- vs physician-led titration (Table); in the older and younger groups, HbA1c (p=0.46 and p=0.29) and fasting SMPG (p=0.56 and p=0.15) reductions were similar between self- vs physician-led titration. Attainment of the fasting SMPG target (4.4–7.2 mmol/L) without confirmed (<3.0 mmol/L) or severe hypoglycaemia was slightly higher in older people; differences in self- vs physician-led titration were not significant in older or younger groups (p=0.19 and p=0.05). Incidences of hypoglycaemia at any time of day (24 h) appeared slightly higher in the ≥65 years, physician-led group. There was no evidence of heterogeneity of effect of self- vs physician-led titration on hypoglycaemia (p>0.05). Adverse events were similar in each group.

Conclusion:
Self-titration of Gla-300 resulted in similar glycaemic target achievement to physician-led titration, without an increased risk of hypoglycaemia, irrespective of age. There was a trend for more people to reach fasting SMPG targets without hypoglycaemia with self- vs physician-led titration, including those ≥65 years.

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Thermogenesis in Hyperthyroidism and Effect of Anti-Adrenergic Therapy – The HEAT study

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Background/Introduction:
Patients suffering from hyperthyroidism experience symptoms such as weight loss and heat intolerance. It is known, that thyroid hormones induce the activation of brown adipose tissue (BAT) and thus increases energy expenditure (EE), which may explain these symptoms. BAT is activated by norepinephrine acting on the β3 adrenergic receptor. The non-selective beta blocker Propranolol is used to alleviate the symptoms of hyperthyroidism. In this study, we wanted to investigate, whether an acute dose of Propranolol reduces EE in patients suffering from hyperthyroidism.

Methods:
In this prospective interventional study, EE of 11 patients with hyperthyroidism was measured by indirect calorimetry before (EEbaseline) and 90 minutes after an single dose of 80mg Propranolol (EEpropranolol). Additionally, in all patients thyroid hormone status (TSH, free T4 and free T3) was assessed. Furthermore, Dual Energy X-ray Absorptiometry (DXA) was used to calculate patients’ body composition.
The primary endpoint was the difference in energy expenditure before and after an acute dose of Propranolol. Secondly, we wanted to know if thyroid hormone levels (fT4 and fT3) correlate with EEbaseline normalized to the lean body mass (EEnormalized= EEbaseline/ lean mass [kg]).

Results:
Patients' EEbaseline was approximately 20% (294 kcal/24h) higher than their estimated EE. Energy expenditure before Propranolol (mean EEbaseline= 1695 kcal/24h) decreased after the acute dose of Propranolol (mean EEpropranolol= 1630 kcal/24h) significantly (p=0.0049) by about 4%.
EE normalized to the lean body mass showed a significant, positive correlation to both fT3 (p=0.0161, R2=0.4926) and fT4 (p=0.0488, R2=0.3655).

Conclusion:
Patients with hyperthyroidism have a strongly increased EE, which can be significantly reduced by the non-selective beta blocker Propranolol. In addition, the increased EEbaseline in patients with hypertyhroidism seems to be strongly influenced by fT3.

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Caring for children and adolescents with a difference of sex development in Switzerland

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Background/Introduction:
Since 2000 understanding of biology of sex development increased tremendously thanks to genetic research. This lead to new classification for persons with disorders/differences of sex development (DSD) based on genetics, and guidelines from the UK recommend revising medical care for persons with DSD by setting up interdisciplinary DSD teams. In Switzerland, persons with DSD asked for better care, stimulating the Swiss National Ethics Commission in 2012 to recommend improved treatment of DSD persons. We aimed to describe the current situation of medical care of DSD in Switzerland.

Methods:
We sent a questionnaire to pediatric endocrinologists of eight hospitals in Switzerland who were either part of the Working Group DSD of the Swiss Society for Pediatric Endocrinology and Diabetology (AG DSD SGPED) or who committed to set up a DSD cohort. We asked them to estimate numbers of treated DSD persons, indicate specialists involved in DSD care and report DSD-related research projects.

Results:
The eight clinics cover >85% of all newborns in Switzerland. Each year, around 24 newborns and 24 children and adolescents were diagnosed with complex DSD, e.g. ambiguous genitalia. In total, the eight clinics care for about 750 children with a DSD diagnosis according to the Chicago consensus classification. Of those, 90 had complex DSD, 130 congenital adrenal hyperplasia, and 130 Turner syndrome.
Most clinics used the UK guidelines and 7/8 had established interdisciplinary DSD-teams including specialized pediatricians from many areas, geneticists, general psychologists or social counselors. Only few clinics had specialized psychologists, social counselors, nurses, or ethicists.
Young adults with DSD were transitioned to adult medicine at age 16-25 years, but it was unclear who can provide the optimal care for them, because there were hardly any adult physicians specialized on DSD.
All participating clinics indicated to establish a Swiss DSD cohort, and several clinics had their own research projects, including basic science, ethics and epidemiology.

Conclusion:
We identified gaps in psychological care, in the collaboration with adult medicine and with associations of DSD individuals, and in epidemiological monitoring of DSD. Few clinics had already included specialized psychologists in their DSD team. The new Swiss DSD cohort

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The challenge of carbohydrate consistency in hospitalised patients with type 2 diabetes

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Background/Introduction:
Similar to the outpatient setting, nutrition is recognized as an important aspect of diabetes care in hospital. Since carbohydrate (CHO) intake provides the primary nutritional effect on blood glucose, meal CHO content needs to be taken into consideration when dosing insulin. The aim of this analysis was to assess meal adequacy of hospitalized patients with insulin-treated type 2 diabetes in terms of energy provision, macronutrient distribution and CHO consistency.

Methods:
Oral nutritional intake in a cohort of 82 hospitalized non-critical care patients with type 2 diabetes on insulin therapy (age 67(SD 12)yrs, HbA1c 8.6(1.8)%, diabetes duration 15(12)yrs) was assessed using food diaries for up to 15 days or until hospital discharge. Meal-specific nutrient information (CHO, protein, fat and energy content) was retrieved from the hospital kitchen food database. Dietary intake was related to patient characteristics and nutritional recommendations (Acceptable Macronutrient Distribution Ranges, AMDR). In a subset of patients (n=41), CHO intake was related to glucose levels based on blinded continuous glucose monitoring (CGM) data. CGM data was divided into daytime (0800-00:00) and nighttime (00:00-08:00) periods. The glycaemic target range was set at 5.6-10.0mmol/l.

Results:
On average, 25 meals per patient were assessed. Mean CHO intake was 59g for both breakfast and dinner (SD = 22g and 18g, respectively) and 51(18)g for lunch. Snacks provided 7(18)g of CHO. Mean energy intake per day was 1560(482)kcal. The contribution of CHO to energy provision was 47(8)% for breakfast, 42(7)% for dinner and 40(5)% for dinner. Across all meal types, fat and protein contributed to 43(29)% and 19(16)% of energy intake. Age, Charlson comorbidity index and female sex were inversely related with energy intake (all p<0.05). All meals provided macronutrients within AMDR, but showed rather low CHO contribution (mean contribution to energy across all meals 43%). With respect to the variability of carbohydrate consumption between days, as assessed by the standard deviation, total daily CHO intake varied by 54g. Between meals, variability of CHO intake was 16g for breakfast, 17g for lunch and 23g for dinner. Variation of dinner CHO intake was significantly greater compared with variation of CHO intake at breakfast and lunchtime (both p<0.02). Variability of dinner CHO intake was positively correlated with proportion of time spent below the glycaemic target range (p=0.025) and burden of hypoglycaemia (area under the glucose curve below 3.5mM, p=0.041).

Conclusion:
Although hospital meals proved nutritional adequacy in terms of energy content and macronutrient distribution, CHO intake between days was shown to be inconsistent, especially at dinnertime. The latter was associated with increased time spent below the glycaemic target range and nighttime burden of hypoglycaemia. Decreasing the variability of CHO exposure may provide a practical way to improve glucose control in hospital.

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Polyostotic fibrous dysplasia in a patient with McCune-Albright syndrome.

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Introduction:
McCune-Albright is a multi-organ syndrome with skeletal, skin and endocrine manifesta-tions.

Case Report:
A 30-year-old man with polyostotic fibrous dysplasia presented at our outpatient clinic for further evaluation. Diagnosis of fibrous dysplasia was first made at the age of 6 years after a pathological left-sided femoral fracture. During childhood and adolescence, the patient suffered three re-fractures necessitating several orthopedic interventions. A CT-scan of the thorax in 2015 revealed multiple lesions of the ribs and scapula, further lesions were detected in the bone scan. The personal history was also remarkable for a liver operation due to giant-cell-hepatitis as a neonate. There was no history of precocious puberty. Clinical examination showed a normal-weight young man, with a 5x6cm café-au-lait spot located at the gluteal region. Further clinical and laboratory examinations could exclude an endocrinopathy (i.e. acromegaly, thyreotoxicosis or Cushing's syndrome). Based on the personal history and the clinical and scintigraphic findings, a diagnosis of McCune-Albright syndrome was made and treatment with i.v. bisphosphonate was started.

Comment und conclusion:
McCune-Albright syndrome (MAS) is a rare disease with a prevalence between 1:100'000 and 1:1'000'000. It is caused by a post-zygotic gain-of-function mutation in GNAS1 gene, located on the long arm of chromosome 20 at position 13.3, leading to increased Gs-protein alpha-subunit signalling and subsequently overproduction of cyclic AMP (cAMP). MAS is characterized by fibrous dysplasia, café-au-lait spots and syndromes with endo-crine overfunction. Girls typically present with precocious puberty (PP). However, PP is less common in boys. Apart from PP, a wide range of other endocrinopathies have also been associated with MAS, such as acromegaly, Cushing's syndrome, thyreotoxicosis and renal phosphate wasting. Fibrous dysplasia is associated with increased bone resorption and osteoporosis, where bisphosphonates represent the standard treatment in symptomatic patients. Café-au-lait lesions in MAS appear early in life and are the first findings of the disease. They are characterized by irregular borders described as "coast of Maine". Hepatobiliary dysfunction and hepatitis are very rare manifestations of MAS, where defect hepatic proteins interfere with the normal production of biliary components.

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"TOASST" (Taper Or Abrupt Steroid STop): design of a randomized controlled trial evaluating an unresolved clinical question.

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Background/Introduction:
No data from RCTs are available on whether and how to taper glucocorticoids (GCs) after successful systemic therapy, and the risk for suppression of the hypothalamic-pituitary-adrenal (HPA) axis does not correlate with treatment duration or cumulative GC dose. The power of the ACTH stimulation test to predict the need of continued GC administration is unknown. We aim to assess the safety of rapidly terminating GC treatment irrespective of biochemical status of the HPA axis, provided glucocorticoid cover is ensured in situations of stress.

Methods:
We aim to include 573 patients with clinically stable inflammatory, autoimmune, or other GC-treated disease (treatment duration ≥ 28 days; cumulative dose ≥ 420 mg, average daily dose ≥7.5 mg, current daily dose at trial entry ≥7.5 mg prednisone-equivalent), where the treating physician deems it feasible to terminate GC therapy.
Participants are randomized 1:1 to tapering over 4 weeks (standard treatment arm) or matching placebo (abrupt treatment stop; intervention arm). A 250 mcg ACTH test is performed upon inclusion, the result of which is concealed to treating physicians and investigators. Participants are instructed about stress GC cover and supplied with an emergency prednisone tablet. Follow-up is scheduled over 6 months.

Results:
The primary outcome measure is time to first occurrence of hospitalization, death, initiation of unplanned systemic GC therapy, or adrenal crisis.
Secondary outcome measures include: Time to first occurrence of individual components of the primary outcome; cumulative overall systemic glucocorticoid dose; cumulative systemic glucocorticoid dose administered to treat or prevent adrenal failure; cumulative systemic glucocorticoid dose administered to treat relapse of disease, signs and symptoms of GC-deficiency; general health status as self-assessed by the patients; performance of the 250 mcg ACTH test.

Conclusion:
This will be the first randomized controlled trial to evaluate the feasibility and safety of rapid glucocorticoid withdrawal in comparison with a tapering regime in stable patients after prolonged systemic GC therapy. If tapering proves to be unnecessary, the duration and treatment-related risks and side effects of GCs can be reduced for future patients.

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Copeptin as a diagnostic marker for malignant SIADH?

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Background/Introduction:
Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a very common condition in hospitalized patients. It is crucial to establish the cause of SIADH especially in order to exclude or detect an underlying malignancy. As malignant tumors (e.g. small cell lung cancer) may produce arginine vasopressin (AVP), we hypothesized that its stable surrogate marker copeptin might be used as a diagnostic tool.

Methods:
We analyzed 146 patients with SIADH from two prospective observational studies in Switzerland (NCT01456533) and Germany (NCT01341665) who were included while presenting at the emergency department. Patients underwent a standardized diagnostic assessment at admission including the measurement of copeptin levels. The final categorization into malignant or non-malignant SIADH was based on patient's history and clinical data including new findings during the hospitalization.

Results:
39 patients (median age: 63 years, 51% female) were diagnosed with malignant and 107 (median age: 73 years, 68% female) with non-malignant SIADH. Serum sodium levels were higher in malignant versus non-malignant SIADH: median (IQR) 124 mmol/l (120; 127) versus 120 mmol/l (117; 123) (<0.001). Median (IQR) copeptin levels of patients with malignant SIADH were 11.1 pmol/l (5.2; 37.1) and 10.5 pmol/l (5.2; 25.2) in non-malignant SIADH (p = 0.21).
Between different tumor entities, patients suffering from small cell lung cancer showed the highest copeptin values, but a significant difference in copeptin levels between tumor entities was not observed (p = 0.47).

Conclusion:
We found no difference in copeptin levels between malignant and non-malignant SIADH. Copeptin is not a suitable diagnostic tool to exclude or detect an underlying malignancy in patients with SIADH.

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Primary Adrenal Insufficiency - a rare Cause of Hypercalcemia

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Background/Introduction:
Hypercalcemia is a common disease found in patients admitted to hospital and in the emergency department. Most cases are due to primary hyperparathyroidism or malignancy. Adrenal insufficiency (Addison's disease) is a rare but important cause of hypercalcemia. Adrenal insufficiency causes hypovolemia and as a consequence a reduction in glomerular filtration rate, as well as an increased renal tubular calcium absorption. In addition, there is an increased calcium release from bone.
We report on a 46-year-old patient with primary adrenal insufficiency presenting with acute severe hypercalcemia and acute kidney injury.

Methods:
Case report, tertiary referral hospital

Results:
A 46-year-old male patient was transferred to the emergency department of our hospital from a local rehabilitation clinic, where he was found to have severe hypercalcemia (albumin corrected calcium peak 3.96 mmol/l) and an acute kidney injury (Creatinine peak 368 µmol/l). Two months before, he was treated in the intensive care unit for acute necrotized pancreatitis and an INR of 7.0 (because of a combined thrombophilia, he was under medication with Phenprocoumon).
On admission, the patient appeared slightly confused and tired, the blood pressure was 117/96 mmHg. The results of the blood test showed the known hypercalcemia as well as an acute kidney failure, the ionized Calcium was 1.89 mmol/l, INR was 4.2. EKG showed no pathological findings. The patient was referred to the intensive care unit for cardiac monitoring and lowering of calcium levels, where an intravenous rehydration was started. Additionally, Furosemide and Calcitonin were added as well as Methylprednisolone. Further investigations showed a suppressed PTH, an undetectable PTH-related peptide, as well as low levels of 25-OH vitamin D and 1,25-OH vitamin D. There was no evidence of malignancy. The basal serum cortisol was low at 94 nmol/l on admission. Two weeks later, the basal serum cortisol was 208 nmol/l and rose to a maximum of 235 nmol/l one hour after injection of 250µg ACTH (SynACTHen®), establishing the diagnosis of primary adrenal insufficiency. Additionally, Metanephrine was undetectable, while Normetanephrine and Methoxytyramin were unremarkable. Plasma aldosterone level was also normal, and no hyperkalemia was observed at any time. The calcium level normalized completely after substitution of hydrocortisone. Retrospectively, the CT scan at admission two months earlier, showed hemorrhage of the adrenals as cause of the adrenal failure. A diagnosis of primary adrenal insufficiency with involvement of cortex and medulla was made.

Conclusion:
Severe hypercalcemia can be the presenting symptom of an adrenal insufficiency. Adrenal insufficiency should therefore be searched after exclusion of more common diseases that induce hypercalcemia.

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Leptin, adiponectin and sDLK1 levels in a patient with familial lipodystrophy during pregnancy

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Background/Introduction:
Lipodystrophy is characterized by decreased and dysfunctional fat mass, severe insulin resistance, and decreased fertility. Patients with lipodystrophy lack adipokines such as leptin (related to fat mass) and adiponectin (related to insulin sensitivity). Leptin replacement is a promising treatment option for these patients. DLK1 (Delta-like 1 homolog, also known as FA1 (fetal antigen 1) or Pref-1 (preadipocyte factor 1)) is a protein highly expressed in the fetus and in the placenta. Soluble DLK1 (sDLK1) arises by enzymatic ectodomain clipping of the transmembrane form. sDLK1 inhibits adipogenesis and has been linked to fetal growth and maternal metabolism during pregnancy.

Methods:
We describe the rare case of a patient with lipodystrophy who became spontaneously pregnant at the age of 33 years and we followed the levels of adiponectin, leptin and sDLK1 during her pregnancy. Serum levels were measured by ELISA in the patient and in 7 healthy female controls (median age 28 (range 20-35) years; normal glucose tolerance). The patient was referred with poorly controlled diabetes and severe insulin resistance for better management (intensified, high dose insulin therapy during pregnancy). On physical examination, subcutaneous adipose tissue was virtually absent in the arms, legs and truncal areas; skeletal muscles appeared hypertrophic with prominent peripheral veins of the limbs. Prominent acanthosis nigricans was observed on the neck and arm pits. Facial fat accumulation created the impression of cushingoid appearance. Overall, the phenotype was consistent with the Dunnigan type lipodystrophy (FPLD2).

Results:
The patient had low levels of both adiponectin and leptin at baseline (before and after pregnancy), consistent with the clinical diagnosis of lipodystrophy. During pregnancy, there was a marked rise in serum leptin (but not of adiponectin), up into a low-normal range. Moreover, sDLK1 (low normal at baseline) also rose during pregnancy.

Table 1:
Adipokines during pregnancy in the patient, and controls; median and ranges (in parenthesis).

	Patient (n=1)			Controls (n=7)
Parameter	before	during	after pregnancy	non-pregnant
adiponectin (mg/l)	1.9	(1.2-1.7)	(1.7-1.9)	12.4 (2.4-13.6)
leptin (ng/ml)	0.5	(2.3-4.6)	(0.1-0.7)	10.5 (2.9-21.2)
sDLK1 (ng/ml)	4.1	(5.9-18.9)	(4.2-5.2)	6.4 (3.7-34.0)

Conclusion:
There was an increase in leptin and sDLK1 during pregnancy. The patient's glucose values and insulin requirements remained high over the period of our follow-up. It is difficult to estimate how improved metabolism and improved motivation contributed to the reasonable control of glycaemia achieved during her pregnancy, but it appears likely that fetus-/and or placenta-derived leptin and sDLK1 made an important contribution to the maternal serum levels in this particular patient.

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Effect of IL1-receptor antagonist on hemodynamics and Renin-Angiotensin-Aldosteron System in obese individuals

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Background/Introduction:
Interleukin (IL)-1 antagonism leads to a decrease in blood pressure (5mmHg) in obese individuals. The underlying mechanism is unknown. Based on experimental data in animals we hypothesised a blood-pressure lowering effect of IL-1-antagonism via modulation of the Renin-Angiotensin-Aldosteron System (RAAS).

Methods:
In this post-hoc explorative study, we examined short- (2 days) and long-term effects (4 weeks) of IL-1 antagonism (anakinra/Kineret®) on RAAS-peptide-profiles and on hemodynamic parameters assessed by a non-invasively measurement using HOTMAN® system in 128 obese (BMI > 30kg/m2) individuals with at least one feature of the metabolic syndrome from two previous interventional trials (CortIL trial a prospective interventional trial (n= 61) and TestIL trial, a placebo controlled-double blinded interventional trial (n=67)).

Results:
Upon IL-1 anatagonism circulating levels of angiotensin II, angiotensin I, aldosteron and renin remained unchanged after short- and long-term treatment, respectively. In contrast, the vasodilatatory angiotensin 1-7 peptide significantly increased after 4 weeks compared to placebo (in between group difference 16.35 pmol/L [1.22 to 30.17], p=0.028), without short-term effect on day 2. Non-invasive hemodynamic measurement revealed a decrease in the stroke systemic vascular resistance index (SSVRI) with an in between group difference of -62.65 dyn.sec.cm-5.m2 [95%CI -116.94 to -18.36], p=0.008 (consistent with a 25%-decrease) after 4 weeks of treatment compared to baseline.

Conclusion:
IL-1 antagonism in obese individuals with features of the metabolic syndrom led to an increase of the vasodilatatory angiotensin 1-7 peptide and a decrease in peripheral vascular resistance, reflected by the SSVRI after 4 weeks of treatment. These findings point to a possible blood pressure lowering mechanism via modulation of the RAAS-system of IL-1 antagonism.

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Association between glycaemic control and fracture risk in diabetic patients: a nested case control study

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Introduction: Diabetes is associated with an increased risk of non-vertebral fractures in both, type 1 (T1DM) and type 2 diabetes (T2DM). Pathophysiological mechanisms contributing to skeletal fragility are multifactorial and differ between diabetes types. We aimed to evaluate the association between diabetes control and the risk of low-trauma fractures since the impact of glycaemic control on fracture risk remains unclear.

Material and Methods: We conducted a nested case-control study within a cohort of patients with incident T1DM or T2DM between 1995 and 2015 based on the UK-based Clinical Practice Research Datalink. We identified all patients with a low-trauma fracture after the diabetes diagnosis. Using risk-set sampling, we matched them to 4 diabetes patients with no recorded fracture, matching on age, sex, general practice, index date, diabetes type, and diabetes duration (follow-up time between diabetes onset and fracture date). We characterized the study population with regard to comedications and comorbidities, and used conditional logistic regression analyses to assess the association between diabetes control (based on HbA1c-levels) and the risk of low-trauma fractures. We calculated crude and adjusted odds ratios (aOR), adjusting for BMI and smoking, as well as for specific diabetes complications and medications.

Results: We identified 566 T1DM cases and 2225 T1DM matched controls, as well as 8859 T2DM cases and 35416 T2DM matched controls. T1DM and T2DM patients had a mean of 8.5 (SD 8.4) and 11.1 (SD 9.6) recorded HbA1c-values, and median disease duration of 4.2 years (Q_1 1.9, Q_3 7.6) and 4.5 years (Q_1 2.0, Q_3 7.9), respectively. In T1DM patients with a 3-year mean HbA1c >8.0%, fracture risk was significantly increased (aOR 1.46; 95%CI, 1.09-1.97) compared to T1DM patients with HbA1c-levels <8.0%. In T2DM patients with mean HbA1c-levels of 8-9% and >9%, aORs were 0.91 (95%CI, 0.84-0.99) and 0.96 (95%CI, 0.88-1.06), showing no elevated fracture risk compared to HbA1c-levels <8.0%. Comorbidities associated with micro- and macrovascular complications of diabetes, such as diabetic retinopathy, chronic renal failure, and coronary heart failure, were all associated with an elevated fracture risk

Conclusion: The impact of glycaemic control on low-trauma fracture risk differs in T1DM and T2DM patients with short term disease. While poor glycaemic control (HbA1c levels >8%) elevated the fracture risk in T1DM patients no such association was observed in T2DM. This could be attributed to a protective effect of insulin resistance in early disease. Further studies are needed to evaluate other factors related to fracture risk in T2DM (e.g.disease duration or comorbidities).

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Interferences in thyroid function tests due to anti-streptavidin or anti-sulfo-ruthenium antibodies: an underestimated challenge.

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Background/Introduction:
Assay interferences in thyroid function tests (TFT) can have serious clinical consequences because they can lead to unnecessary investigations, anxiety, and even unnecessassary medical or surgical treatment. Rare isolated cases of TFT interferences due to antibodies to assay reagents have been reported. As part of a systematically program of TFT assay interference detection and characterization, we report here our experience with anti-streptavidin and anti-sulfo-ruthenium antibodies.

Methods:
TFTs were measured using the Roche ECLIA platform, including the second generation free thyroxine (FT4) assay. TFT interferences were suspected in presence of high FT4 levels and clinically unexplained, unsuppressed TSH levels, as compared to reference levels from 4462 participants of the local CoLaus cohort. Samples with suspected interferences were re-assayed after incubation with IgM-fixing HBT tubes. FT4 and TSH were also measured on the Abbott Architect platform. Anti-streptavidin antibodies or anti-sulfo-ruthenium antibodies were detected through pre-incubation of the samples with an excess of streptavidin or sulfo-ruthenium, respectively.

Results:
We identified 7 cases of TFT assay interferences due to anti-streptavidin antibodies and 1 case due to anti-sulfo-ruthenium antibodies. In 6 cases from the former group, pretreatment with HBT led to a marked reduction in plasma levels of FT4 and FT3 and an increase in plasma TSH levels. FT4 and TSH levels were all within the normal range when assayed using the Abbott platform. Serial measurements for 3 cases showed that interferences were time-limited and entirely reversible. The magnitude of assay interference was larger for FT4 than for TSH.

Conclusion:
Clinicians and laboratory physicians should be aware of TFT assay interferences due to anti-streptavidin antibodies, because they are not excessively rare. These antibodies are most frequently of the IgM subclass and affect the measurements of FT4, FT3 and, to a lesser extent, TSH. We will discuss our institutional strategy for detecting and characterizing these and other TFT assay intereferences.

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Switching to insulin glargine 300 U/ml improves glycemic control in patients with type 2 diabetes: real-world effectiveness in Switzerland

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Background/Introduction:
Insulin glargine 300 U/ml (Gla-300) is a long-acting once-daily basal insulin (BI) with improved, more stable and smoother pharmacokinetic and pharmacodynamic profiles as compared to insulin glargine 100 U/ml (Gla-100). These properties have been shown to translate into an effective HbA1c reduction with the advantage of a lower rate of hypoglycemia in randomized controlled trials of Gla-300 vs Gla-100. In this study we assessed the effectiveness and safety of Gla-300 under real-world conditions in Switzerland.

Methods:
The prospective observational multicenter study TOP-2 explored the effectiveness of Gla-300 in adult patients with type 2 diabetes (T2D) uncontrolled (HbA1c 7.5-10%) on their previous BI in Germany, Austria and Switzerland. Primary endpoint (EP) was the rate of patients achieving fasting plasma glucose (FPG) of ≤ 6.1 mmol/L after 6 and 12 months, respectively. Secondary EPs included changes in HbA1c, FPG, body weight (BW) and insulin dose as well as hypoglycemia incidence and safety. Here we report the results for the Swiss patient cohort at 12 months.

Results:
The documented 62 patients (29 women) had a mean age of 65 years, a mean diabetes duration of 14 years, a mean body mass index (BMI) of 31 kg/m2 and were mainly switched from Gla-100 (44%) to Gla-300. Most commonly associated oral therapy was metformin (65%). The mean individual HbA1c target chosen by the investigators was 7.4%. Effectiveness and hypoglycemia EPs are shown in the table below. After 12 months of therapy Gla-300 significantly reduced HbA1c by 0.7% (p<0.0001) reaching a mean final HbA1c of 7.6%. Likewise, Gla-300 significantly reduced FPG by 1.8 mmol/L (p<0.0001) reaching a mean final FPG of 7.4 mmol/L. After one year 57% of patients achieved their individual HbA1c target, 32% achieved FPG ≤ 6.1 mmol/L and 55% achieved FPG ≤ 7.2 mmol/L. Gla-300 was uptitrated to a mean dose of 40 units per day. Confirmed symptomatic hypoglycemia incidence after 12 months was low at 8.1% and a rate of 0.35 events per patient year. Only one patient experienced severe hypoglycemia. BW remained stable and was not significantly altered after 1 year (mean change from baseline: -0.9 kg; p=0.37).

Conclusion:
Switching BI to Gla-300 improved significantly overall glucose control in patients with T2D and glycemic targets could be achieved with a low rate of hypoglycemia under real-world conditions in Switzerland.

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Glucagon-like peptide-1 (GLP-1) receptor imaging in patients with post gastric bypass hypoglycemia

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Background/Introduction:
Months to years after Roux-en-Y gastric bypass surgery, post gastric bypass hypoglycemia (PGBH) can occur after food intake. The incretin hormone GLP-1 has been found to play a pivotal role in the development of PGBH. ^{68}Ga-DOTA-exendin-4 is a specific tracer for GLP-1 receptors in PET/CT. The aim of this study is to investigate the GLP-1 receptor expression of the pancreas in vivo in patients with PGBH.

Methods:
^{68}Ga-DOTA-exendin-4 PET/CT was performed in 5 patients with PGBH (5 female, mean age 38.2 y). The sum of the standard uptake value (SUV) of the pancreas volume was measured by two readers and compared to a control group consisting of 5 insulinoma patients (4 female, 1 male, mean age 56.6 y). The tumour-free pancreatic tissue was measured in the control group and normalized SUV sum of the volume of the insulinoma was added.

Results:
The median SUV sum of the pancreas in the PGBH group was 4334 (range 2419-6520) and in the control group 1975 (range 1406–2960). The expression of GLP-1 receptors in the pancreas in patients with PGBH is significantly higher than in the normal pancreatic tissue of patients with insulinoma, as shown by the unpaired Mann-Whitney-test (p-value of 0.037).

Conclusion:
Potential explanations for the increase of GLP-1 receptors in the pancreas of PGBH patients, compared to normal pancreatic tissue of patients with insulinoma may be: i) increase of β-cell mass in patients with PGBH, ii) downregulation of β-cell mass in the normal pancreas in patients with insulinoma, iii) a combination of both and/or limitations due to iv) small sample size.

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Copeptin after Arginine Stimulation - A new Test for Diabetes Insipidus?

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Background/Introduction:
It is crucial to discriminate between diabetes insipidus and primary polydipsia as treatment differs considerably. Available diagnostic methods are cumbersome and misleading. Herein, we hypothesized that copeptin measurements after arginine stimulation provide a new diagnostic approach to diabetes insipidus.

Methods:
Patients with central diabetes insipidus or primary polydipsia and healthy controls (adults and children) were included in this prospective diagnostic study. Copeptin levels were measured at 0, 30, 45, 60, 90, 120 minutes after arginine stimulation. The primary endpoint was the diagnostic accuracy of copeptin levels at each measurement after stimulation.

Results:
31 (60%) of 52 patients had primary polydipsia, 12 (23%) complete diabetes insipidus and 9 (17%) partial diabetes insipidus. Copeptin levels after arginine stimulation increased in primary polydipsia (median [IQR] baseline: 3.5 pM/L [2.5, 5.2], maximal: 6.7 pM/L [4.7, 9.5], p<0.001), whereas no increase was seen in diabetes insipidus (2.1 pM/L [1.5, 2.5]), maximal: 2.2 pM/L [1.6, 3.0], p=0.12). A cut-off of 3.5 pM/L at 60 minutes provided the highest diagnostic accuracy to discriminate between diabetes insipidus and primary polydipsia: 0.94 [95% CI: 0.84, 0.98], (sensitivity 90.5%, specificity 96.8%). In 20 healthy adults and 42 children copeptin levels increased significantly after stimulation (3.6 pM/L [IQR: 2.4, 6.9] to 7.3 pM/L [4.3, 9.1] and 4.4 pM/L [3.2, 6.2] to 6.1 pM/L [4.7, 8.2]).
To justify the established cut-off we collected additional experimental data of 46 patients with diabetes insipidus or primary polidipsia and 30 healthy adults. Data of this second cohort are currently being evaluated and will be presented at the SGED meeting in November 2018.

Conclusion:
Arginine is a potent stimulus of the neurohypophysis. Copeptin levels after arginine stimulation are an innovative tool to discriminate between central diabetes insipidus and primary polydipsia with a high diagnostic accuracy.

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A novel diagnostic approach to factitious hypoglycemia

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Background/Introduction:
Factitious hypoglycemia is a rare aetiology of hypoglycemia caused by the surreptitious use of insulin or insulin secretagogues. Confirmation of the diagnosis can be difficult, particularly because of the strain on the patient-doctor relationship, with the patient feeling mistrusted and the doctor feeling deceived. Laboratory hallmark of factitious hypoglycemia are high plasma insulin values in conjunction with low C-peptide and proinsulin levels. However, there are caveats regarding interpretation of insulin values. Due to variable cross-reactivity of commercially available immuno-assays with human and synthetic insulins, detected insulin levels may either be low or high.

Methods:
We describe the diagnostic work up of factitious hypoglycemia in a diabetic patient highlighting the limitations of insulin immuno-assays and presenting an alternative LC-MS/MS analysis.

Case Report:
Recurrent episodes of syptompatic hypoglycaemia were observed in a 51 year old man with mixed pancreatic/type 2 diabetes who was treated with metformin and insulin degludec, whilst hospitalized in a psychiatric clinic because of longstanding alcohol abuse. Despite withholding the antidiabetic treatment for more than 14 days further hypoglycemic events occurred, with blood-glucose nadir < 2.5 mmol/L. The patient strongly denied self-administration of insulin and, therefore, hypoglycemia was initially attributed to his alcoholic liver disease. Because of persisting hypoglycemic events the patient was referred to our endocrine clinic. The following fasting test results were obtained with concomitant blood-glucose of 3.9 mmol/L: C-peptide 0.18 ng/mL (ref. 0.9 - 7.1 ng/mL), pro-insulin 4.7 pmol/L (ref. < 10 pmol/L) and insulin 1.7 mU/L (ref. 2.6 - 24.9 mU/L). These results would in principle be compatible with a non-insulin dependent cause of hypoglycemia (as for instance the postulated hepatopathy). However, since the used standard insulin-assay detects human insulin exclusively (Elecsys, Roche Diagnostics) we additionally measured the sample using an unspecific assay with cross-reactivity for various synthetic insulins (ARCHITEC, Abbott Laboratories). The latter detected a clearly increased insulin level (1425 pmol/L; ref. 57 - 144 pmol/L) suggesting exogenous insulin administration. Using an in-house mass spectometry approach (UPLC coupled to a triple quadrupole mass spectometer Xevo TQ-S Waters), we were able to identify insulin degludec as the cause of the elevated insulin levels and the resulting hypoglycemia. By confronting the patient with these results he admitted the ongoing surreptitious use of insulin degludec to intentionally induce hypoglycemia.

Conclusion:
Diagnosis of factitious hypogylcemia can be cumbersome. For a correct interpretation of the laboratory findings one should be aware of the properties of the insulin assay used, especially the cross-reactivity for human and different synthetic insulins. Mass spectrometry enables distinction between endogeneous and exogenous insulins within the same measurement, including the identification of synthetic insulins. Mass spectrometry-based insulin measurement may therefore represent a novel approach to uncover factitious hypoglycemia.

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Prevalence of diabetes mellitus and impaired fasting glucose among TB/HIV co-infected patients in Kampala/Uganda

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Background/Introduction:
The burden of diabetes mellitus (DM) is increasing world-wide. The highest increase in prevalence is expected in sub-Saharan Africa putting this region in the challenging situation of facing a double burden of infectious and non-communicable diseases. Strong efforts have been undertaken to curb tuberculosis (TB); however, these efforts may be undermined by the growing epidemic of DM. For patients with DM, previous studies found a 2-4 fold increased risk of developing active TB, TB treatment failure and relapse. On a global scale, up to 15% of TB cases might be attributable to DM. The goal of this retrospective analysis was to determine the prevalence of DM and impaired fasting glucose (IFG) in TB/HIV co-infected patients at a large tertiary TB/HIV-clinic in Uganda.

Methods:
This is a sub analysis of data from the observational study entitled "Study on Outcomes related to TB and HIV drug concentrations" (Sekaggya et al., Clin Infect Dis., 2018). Participants were enrolled at the Infectious Diseases Institute, Kampala, Uganda, which currently serves 8000 outpatients. All participants were HIV-infected adults with newly diagnosed pulmonary TB. Plasma glucose measurements were done at week 2, 8 and 24 of anti-TB treatment. DM was defined as fasting plasma glucose (FPG) ≥126 mg/dL and IFG as FPG in the 100-125 mg/dL range. FPG was determined from a venous blood sample after >8 hours of fasting using a Hemocue® glucose 201+ analyser. Data are presented as median (IQR). Written informed consent was obtained from all study participants prior to enrolment.

Results:
A total of 107 study participants had at least one plasma glucose measurement during anti-TB treatment and were subsequently included in this sub analysis. The median age was 34 (29–40) years, and 69.2% were male. The median BMI was 19.2 (17.7-21.3) kg/m2, the median CD4 count was 182 (64-347) cells/mm3, and 77.6% were ART naïve at study inclusion. TB treatment outcome was as follows: 80 (74.8%) participants were cured, 9 (8.4%) completed treatment, 2 (1.9%) had treatment failure, 3 (2.8%) died, 2 (1.9%) were lost-to-follow-up, and 11 (10.3%) cases could not be evaluated.
FPG ≥126 mg/dL was found in 8/41 (19.5%) participants at week 2, in 3/63 (4.8%) at week 8, and in 3/89 (3.4%) at week 24. IFG was found in 23/41 (56.1%) at week 2, in 31/62 (50.0%) at week 8, and in 39/89 (43.8%) at week 24. The median FPG decreased significantly during TB treatment (p<0.01).

Conclusion:
Our results confirm previous reports on a high prevalence of DM in the early phase of TB treatment and a gradual decrease of FPG during TB treatment. Although TB treatment was very successful, a high prevalence of IFG (44%) at the end of TB treatment was documented. Further studies are needed to determine the potential progression to DM and TB relapse in these patients with IFG.

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A malignant pheochromocytoma and mutation in the VHL gene – *von Hippel-Lindau disease or not?*

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Background/Introduction:
Adrenal pheochromocytomas are catecholamine-secreting tumors, arising from the chromaffine cells of the adrenal glands. In up to 10% adrenal pheochromocytomas are malignant, a condition defined by the occurrence of metastasis. Approximately 40% of pheochromocytomas are part of a syndromic disease and might exhibit a genetic mutation. Guideline based recommendations for an active genetic screening are conflicting but support this diagnostic step when other syndromic features or a suspicious family history are evident. Gene variations associated with the pathogenesis of pheochromocytoma include mutations i.e. in the SDH genes, RET proto-oncogene, neurofibromatosis type 1 tumor suppressor gene (NF-1), von Hippel-Lindau disease tumor suppressor gene (VHL), TMEM127- and MAX-genes.

The von Hippel-Lindau disease is a very rare disease complex including pheochromocytomas, hemangioblastomas of the retina, the central nervous system and the spinal cord, renal clear cell carcinomas, serous cystadenomas, neuroendocrine tumors of the pancreas, endolymphatic sac tumours of the middle ear and urogenitals cysts. Patients suffering from a mutation of this autosomal-dominant disorder require lifelong screening tests, including MRIs of the entire CNS, testing for plasma metanephrines/normetanephrines and abdominal imaging as well as ENT and urological investigations.

Methods:
Case report

Results:
We present the case of a 61-year-old patient who presented with abdominal pain. CT and MRI scans demonstrated a left sided adrenal mass with a diameter of 6.4 cm. Testing for free plasma metanephrines/normetanephrines confirmed the presence of a pheochromocytoma with a noradrenergic biochemical pattern. Adrenalectomy was performed after sufficient presurgical medical blockade with phenoxybenzamine and a beta blocker. The histological analyses revealed a pheochromocytoma with micrometastes in one of the neighbouring lymph nodes. Clinical work-up was negative for any features suggesting a syndromic disease. Interestingely three brothers have died of appendicitis (8 yrs), stroke (36 yrs) and heart attack (52 yrs) earlier. Due to this noticeable family history screening for hereditary pheochromocytomas was performed and revealed a heterozygous mutation carrier status in the VHL gene (c.492 G>C) . All additional tests (MRI of the CNS, eye investigation, ENT) were normal and post surgical metanephrines are in the normal range now. Similar mutations in the VHL gene are described and characterized with uni- or bilateral pheochromocytomas in those cases.

Conclusion:
A heterozygous mutation in the VHL gene (c.492 G>C) might be associated with the occurrence of pheochromocytomas but not the full picture of von Hippel-Lindau disease. Irrespectively, life long surveillance for von Hippel-Linda disease in the patient and affected family members is meaningful.

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Mosaicism and copy number variations in congenital hypogonadotropic hypogonadism patients

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Background/Introduction:
Congenital hypogonadotropic hypogonadism (CHH) is a rare genetic disease characterized by absent puberty and infertility due to GnRH deficiency. 50% of probands harbor mutations in at least one of the >30 CHH genes, either alone or in combination. Variable expressivity and reduced penetrance are commonly observed in CHH. We hypothesized that mosaicism will be part of the genetic landscape of CHH. Post-zygotic mutations resulting in somatic mosaicism are well-known in disorders such as Turner or McCune Albright syndromes, but have never been described in CHH.

Methods:
DNA from CHH probands was evaluated for mosaicism and copy number variations in the known CHH genes. Whole exome, Sanger, and ultra-deep sequencing were performed.

Results:
We detected and confirmed de novo mosaic mutations in 4 of the 136 CHH probands (3%). Each proband harbors one of the following mosaic mutations: FGFR1 p.Leu630Pro (33.3%), FGFR1 p.Gly348Arg (24.4%), CHD7 p.Arg2428* (34.4%), and HS6ST1 p.Lys67*(15.0%). None of these mutations are found in the gnomAD control database. The two missense mutations are predicted to be damaging by protein prediction algorithms (SIFT and PolyPhen2), and are loss-of-function in vitro. Additionally, we identified a male CHH proband with a copy number variation (duplication) encompassing exons 10-28 of CHD7, which is not reported in the gnomAD control database.

Conclusion:
3% of CHH probands carry de novo mosaic mutations in autosomal dominant CHH genes. Our report highlights (i) mosaicism as a novel mode of inheritance for CHH; (ii) the utility of next-generation sequencing to uncover mosaicism; and (ii) the critical need to screen parental DNA to determine if mutations are de novo, and thus possibly mosaic. Our findings are important not only for diagnostic testing but also for accurate genetic counseling.

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Role of tRNA-derived fragments in maturation of rat pancreatic β-cells

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Background/Introduction:
Newborn pancreatic β-cells possess a strong replicative capacity that is critical to generate an appropriate adult β-cell mass. Thus, impairment in the proliferative potential of newborn β-cells may contribute to diabetes susceptibility at adulthood. The role of non-coding RNAs in the establishment of the functional β-cell mass has started to be unraveled with studies focusing on microRNAs and long non-coding RNAs. However, other classes of non-coding RNAs are also expressed in β-cells, including circular RNAs, piRNAs and tRNA-derived fragments (tRFs). In recent years, in depth analysis of next-generation sequencing data unveiled that tRFs can play important regulatory roles in several cellular processes. The aim of this study was to investigate the potential involvement of tRFs in the establishment of an appropriate functional β-cell mass during the postnatal period.

Methods:
Small RNA-sequencing was performed on samples extracted from immature (postnatal day 10, p10) and mature (3 month old) rat pancreatic islets and differentially expressed tRFs were profiled. Expression of candidate tRFs were verified using a LNA Universal RT miRNA PCR system. For functional analyses, candidate tRFs were inhibited in p10 rat islets using LNA inhibitors and the proliferative capacities of β-cells were assessed by BrdU incorporation and Ki-67 staining. Moreover, expression of several key β-cell proliferation markers were measured in islets by quantitative PCR.

Results:
Small RNA-sequencing led to the indentification of 261 tRFs that are differentially expressed between p10 and adult rat islets. In particular, tRFs aligning to the 5' half of GluTTC, GluCTC and HisGTG tRNAs were found to be highly abundant in p10 rat islets and to be downregulated 2.5-6 folds upon β-cell maturation. These observations suggests a potential contribution of these 5' tRFs in postnatal β-cell maturation. Indeed, concurrent inhibition of these 5' tRFs in p10 islets resulted in a significant reduction in β-cell proliferation. At the mRNA level, this was associated with a mysregulation of several key regulators of β-cell proliferation, such as ccnd2, timp2, and mtor. The expression of 5' tRFs in relevant diabetes models and the molecular bases of 5' tRF regulated β-cell proliferation are currently investigated.

Conclusion:
This study demonstrates that tRFs regulate newborn β-cell mass expansion. A better definition of the role of tRFs in neonatal β-cells will help elucidating the mechanisms governing the generation of an appropriate functional β-cell mass and will contribute to a better understanding of the developmental origins of Type 2 diabetes predisposition.

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Cystatin C alleviates Obesity-Associated Tissue Inflammation and Insulin Resistance

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Background/Introduction:
We recently demonstrated that removal of one kidney (uninephrectomy) in mice reduced high fat-diet (HFD)-induced adipose tissue inflammation and improved hepatic insulin sensitivity. Moreover, uninephrectomized mice revealed increased plasma levels of cystatin C, a circulating factor with suggested anti-inflammatory properties. We, thus, hypothesize that cystatin C alleviates obesity-associated adipose tissue inflammation.

Methods:
6-week-old C57BL/6J wild type (WT) and cystatin-C-deficient mice (CysC KO) were fed a regular chow or HFD (~60% kcal fat) for 20 weeks. Glucose metabolism was assessed by intraperitoneal glucose tolerance tests (ipGTT) and by hyperinsulinaemic-euglycaemic clamp studies. After sacrification, liver and fat depots were analyzed applying Western blotting, rtPCR and histological staining.

Results:
HFD-induced aggravation in glucose tolerance was significantly elevated in CysC KO compared to WT mice (ΔAUC ipGTT 348±85 mmol/l*min in WT vs. 803±106 mmol/l*min in CysC KO, p<0.01). Moreover, hyperinsulinaemic-euglycaemic clamps in HFD-fed mice revealed a significantly lower insulin-mediated inhibition of endogenous glucose production (EGP) in CysC KO compared to WT mice (24.2±3.3 mg/kg*min in WT vs. 44.6±3.7 mg/kg*min in CysC KO, p<0.05), indicating exacerbated hepatic insulin resistance in CysC KO mice. In addition, glucose uptake into inguinal adipose tissue during clamp study was ~50% reduced in CysC KO mice, paralleled by significantly reduced serine473 phosphorylation of Akt (1.0±0.2 in WT vs. 0.3±0.0 in CysC KO, p<0.05). mRNA levels of the pro-inflammatory factor Il-6 (1.0±0.2 in WT vs. 2.8±0.6 in CysC KO, p<0.05) and the pro-fibrotic factor Tgfβ1 (1.0±0.2 in WT vs. 2.2±0.5 in CysC KO, p<0.05) were increased in epididymal fat of HFD-fed CysC KO mice. Similarly, mRNA levels of pro-inflammatory cytokines Il-6 (1.0±0.1 in WT vs. 3.5±0.4 in CysC KO, p<0.05) and Il-1β (1.0±0.1 in WT vs. 1.8±0.2 in CysC KO, p<0.05) were increased in livers of HFD-fed cystatin C-knockout mice, paralleled by signs of hepatocellular injury in histological sections of such mice.

Conclusion:
Our data indicate a beneficial role of cystatin C in obesity-associated (adipose tissue) inflammation and (hepatic) insulin resistance.

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STARD8, a novel candidate gene for 46,XY disorders of sex evelopment.

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Background:
An activation cascade of specific genes sets up the initiation of sex determination leading in males to testes formation and synthesis of testicular hormones. Disruption of this gene cascade may cause a spectrum of 46,XY disorders/differences of sex development (DSD) phenotypes. Here we describe for the first time two sisters suffering from 46,XY DSD, who by whole exome sequencing revealed to carry a X-linked mutation in the StAR-related lipid transfer domain protein 8 (STARD8) gene. STARD8, also known as deleted in liver cancer 3 (DLC-3) is a functional Rho-specific GAP protein, the loss of which enhances perinuclear Ras homolog gene family member A (RhoA) activity. Simultaneously, RhoA is known to play a role downregulating the expression of SOX9 and, thus, inducing the female sexual development pathway. On the other hand, available literature also linked STARD8 with the targeting of focal adhesions and the stimulation of the enzymatic activity of Phospholipase C δ1 (PLCδ1), which is known to lower the levels of active-β-catenin. Moreover, β-catenin has been identified as a key pro-ovarian and anti-testis signaling molecule. To gain new insights in human sex development mechanisms, we aimed to analyze the functional consequences of STARD8 mutations as a putative novel 46,XY DSD- related gene by testing the RhoA phosphorylation-dependent SOX9 expression, as well as by analyzing the subcellular localization and signaling activity of β-catenin. Since the STARD8 knockout NMRI mouse model we generated did not recapitulate the human clinical picture, we chose to test the mutation in a cell system.

Methods:
COS1 cells were transfected with wild type and mutant STARD8. Quantification of activated RhoA (RhoA-GTP) levels in cell lysates was performed by a pull-down assay that specifically binds the active form of RhoA. Subsequently, the RhoA-GTP, total RhoA, SOX9 and STARD8 protein expression levels were analyzed by western blot. Quantitative RT-PCR expression profiling of STARD8, SOX9, and PLCD1 was also performed. Finally, cell immunofluorescence was used to evaluate STARD8 and β-catenin subcellular localization.

Results:
Preliminary results showed an increase in activated RhoA levels and consequent reduced SOX9 protein expression levels with the STARD8 mutant when compared to the wild type. In addition, an increase in the STARD8 protein expression levels was observed in the mutant when compared to the wild type. Alterations in STARD8 and β-catenin subcellular distribution were also observed using cell immunofluorescence when comparing STARD8 wild type and STARD8 mutant transfected COS-1 cells.

Conclusions:
The mentioned results suggest a Sox9 protein expression and β-catenin subcellular distribution, which are STARD8-dependent and mediated by RhoA phosphorylation, that could be triggering sex reversal in the 2 affected patients. Therefore, STARD8 resembles a strong novel candidate gene for 46,XY DSD which might have an important role in sexual differentiation.

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Novel mutation, old locus: characteristics of a novel P450 oxidoreductase mutation (P399_E401Dup), in a patient with a 46, XX DSD phenotype at birth

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Background/Introduction:
P450 oxidoreductase (POR) mutations can present with disordered sexual development (46,XX virilisation/ 46,XY under-masculinisation), perturbed steroidogenesis and mild to severe skeletal malformations. As POR is an obligate electron donating cofactor to many P450s, and this interaction may vary from partner to partner, the phenotypic spectrum of PORD is extremely broad. Therefore, to characterize novel POR mutations, specific testing is required.
Case report: A 46,XX patient, second child of consanguineous Kurdish parents, was born at term with ambiguous genitalia (Prader III) and dysmorphic facial features (frontal bossing, low set ears). Newborn screening for 21-hydroxylase deficiency and ACTH-testing were normal. At age 14 days diagnosis of PORD was made by GC-MS urinary steroid metabolome-analysis showing the pathognomonic pattern of combined impaired activities of 17-hydroxylase and 21-hydroxylase. Genetic analysis revealed a novel homozygous mutation P399_E401Dup in POR.

Methods:
The novel POR variant was characterized by bioinformatic and functional tests using recombinant proteins produced in bacteria, combined with small molecule and protein substrates. The ability of POR wild-type (WT) and P399_E401Dup variant to reduce ferricyanide [measures intactness of the FAD-binding domain of POR], MTT [as an indicator of electron transfer from the co-factor FMN bound inside the POR to its redox partners], and cytochrome c as well as the activity towards the drug and steroid metabolizing P450s were analysed. Effects of the mutation on cofactor (FAD/FMN) binding and activity under varying substrate and cofactor conditions were also investigated.

Results:
The interaction with substrates was altered in the P399_E401Dup. Compared to WT, P399_E401Dup variant showed 51% activity in the cytochrome c reduction assay; in the MTT reduction assay the P399_E401Dup had only 6.2% of WT activity, showing a clear problem in electron transport mechanism. In the ferricyanide reduction assay, a 50% increase in the Michaelis constant (Km) for the FeCN was observed in addition to a 30% loss in maximal velocity. Overall results indicated a structural change by P399_E401Dup mutation in POR, which affects protein conformation and stability.

Conclusion:
POR P399_E401Dup leads to alteration in Km and Vmax for multiple substrates, pointing towards an effect on protein conformation and stability. It also affects steroid production as manifested by alterations in the steroid metabolome of the patient. Previously, a P399_E401Del mutation in a Turkish child was reported, which had reduced activities of CYP17A1, CYP21A2 and CYP19A1. P399_E401 seems a sensitive spot for POR mutations.

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A homozygous SLIT2 mutation identified in a patient with Kallmann syndrome and Dandy-Walker malformation

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Background/Introduction:
Congenital hypogonadotropic hypogonadism (CHH) is a rare genetic disease characterized by absent puberty and infertility due to GnRH deficiency. This disorder is often associated with anosmia and termed Kallmann syndrome (KS). More than 30 genes have been implicated in the pathophysiology of CHH, including genes encoding Fibronectin type-III domain (FN3). Indeed, similar to ANOS1 (the first gene associated with KS), other genes encoding axon-guidance proteins contain FN3 domains and are mutated in CHH (e.g. DCC, NTN1, AXL, FLRT3). Since 50% of CHH genes remain unknown, we hypothesize that other genes encoding FN3 domains will underly CHH.

Methods:
A cohort of 183 CHH probands was screened for genes encoding proteins containing FN3 domains (n=175) and involved in axon guidance (GO:0007411, n= 22). Standard filtering process was used to detect mutations including Minor Allele Frequency (MAF) and in silico predictions (Sift/CADD/PolyPhen). Transcripts (q-PCR) and protein (Western-blot) expressions were assessed to determine mutants behavior and stability.

Results:
Our filtering method identified 62 rare sequence variants (RSVs) in genes encoding FN3 domain and involved in axon guidance. Mutations in several genes of the ROBO pathway (ROBO1-3/SLIT2/DSCAM/PLXN) were identified. In particular, we discovered a homozygous mutation in SLIT2 (p.Asp1074His) - the ligand for ROBO3 - in a KS patient with Dandy-Walker malformation (DWM). This patient presents no change in KS or DWM genes. In vitro assays using the mutant gene demonstrated mRNAs instability leading to a lack of protein production.

Conclusion:
Herein, we describe a homozygous loss-of-function mutation in SLIT2 in a patient with KS and DWM. SLIT2 and the other genes from the ROBO pathway, all coding for FN3 domain, are known to be implicated in GnRH neuron migration and other developmental processes. Notably, the murine SLIT2-KO mimics the large array of phenotypes found in our patient, consistent with clinical and genetic overlap between KS and DWM.

71 S

Insights in promoter transactivation of CBX2 expression

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Background:
The process of sexual differentiation is critical for reproduction in nearly all metazoan. Defects in any of the genes involved in either testicular or ovarian development can result in disorders of sex development (DSD). CBX2/M33 is a chromatin modifier that plays an important role in sexual development and its disorders, highlighted by the fact that M33-deficient mice have male-to-female sex reversal and loss-of-function of CBX2 causes 46, XY DSD in humans. Human CBX2 exists in two isoforms, a 532-amino acid long isoform called CBX2.1, and a second shorter 211-aminoacid isoform named CBX2.2. The promoter of these variants are unknown, however there are hints of differential expression by the isoforms in different cell lines and tissues.

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

Methods:
To locate the CBX2 promoter, candidate regions targeting transcription and the start of translation, were cloned as reporter inserts into the pGL4.17 Vector which lacks a promoter, requires expression of SV40 T antigen, and encodes the luciferase reporter gene luc2. The custom promoter constructs were transfected in Cos-1 cells (SV40 transformed cell type), with reporter activity established by performing a dual-reporter assay measuring firefly and *Renilla* luciferases. Subsequently, CBX2 promoter elements are dissected based on predicted binding sites and expressed in ovarian, testicular and adrenal cell lines (KGN, NT2D-1, and NCI-H295R cells respectively) to determine the regulation of CBX2 expression.

Results:
Utilizing the dual-reporter assay system, we identified an optimal candidate CBX2 promoter construct that exhibited a 3.6 normalized fold change in activity when compared to a negative control (p<0.0074). Preliminary results indicate that this promoter construct may be applied to investigate differential transactivation of CBX2 in cell models recapitulating ovaries, testis and adrenal cells.

Conclusion:
The characterization of a candidate CBX2 promoter could elucidate the inner workings of a CBX2-regulated network and its functional role as transactivator, distinct from its known function as chromatin-modifier. Further study of the impact of CBX2 activation and suppression may shed light on potential pathological mechanisms involved in DSD, and ultimately its diagnosis and management.

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The role of zinc and zinc transporter 8 in beta cell hypoxia induced cell death

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Background/Introduction:
A common feature of type 1 diabetes (T1D) and type 2 diabetes (T2D) is a progressive dysfunction and loss of insulin-producing pancreatic β-cells. Recently, we demonstrated that low oxygen levels result in a reduction of cytosolic zinc concentrations and zinc transporter 8 (ZnT8) expression in pancreatic β-cells. ZnT8 is responsible for the accumulation of zinc into the insulin secretory vesicles of pancreatic β-cells. Here we aim to explore the role of ZnT8 and cytosolic zinc in the viability of β-cells under hypoxic conditions.

Methods:
Wild type and global ZnT8 knockout mice were used for pancreatic islet isolation. Isolated islets were incubated for 24 hours in RPMI medium. Following different treatments, whole islets were stained with 3 μM Calcein-AM (living cells) and 2.5 μM propidium iodide (dead cells), incubated for 15 min at +37°C and vusualized via fluorescent microscope. The islet area occupied by dead cells (PI) was calculated and expressed as ratio vs that occupied by all (live and dead) cells using ImageJ.

Results:
Islets of ZnT8 knockout mice (24 weeks old) survive better under hypoxic conditions (50.3% reduction of cell death; p<0.001) compared to islets from wild-type mice. In order to test whether this effect on survival is mediated by zinc, we exposed islets to exogenous ZnCl. Indeed, islets lacking ZnT8 are more resistant to zinc-mediated cytotoxicity (30.5% reduction of cell death; p< 0.001) compared to wild type islets. In contrast, wild-type mouse islets exhibit reduced cell death under hypoxic conditions if treated with the zinc chelator TPEN (35.73% reduction of cell death vs control, p<0.001).

Conclusion:
Our results show that loss of zinc transporter 8 results in reduced β-cell death in hypoxia and during exposure to exogenous zinc. Similarly, exposure to the zinc chelator TPEN mediates improved cell survival in hypoxia. Although ZnT8 ist important for proper β-cell function, reduction of ZnT8 levels observed under hypoxic conditions may be an adaptive response of the cell to address the increased level of stress, when ZnT8 related high intracellular levels of zinc may become cytotoxic.

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In silico and functional studies of variants in SRD5A2 in search of activating mutations explaining hyperandrogenism, reveal novel loss of function variants only

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Background/Introduction:
Androgens are steroid hormones necessary for human sex development. Multiple steroid biosynthetic pathways lead to androgens like testosterone (T), dihydrotestosterone (DHT), 11-keto-T and 11-keto-DHT that activate the androgen receptor. Steroid reductases 5α (SRD5As) play a key role in androgen biosynthesis. They catalyse the conversion of T to DHT,11-K-T to11-K-DHT, 17-OH-progesterone to 17-OH-dihydroprogesterone or androstenedione to androstanedione leading to DHT through alternative pathways. The SRD5A family has 4 members, but only SRD5A1 / SRD5A2 are involved in steroids biosynthesis. SRD5A2 is expressed in reproductive tissues and has a lower Km than SRD5A1 for common substrates, thus converts them more efficiently. Human SRD5A2 loss-of-function mutations are known and cause 46,XY undervirilisation. Gain-of-function (GOF) mutations have been suggested for androgen excess syndromes, but they have not been found so far. Thus, we aimed at finding GOF mutations in the SRD5A2 gene.

Methods:
We searched databases for candidate variants and performed bioinformatic and functional tests on selected variants. A novel 3D model was constructed to locate the exact position of amino acids in the tertiary structure and predict their effect on protein function and substrate interaction. We then collected n=357 coding SNPs in SRD5A2 from OMIM,dbSNP, HGMD,UNiprot, ClinVar. SNPs were ranked according to their association with phenotypes, location close to enzyme active centres in the 3D model and the predicted shift in ΔΔG energy value they create due to the amino acid substitution. Finally we selected 7 SNPs for functional studies. SRD5A2 variants were epxressed in HEK293 cells and we assayed enzymatic activity by their ability to convert substrates T and progesterone (Prog) to their reduced metabolites DHT and DHProg, respectively.

Results:
All 9 selected SNPs were located within or close to highly conserved areas that form cavities for cofactor or substrate binding. When we used T as a substrate variants R50A and P173S showed partial loss of function with 34% and 28% activity compared to the wt. Variants A49T, P106L, P106A, N122A, L167S, R168C and R227Q revealed loss-of-function with no conversion to DHT. When we used Prog as a substrate all variants showed decreased enzymatic activity. As predicted in our in silico analysis, all coding SNPs affected enzymatic activity in vitro.

Conclusion:
We provide a novel protein model for studies of SRD5A2. No GOF variants were identified, but we characterised 7 novel loss-of-function SRD5A2 variants, which might be clinically important. Presumably individuals carrying these SNPs show a minor phenotype that is not recognized yet. Increased activity of SRD5A enzymes in androgen excess disorders might be due to increased gene expression or decreased metabolism regulated at the transcriptional or posttranslational level.

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Positive regulation of the human PAX8 promoter by PAX8 and the PAX8-PPARgamma fusion protein

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Background/Introduction:
PAX8 plays a key role in thyroid development and the regulation of several thyroid-restricted genes. Moreover, chimeric proteins fusing the DNA-binding domain of PAX8 with PPARγ1 play a role in the pathogenesis or proliferation of follicular thyroid cancers.

Methods:
A series of human wild type PAX8 promoter constructs (hPAX8P; up to -1128 bp) were transiently transfected into thyroid (PCCL3), kidney (TSA), and cervical cancer (HeLa) cells. Plasmids encoding the transcription factors PAX8, TTF-1/NKX2.1, TTF-2/FOXE1, and the fusion gene *PAX8-PPARγ1* were cotransfected with the various deletion mutants.

Results:
The basal activity pattern was similar among the different cell lines and showed a significant increase with sequences upstream of -640 bp. The transactivation was much higher in PCCL3 cells (~130-fold for the -1128 construct), compared to TSA (~20-fold) and HeLa cells (~10 fold). Cotransfection with PAX8, but not TTF-1 or TTF-2, stimulated the hPAX8P significantly, suggesting that PAX8 regulates its own promoter. This autoregulation was present with the PAX8 isoforms A, B, and C, but attenuated with isoform D. The PAX8-PPARγ1 fusion protein PPFP activated the promoter constructs to a similar extent. Reporter and gel shift assays indicate the presence of a PAX8 response element between -695 and -640 bp.

Conclusion:
These data suggest that some, but not all, PAX8 isoforms exert an autoregulatory effect on the PAX8 promoter, an effect that is also retained by the PAX8-PPARγ fusion protein. Activation of the PAX8 promoter by the fusion protein may result in alteration of PAX8 dosage, thereby contributing to proliferation of thyroid follicular cells.

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The GLP-1 receptor agonist liraglutide improves hepatic inflammation and fibrosis in mouse non-alcoholic steatohepatitis.

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Background/Introduction:
Obesity is rapidly rising worldwide with the consequence of increasing the prevalence of type 2 diabetes (T2D) and related complications such as non-alcoholic fatty liver disease (NAFLD). NAFLD is now the most common cause of chronic liver disease in Western countries, affecting about 30% of the general population, up to 70% of diabetic patients and 90-95% of obese individuals. Some patients with NAFLD can display non-alcoholic steatohepatitis (NASH), a progressive subtype of NAFLD, which can result in cirrhosis, hepatocellular carcinoma and liver-related mortality. Despite the life-threatening aspects of NASH disease, validated pharmaceutical treatments are still lacking. GLP-1 receptor agonists (GLP-1RAs) are currently widely used in the treatment of T2D. Therefore, our study aims to assess the potential beneficial effects of the long-acting GLP-1RA liraglutide on liver disorders associated with T2D.

Methods:
Wild-type C57BL/6 male mice were fed a methionine-choline-deficient (MCD) diet to induce liver manifestations of NASH (steatosis, hepatocyte ballooning, inflammation, fibrosis). After 3 weeks on MCD diet, mice were infused with either liraglutide 16 µg/d or saline solution for 4 weeks using micro-osmotic pumps (alzet model 1004) implanted subcutaneously. Gene expression was assessed by RT-qPCR. Levels of steatosis and fibrosis were quantified on liver sections stained with Oil Red O or Sirius Red and pathological scores were evaluated by a blinded pathologist.

Results:
Liraglutide-infused mice had similar body and liver weights than controls. Pathological scores showed mild fibrosis and a decrease in lobular inflammation in the treated vs control group despite similar degree of steatosis. Oil Red O staining confirmed that hepatic fat accumulation was not affected by liraglutide administration. Moreover, the expression of genes involved in de novo lipogenesis (SREBF1, FASN) and β-oxidation (CPT1A, ACOX2) was unchanged by the treatment. The expression of genes involved in glucose (PFKL, GCK, PCK1, SLC2A2), triglyceride (PNPLA2, DGAT2), glycogen (GYS2, PYGL) and bile acids (CYP7A1, CYP7B1, CYP8B1, ABCC4, SLC51B, SLCO1A1) metabolism was also unaffected by liraglutide infusion. Sirius Red staining did not reflect an influence of liraglutide on structural collagen accumulation, nevertheless the expression of profibrogenic genes (COL1A1, COL3A1, TIMP1, MMP13, SERPINE1, TGFB1) was significantly downregulated by GLP-1RA administration. Similarly, inflammation and immune cell markers (TNF, TNFR1A, ITGAX, ADGRE1) and genes involved in hepatic stellate cells activation (ACTA1, VIM) were downregulated.

Conclusion:
The long-acting GLP-1RA liraglutide reduces liver inflammation and fibrosis despite no influence on lipid deposition. This suggests anti-inflammatory and anti-fibrotic actions of liraglutide that are independent of glucose and lipid metabolism. Hence, these experiments show promising actions of liraglutide on NASH in addition to their known antidiabetic effects.

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The recruitment of intracellular lipids in INS-1E β-cells is essential to glucose-stimulated insulin secretion.

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Background/Introduction:
Chronic exposure to elevated glucose levels impairs beta-cell function and eventually leads to cell death. This effect, referred to as glucotoxicity, has been described to be worsened by chronic free fatty acids (glucolipotoxicity). However, the associated turnover of the stored lipids and the consequences on glucose-stimulated insulin secretion remains a matter of debate. The aim of this study was to determine the contribution of the turnover of de novo lipid synthesis versus exogenous saturated and unsaturated fatty acids on the function of INS-1E beta-cells.

Methods:
INS-1E beta-cells were cultured for 3 days at standard 11.1 mM (control) and high 25 mM glucose in the presence or absence of BSA-complexed 0.4 mM palmitate or oleate, or a mix of both (2 x 0.2 mM) fatty acids. Lipid accumulation and mobilization were assessed by quantifying Bodipy probe fluorescent signal after the 3 days of treatment along a 12h time course at low 5.5 mM glucose. Maximal lipid storage capacity was determined by co-incubating cells with the lipase inhibitor Orlistat during the 3 days of treatment. INS-1E beta-cell function was assessed by 96-well online kinetic measurements of insulin secretion (using luciferase-based C-peptide substitution) upon glucose stimulation with or without Orlistat pre-treatment.

Results:
Chronic treatment with high glucose increased cellular lipids 1.5-fold compared to control (de novo lipid synthesis). This effect was potentiated by the addition of oleate in the medium as it increased lipid accumulation by 25-fold compared to control ($p<0.0001$). Palmitate did so to a lesser extent (7-fold), while the mix of both fatty acids showed an intermediary lipid accumulation profile (15-fold, $p<0.01$). The inhibition of cell lipases by Orlistat indicated a maximal lipid accumulation capacity of 40-fold the control ($p<0.0001$), revealing a substantial lipid turnover in INS-1E beta-cells. However, the blockade of beta-oxidation by Etomoxir during the 3 days of treatment did not further increase lipid accumulation. Intracellular lipids were differently mobilized according to the culture conditions. Over 12h at low glucose, more than 80% of the lipids stored by the cells previously treated with high glucose plus palmitate were mobilized within 3h. Concomitantly, about 75% of the lipid pool in cells treated with high glucose plus the mix of palmitate and oleate was mobilized versus only 30% for the cells treated with high glucose plus oleate. Preventing the cells from mobilizing their stored lipids using Orlistat blunted glucose-stimulated insulin secretion in all conditions.

Conclusion:
INS-1E beta-cells chronically exposed to free fatty acids massively store neutral lipids that can be rapidly mobilized. This turnover depends on the chemical identity of the fatty acids, the saturated palmitate being mobilized much faster than the unsaturated oleate. The mobilized lipids are preferentially required for insulin secretion rather than being used as an energy source.

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CORE-miRNAs collectively regulate skeletal muscle cell differentiation through the p38 MAPK-myogenin pathway

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Background/Introduction:
Skeletal muscle is a key target tissue for regulating whole body metabolism. Decreased muscle mass during the aging process contributes to deteriorated metabolism and, next to obesity, is a major driver for the increasing prevalence of type 2 diabetes. Strategies to improve regeneration and glucose metabolism in skeletal muscle are therefore urgently needed to prevent the age-related increase in this disease. We have previously reported a group of 5 microRNAs (Let7, miR-29, miR-125, miR-199, miR-221) that are sufficient to rescue differentiation of primary skeletal muscle cells in which miRNA synthesis was genetically disrupted and termed them CORE-miRNAs (cooperative repressors). Here, we test the mechanisms by which these CORE-miRNAs affect glucose metabolism and regeneration of skeletal muscle in vitro and in vivo.

Methods:
Primary mouse or human myoblasts were transfected with control inhibitors or inhibitors of all 5 miRNAs (antagomirs-5x, Ant-5x) or with control mimics or mimics of all 5 miRNAs, then differentiated for 48 hours. mRNA decay was assessed by treatment with Actinomycin D, mechanisms of cooperativity between CORE-miRNAs on myogenin promoter or myogenin 3`UTR activity were analysed with luciferase assays, cell differentiation and the activation of p38 mitogen activated protein kinase (MAPK) was measured by western blotting and glycogen synthesis was assesed using uptake of 14C-labeled D-glucose. In vivo, muscle mass and fiber morphology was measured after injection of Ant-5x during cardiotoxin induced muscle regeneration in the tibialis anterior muscles (TA) from both young and aged mice.

Results:
CORE-miRNAs improved muscle differentiation in vitro as transcription of myogenin (2-fold, $p<0.05$) and embryonic myosin heavy chain (3-fold, $p<0.05$) were significantly elevated 24 hours earlier in the Ant-5x differentiated myotubes as compared to control. Mechanistically, mRNA stability of myogenin and embryonic myosin heavy chain did not differ between groups and no cooperative effects of the 5 miRNAs on the 3`UTR of myogenin could be detected. However, myogenin promoter activity was induced following Ant-5x transfection as compared to control (3-fold, $p<0.0001$) and phosphorylation of p38 MAPK, an important inducer of the myogenin promoter, was significantly increased in Ant-5x versus control samples (+50%, $p<0.001$). Improved muscle differentiation by the CORE-miRNAs translated into improved insulin stimulated glycogen synthesis (+30%, $p<0.05$, Ant-5x versus control myotubes). Importantly, CORE-miRNAs improved muscle regeneration in vivo as Ant-5x treatment significantly increased muscle mass and the amount of small newly formed fibers in both young and aged mice (muscle mass: +10-20%, fiber number: +20%, $p<0.05$).

Conclusion:
A set of only 5 miRNAs (CORE-miRNAs) collectively regulates differentiation and glucose metabolism in skeletal muscle via the p38 MAPK-myogenin pathway. This effect is downstream of direct target regulation by this group of miRNAs and does not involve binding of the miRNAs to the myogenin 3`-UTR region. We propose that CORE-miRNAs can be used as drug targets to prevent the detrimental effects of aging and type 2 diabetes on skeletal muscle regeneration and metabolism.

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Transcriptome profiling of migrating GnRH neurons in mice

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Background/Introduction:
Gonadotropin releasing hormone (GnRH) deficiency causes congenital hypogonadotropic hypogonadism (CHH), characterized by absent puberty and infertility. When associated with anosmia it is termed Kallmann syndrome (KS). Human and murine studies have been instrumental to identify more than 30 CHH genes involved either in GnRH neuron fate specification or migration (KS) or in the homeostasis of the GnRH neuronal network. More than 50% of patients have no genetic etiology indicating that novel genes are yet to be identified. Several classes of molecules are known to shape GnRH neuron migration from nose to brain during development, although the exact molecular mechanisms are largely unknown. We hypothesize that a specific spatio-temporal gene expression patterns define GnRH system development and may help identifying novel genes underlying KS. To test this hypothesis, we defined the transcriptomic landscape of the developing GnRH system.

Methods:
GFP+ GnRH neurons and GFP- control cells have been FACS-isolated from nose and brain microdissections collected from GnRH::GFP mouse embryos corresponding to distinct steps of neuronal migration. After RNA extraction, libraries and RNA sequencing have been performed using the BRBseq pipeline. Differential gene expression analysis (DGE) was performed using DESeq2 and followed by gene set enrichment analysis (GSEA).

Results:
More than 13000 genes have been detected in the analyzed samples. DGE on GnRH negative cells (nose vs brain) was followed by systematic validation on available ISH data from Allen Brain Atlas confirming microdissection specificity. Specificity of cell sorting was confirmed by comparing GnRH expression in GFP+ vs GFP- cells. Expression analysis of CHH gene mouse orthologues revealed that most KS genes are higly expressed during the embryonic stages, consistent with a critical role in GnRH neuron development. Principal component analysis and hierarchical clustering confirmed that GnRH neurons in the nose and brain have distinct molecular signatures, suggesting that specific biological processes take place at different developmental stages. Indeed, using GSEA and pathways analysis, we identified specific sets of genes involved in early (e.g. cell migration and adhesion) or late neuronal development (e.g. axon projections, neuron differentiation). Finally, DGE of genes encoding for extracellular and/or membrane protein in GFP negative cells revealed the presence of tissue specific molecular signatures suggesting a contribution of the surrounding microenvironment in modulating GnRH neuron behavior at different migratory stages.

Conclusion:
We report the first transcriptomic analysis of the developing GnRH system. We used this approach to identify candidate genes involved in different aspects of GnRH neuron development. Combining these data with genetic analysis in CHH patients will help identifying novel candidate CHH genes.

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Biochemical, structural and functional characterization of a novel P450 oxidoreductase mutation causing virilization in a 46,XX patient

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Background/Introduction:
Cytochrome P450 oxidoreductase deficiency is a form of congenital adrenal hyperplacia (CAH) and results in loss of steroid production from cytochrome P450 proteins. Mutations in POR cause mild to severe forms of CAH with and without bone malformation symptoms resembling Antley-Bixler syndrome. Here we are reporting a novel R550W mutation in POR identified in a 46,XX patient with signs of aromatase deficiency. Child was born of first pregnancy and mother presented with signs of virilization (deepening of voice and hirtuism) from the 6th month. The daughter was born with body length of 49 cm and weighed 2.74 Kg at birth. At 7th day fused labioscrotal folds (genital tubercle 1.5cm with urethral opening, Prader stage 3) were observed. Sequencing of CYP19A1 gene did not reveal any defects and later on candidate gene screening for DSD revealed compound heterozygous mutations c.70_71delTC / p.Leu25PhefsTer93 and c.1648C>T /p.Arg550Trp in POR.

Methods:
We analyzed the ability of POR wild-type (WT) and Arg550Trp mutation to reduce ferricyanide, MTT, cytochrome c and activity towards the drug and steroid metabolizing cytochrome P450. POR WT and Arg550Trp were expressed and produced as recombinant proteins in bacteria (E.coli BL21(DE3))and combined with recombinant P450 proteins and small molecule substrates for enzyme assays. The CYP19A1 was produced in E.coli BL21(DE3) cells with chaperons GroEL and GroES for folding and purified by metal chelate column chromatography.

Results:
We found severe effects of Arg550Trp mutation on activities with different substrates. As compared to WT, the Arg550Trp mutation showed 41 % of the WT activity in cytochrome c only 7.7 % activity towards reduction of MTT. A 2.75 fold increase in Michaelis constant (Km) was observed for the POR Arg550Trp in ferricyanide reduction assays compared to WT POR. Further ongoing assays with aromatase activity (D4A to E1) and change of NADPH in assays will provide detailed information.

Conclusion:
The mutation Arg550Trp is located in the NADPH binding region of POR. Computational analysis predicted instability in the NADPH binding region of POR, which may affect aromatase (CYP19A1) activity to a higher degree than other partner enzymes because CYP19A1 requires 6 molecules of NADPH per reaction cycle compared to 2 molecules of NADPH for other cytochrome P450 partners of POR. Therefore, an adverse effect on CYP19A1 activity due to Arg550W mutation in POR is predicted.

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Generating a human gonadal cells model from terminal differentiated fibroblast-derived induced pluripotent stem cells

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Background/Introduction:
Differentiation of the gonads in men is closely dependent on Sertoli cells maturation. Differences of sex development (DSD) are caused by variations in this process. The study of the mechanisms underlying these complex conditions is crucial for optimal clinical management and Sertoli cells would be an ideal model for this purpose. However, there are two main obstacles for the study of human Sertoli cells. Firstly, mature human Sertoli cells lose their proliferation abilities in culture. Secondly, the currently available models like human NT2D1 and primary Sertoli cells (HSerCs) have limitations to mimic the particular characteristics of DSDs Sertoli cells. To establish a patient-specific cell model to study human testis formation, we differentiated human fibroblasts-derived induced pluripotent stem cells (iPSCs) into human Sertoli-like cells.

Methods:
We reprogrammed human fibroblasts into iPSCs by lentivirus transduction of reprograming factors (Oct4, SOX2, NANOG, LIN28, KLF4 and C-MYC). Subsequently, we guided the differentiation of iPSCs into SLCs by growth factors and characterized this new model by new generation sequencing techniques including 44.946 genes expression analysis. In a more detailed analysis, we selected 23 gene markers for the different stages of Sertoli cell development including SRY-Related HMG-Box 9 (SOX9), vimentin (VIM), Cytochrome P450 Retinoid Metabolizing Protein (CYP26B1) and Proto-Oncogene Tyrosine-Protein Kinase Src (SRC). We additionally tested whether SLC are able to create three-dimensional structures in gel matrix and the expression of claudin-11 (CLDN-11) in tight junctions.

Results:
This approach revealed that SLCs expressed Sertoli cell markers such as SOX9 and VIM. When compared the other current models (NT2D1 and HSerCs cells), SLCs showed a reduction of the germ cell markers POU5F1, DPPA2, DPPA4 and NANOG and an increased expression of Sertoli cell markers AMH, FGF9, CYP26B1, PTGDS, HSD17B3, SRC, DHH and INHBB. We additionally demonstrated that the protein expression and location by SLCs of SOX9 in the nucleus and claudin-11 in the tight junctions is similar to normal human Sertoli cells.

Conclusion:
Harnessing the power of iPSCs we were able to generate Sertoli-like cells that show genetic and functional similarities to human Sertoli cells. Thanks to this novel approach, Sertoli-like cells may become an alternative source of patient-specific Sertoli cells models that may boost the understanding of the individual complexities of DSD patients.

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Regulation of beta-cell function by an intronic insulin circular RNA

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Background/Introduction:
We previously showed that pancreatic islets express several circular RNAs (circRNAs) and that some of them are differentially expressed in mouse models of diabetes and contribute to the modulation of insulin secretion and beta-cell mass. In this study, we searched for new circRNAs generated from key beta-cell genes and investigated in detail the expression and function of a particular circRNA generated from the intron of the insulin 2 gene.

Methods:
Annotation of circRNAs in our previously published mouse islet RNA-sequencing data was performed using a specific circRNA pipeline. Expression of selected circRNAs in the mouse beta-cell line Min6 and in rat islets was verified by qPCR and by sequencing of the amplified PCR products. Insulin circRNA expression was also confirmed in human islets. Circularity was assessed by RNase R and actinomycin D treatments in rat islets. CircRNA expression was measured in several rat tissues and in the islets of NOD mice (type 1 diabetes model) and of db/db mice and GK rats (type 2 diabetes models). Insulin secretion, beta-cell proliferation, apoptosis, and changes in mRNA expression were assessed after silencing of the circRNA in rat islets.

Results:
Computational analysis of high-throughput sequencing data of mouse islets led to the prediction of 19,567 circRNAs, of which 12,000 were not previously annotated. Predicted circRNAs derived from insulin 2 (Ins2), Gck, Glp1r, Pcsk1 and Slc30a8 were detected in Min6 cells and rat islets. An intron 2 lariat-derived Ins2 circRNA (lariat circIns2) was found to be conserved both in rodent and human islets. This circRNA was resistant to RNase R treatment and its level was stable after inhibition of transcription with actinomycin D for 4 hours, confirming its circularization. The lariat circIns2 was exclusively expressed in islets and was not detectable in any other analyzed tissue. The expression of this circRNA was unaffected in the islets of prediabetic NOD mice but was decreased in the islets of type 2 diabetes animal models db/db and GK. Reduction of lariat circIns2 levels in rat islets resulted in impaired glucose- and KCl-stimulated insulin secretion. Beta-cell proliferation tended also to be reduced, whereas apoptosis was unaffected. Accordingly, mRNA sequencing analysis revealed downregulation of gene pathways involved in insulin secretion and proliferation, and qPCR data confirmed a decreased expression of several key exocytosis genes.

Conclusion:
Pancreatic islets contain a circRNA derived from the insulin transcript which is expressed at reduced levels in type 2 diabetes models and is essential for optimal insulin secretion. Thus, the transcript of the insulin 2 gene is not only providing the code for insulin biosynthesis but is also generating a circRNA promoting the release of the hormone in response to nutrients. A better understanding of the role of this and other circRNAs will help elucidating diabetes etiology.

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Differential ribonucleotide reductase (RRM) pathway modulation upon chemotherapeutic treatments in preclinical models for ACC

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Background/Introduction:
Adrenocortical carcinoma (ACC) is a rare and highly metastatic malignancy. Even though recent molecular and diagnostic advancements have been achieved, novel therapeutic strategies are still not in sight. The current clinical gold standard Etoposide, Doxorubicin, Cisplatin, and Mitotane is not satisfying and poses severe dose-limiting normal tissue toxicities. Cisplatin, Gemcitabine and 9-cis-Retinoic acid are as single agents repeatedly under discussion for the treatment of ACC patients. Here we investigated single and combined treatment modalities and also the biological significance of ribonucleotide reductase (RRM) pathway in the context of drug resistance.

Methods:
In recent years it has been recognized that clinical translation of novel therapeutic strategies for patients with ACC often fails. These disappointing results indicated that previously utilized tumor models only poorly predicted clinical applicability of novel pharmacological approaches. Thus, Cisplatin (C), Gemcitabine (G) and 9-cis-Retinoic acid (RA) were investigated in the classical adrenocortical NCI-H295R tumor model and for the first time in the newly developed MUC-1 cell line. In these experiments, we assessed the impact of single and combined drug treatments on tumor cell viability as well as on RRM1 and RRM2 gene expression.

Results:
While C inhibited cell viability of NCI-H295R cells in a dose-dependent manner (40 µM: 66%; 120 µM: 23%: 160 µM 17%; all P<0.001), less therapeutic efficacy was detectable against MUC-1 (40 µM: 89%; 120 µM: 70%; 160 µM: 70%; all P<0.001; vs 100% controls). Accordingly, RA displayed high therapeutic efficacy against NCI-H295R (75 µM: 71%; 150 µM: 34%; all P<0.001) while weaker effects were observed for MUC-1 (75 µM: 103% P>0.05 ns; 150 µM: 90% P<0.01; vs. 100% controls). Moreover, G also significantly reduced viability in both tumor models. However, this could not be further enhanced by higher G dosages (NCI-H295R, 1 µM: 78% P<0.001; 25 µM: 96% P>0.05 ns; MUC-1, 1 µM: 87%: 25 µM: 85%: all P<0.001). Of note, combined treatment of G and C led to additive reduction of cellular viability in both NCI-H295R (G: 106% P>0.05 ns; C: 19% P<0.001; G + C: 10% P<0.001) and MUC-1 (G: 107% P>0.05 ns; C: 63% P<0.001; G + C: 46% P<0.001). Interestingly, G induced also a dose-dependent increase of both RRM1 and RRM2 gene expression, which was completely abolished with concurrent C treatment in both NCI-H295R (RRM1, G: 791% P<0.001; G + C: 188%; RRM2, G: 336% P<0.001; G + C: 60%) and MUC-1 cells (RRM1, G: 275% P<0.01; G + C: 97%; RRM2, G: 474% P<0.01; G + C: 175%; vs. 100% controls), respectively.

Conclusion:
C, RA and G demonstrated anti-tumoral effects in two preclinical models for ACC. Moreover, combined treatment of G and C reduced cell viability in an additive manner. Interestingly, concomitant inhibition of G-induced activation of RRMs was observed, enzymes which regulate the dNTP pool and thereby cell division and repair. Our findings suggest that combined treatment of G + C, alone or in combination with clinically relevant RRM2 inhibitors, might be a promising strategy for ACC patients.

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Role of cell type-specific IL-1β overexpression in type 2 diabetes mouse models

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Background/Introduction:
Pancreatic islet inflammation contributes to the impairment of insulin secretion in patients with type 2 diabetes. This inflammatory process seems to be partly governed by IL-1β. However, the cellular sources of IL-1β in islets are still unclear. While beta cells are the most abundant cell type in islets, it is unclear if they are able to process pro-IL-1β to the active form. On the other hand, macrophages and other myeloid cells are potent producers of IL-1β, but rare in numbers in pancreatic islets.

Methods:
We used genetic mouse models to overexpress of pro-IL-1β in specific tissues. A constitutive system was used to overexpress pro-IL-1β in myeloid cells and an inducible system was used to overexpress pro-IL-1β in beta cells. We assessed measures of glucose metabolism and inflammation in vivo and ex vivo.

Results:
Overexpression of pro-IL-1β in myeloid cells resulted in an impaired glucose phenotype at 23 weeks of age, while overexpression of pro-IL-1β in β cells resulted in an impaired glucose phenotype at 52 weeks of age (44 weeks after induction). Local alterations of inflammation did not cause detectable changes in systemic inflammation.

Conclusion:
Pro-IL-1β overexpression in myeloid- or beta cells alone was sufficient impair glucose metabolism in mice. The site of pro-IL-1β overexpression was relevant for the time point of the change in metabolism.

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A short bout of HFD desynchronizes feeding behaviour in mice thereby affecting glucose and lipid metabolism

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Background/Introduction:
A short bout of HFD impairs glucose tolerance and induces hepatic steatosis in mice. While prolonged HFD-induced metabolic complications are partly mediated by increased food intake during the light (inactive) phase, such link has not yet been established in short-term HFD-fed mice. Herein, we hypothesised that a short bout of HFD desynchronizes feeding behaviour thereby contributing to glucose intolerance and hepatic steatosis.

Methods:
12-week-old C57BL/6J mice were fed a regular chow or high fat diet (HFD, ~60% kcal fat) for 4 days. Food intake was determined in metabolic cages and glucose metabolism was assessed by performing intraperitoneal glucose tolerance tests. Upon scarification, liver and fat depot weights were measured and tissue was collected for analysis. Western blots, rtPCR and a colorimetric assay for the assessment of liver triglyceride levels were performed.

Results:
Changing diet from regular chow to HFD led to an immediate increase in food intake already during the 1st light phase (p<0.05), suggesting that HFD desynchronizes feeding behaviour instantly. As expected, 4 days of ad libitum HFD-feeding impaired glucose tolerance (p<0.05). Such effect was prevented in mice receiving intermittent HFD-feeding for 4 days (i.e. mice that had no access to food during the light phase) indicating that desynchronized feeding behaviour contributes to short-term HFD-induced glucose intolerance. Of note, food intake was similar between the groups, as was body weight. However, intermittent HFD-fed mice revealed higher inguinal fat depot weights (p<0.1), whereas liver weight was lower in intermittent fed mice (p<0.05). Phosphorylation of hormone sensitivity lipase (HSL) was elevated in inguinal fat depots of intermittent HFD-fed mice (p<0.01), indicating increased lipolysis. In support of increased FFA flux to the liver, hepatic PPARα mRNA expression was elevated in intermittent HFD-fed mice (p<0.05). In agreement, liver triglyceride levels were increased in intermitted HFD-fed mice (p<0.05).

Conclusion:
Desynchronized feeding behaviour induced by a short bout of HFD impairs glucose tolerance and impacts on liver lipid metabolism.

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Data mining and computational analysis of human growth hormone gene (GH1) sequence in normal population to identify potential variants with disease-causing effects.

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Background/Introduction:
Mutations in the GH1 gene cause isolated growth hormone deficiency. Several disease-causing mutations from patients with IGHD have been reported. These mutations have been shown to (a) produce shorter isoforms of GH that does not bind to growth hormone receptor, (b) cause diminished secretion of GH or (c) result in misfolded GH protein. Large sequencing studies from the non- clinical population show several hundred genetic variations in the GH1 gene. Role of common polymorphic variants in GH1 gene in relation to effects of GH protein has not been systematically studied. We searched the the genomics data to find and analyze the effects of potentially disease-causing variants in the GH1 gene.

Methods:
We used hidden Markov Model methods to generate position-specific scoring matrices for analyzing the sequence conservation of GH amino acids across species using both structural and genomics data. A potential list of structurally and functionally important residues was compiled for further analysis. Computational molecular dynamics using AMBER and GH-GHR interaction analysis was performed to study the effects of potentially disease-causing variants.

Results:
We generated an evolutionary conservation score of all the amino acids in the human growth hormone sequence by comparing with all the GH sequences in the Uniref90 database. The Arg16, His21, Gln84, Asp169, Lys172, Cys189 residues are functionally conserved while residues Ala17, Ala24, Cys53, Ser79, Leu162, Cys172 structurally conserved. A detailed contact map of GH with amino acids in GHR revealed that GH residues His18, His21, Phe25, Leu45, Pro48, Ser62, Asn63, Tyr164, Lys172, Glu174, Ile179, Cys182, Cys189, Gly190 and Pro2, Ile4, Arg8, Asn12, Leu15, Arg16, Asp116, Glu119, Gly120, Thr123 interact with the GHR via hydrogen bonding or Vander Waal interactions. We found several potentially disease-causing variants in the GH1 gene from sequencing data deposited from non-clinical samples. Three different categories of changes in the amino acid sequence of GH were observed. Mutations at the interface of GH-GHR interactions were predicted to affect binding and affinity of GH towards GHR, while 31 mutations were found to cause structural instabilities. An overview of GH1 variants with the potential to cause IGHD will be presented.

Conclusion:
Identification of potentially negative effects of variations in the GH1 gene from non-clinical populations can be utilized to study links to growth variations. Identification of potentially disease-causing variants in GH1 will help in the further functional characterization of these variants when these are later found in patients with growth hormone deficiency.

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Analysis of the ligand binding domain of the thyroid hormone receptor for the rational design of an efficient protein-based biosensor for the detection of thyroid hormone disrupting chemicals.

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Background/Introduction:
Thyroid hormone disrupting chemicals (THDCs) are present in the environment, food and everyday consumer products. THDCs interfere with thyroid hormone signaling by interacting with thyroid hormone receptors (THRs) which causes alterations in metabolism regulated by the thyroid hormone e.g. macronutrient metabolism, cardiovascular function, and normal brain development. Therefore, there is a necessity for detection and monitoring of these pollutants in the environment. THRs belong to the nuclear receptor superfamily and have two highly conserved domains: DNA binding domain (DBD) and ligand binding domain (LBD). The LBD is responsible for the ligand selectivity and could be used as a bio-recognition element for THDCs detection. Moreover, optimized LBDs with increased affinity may act as better bio-recognition elements due to their increased sensitivity towards THDCs.

Methods:
Sequence alignments of LBD of THR across the species were carried out to locate the differentially conserved positions. Using information theoretic measures (Cumulative Relative Entropy (CRE)) we analyzed the LBD of thyroid hormone receptors and compared THRs with estrogen receptors (ER). We performed Docking simulations with the selected THDCs and THR using AutoDock Vina. Two different datasets for virtual screening were used (1) The THR subset of the Database of Useful Decoys: Enhanced (DUD-E) and (2) compiled list of selected THDCs. The results of the docking were assessed by determining the area under the curve (AUC) value of the receiver operating characteristic (ROC) curve. Ligplus software was used to find the THR residues in contact with ligands. On the basis of interaction and conservation, some residue were selected for the site-directed mutagenesis using FoldX program followed by MD simulations.

Results:
Based on highest CRE scoring twenty positions were selected and predicted to impart functional specificity to THR as well as other TH-like receptors. Docking Results have shown that more than 40 suspected THDCs have scored well in the docking simulations. AUC values (THRA= 0.8085, THRB= 0.8016) are also in good agreement of assessment of the docking results. Few residues were selected from the ligand binding domain of the THR in order to achieve high binding affinity towards THDCs.

Conclusion:
Selected residues could be used for rational design of LBD with an enhanced affinity towards ligands and applied towards the development of sensitive protein-based biosensors to detect THDCs.

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Clinical and genetic overlap between Kallmann and Cornelia de Lange Syndrome

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Background/Introduction:
Kallmann syndrome (KS) is defined as the association of isolated GnRH deficiency and ansomia due to defects in the development of the olfactory system and GnRH neuron network. KS patients exhibit hypogonadotropic hypogonadism, as well as other phenotypes such as cleft lip palate, hearing loss, skeletal malformation among others. KS is a genetically heterogenous disease with > 30 loci known to date. CdLS is characterized by distinctive facial features, psychomotor delay, growth retardation and upper limb malformation. A subset of CdLS patients exhibit cryptorchidism, micropenis, and/or delayed puberty, suggestive of hypogonadism, although formal endocrine evaluation is lacking. In terms of genetics, heterozygous mutations in 6 genes involved in the cohesion complex have been described in patients with CdLS.

Methods:
Given the clinical overlap between the two syndromes, we evaluated a cohort of KS patients (n = 180) for mutations in the known CdLS genes (SMC3, NIPBL, SMC1A, RAD21, HDAC8, MAU2) and performed detailed phenotyping focusing on CdLS phenotypes. Structural modeling and in vitro assays were performed on identified mutations.

Results:
We identified a de novo heterozygous mutation in SMC3 (p.C549Y) and a heterozygous frameshift mutation in NIPBL (p. P2761Cfs*4) in two KS patients who have additionally CdLS. Neither of these variants were seen in the control population in gnomAD. SMC3 C549 residue is located in the hinge domain of SMC3, and C549Y enhances the hinge binding to SMC1 in vitro. Further, Smc3 is highly expressed in embryonic nose and hypothalamus, in adult hypothalamus, as well as GnRH cell-lines. The NIBPL P2761Cfs*4 mutation may escape nonsense-mediated decay, and thus lead to a truncated NIBPL protein lacking 39 amino acids on the N-terminal region.

Conclusion:
We identified pathogenic mutations in SMC3 and NIPBL, genes encoding key components of the cohesin complex, in 2 patients with KS and CdLS. In order to investigate the implication of these mutations in the etiology of KS, we will use GnRH3:GFP zebrafish model to explore the role of SMC3 and NIPBL in GnRH neuron development. Further, we will expand our genetic screening to a larger cohort of KS patients with or without additional CdLS features.

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Impaired Proinsulin but not Impaired Central POMC Processing Mediates PC1/3-related Obesity

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Background/Introduction:
Prohormone convertase 1/3 (PC1/3) processes various precursor peptides into their respective mature forms. Humans with inactivation mutations in PC1/3 suffer from multi-hormonal issues including sever obesity and hyperglycemia. In addition, the gene that encodes for PC1/3 is strongly linked to obesity in risk association studies. Further, individuals with Prader-Willi Syndrome, a genetic disorder characterized by life-threatening hyperphagic obesity, were recently found to express reduced levels of PC1/3. The mechanistic link between PC1/3 and obesity is still elusive and it is postulated that lack of maturation of central satiety hormones mediates this phenotype.

Methods:
We used genetic mouse models (cre-lox system) to ablate PC1/3 in specific target tissues of the brain and in the periphery. We used constitutive (life-long) and inducible systems to manipulate PC1/3 levels and assessed food intake, body weight development, glycemia and energy expenditure in the resulting mouse strains.

Results:
Ablation of PC1/3 in pro-opiomelanocortin (POMC) neurons which secrete the major central anorectic peptide POMC, had only minor effects on metabolic parameters including food intake and obesity. A more general brain-specific PC1/3 knockout in all cholinergic neurons (chat-cre) had no effect on all parameters assessed. In contrast, deletion of PC1/3 in pancreatic beta cells at 8 weeks of age induced hyperglycemia and obesity. This phenotype was found to be mediated by increased food intake and fat mass but not by altered energy expenditure. PC1/3 cleaves two satiety peptides in the beta cell, proinsulin and proIAPP (proamylin). Indeed, the level of proinsulin was increased while mature insulin was undetectable in the circulation of these beta cell-specific PC1/3 knockout mice. Surprisingly, the satiety hormone proIAPP was fully processed in the absence of PC1/3 and the absolute level of mature IAPP was increased following PC1/3 ablation, suggesting that PC1/3-related obesity is not caused by lack of IAPP. In a preliminary study, insulin replacement therapy reduced glycemia and prevented weight gain following knockout induction.

Conclusion:
The observed severe hyperphagic obesity phenotype described in humans with global PC1/3 deficiencies may be mediated by peripheral misprocessing of proinsulin and not as postulated so far by central lack of mature satiety hormones.

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Air pollution induced-diabetes is mediated via the gut

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Background:
Besides classical risk factors such as sedentary lifestyle and unhealthy diet, air pollution has emerged as an unexpected risk factor for type 2 diabetes. However, the causal mechanism remains poorly understood. It is believed that inhaled air pollution particles cause an inflammatory response in the lung, which precipitates systemic inflammation and diabetes. However, air pollution particles also reach the gut by mucociliary clearance and ingestion and could thus be linked to diabetes. The aim of our study is to assess whether air pollution particles mediate diabetes via lung or gut exposure.

Research Design and Method:
To differentiate between the effects of air pollution particles reaching the lungs versus the gut, male C57B6/N mice were exposed to diesel exhaust particles (DEP; weekly dose 60µg) either by oral gavage (5 days/week) or intratracheal instillation (twice/week) for up to 6 months. Glycemia was monitored by glucose tolerance tests and immune cells characterized by flow cytometry and PCR.

Results:
Although mice receiving DEP by intratracheal instillation had increased monocyte recruitment to the lungs, they did not show any impairment in glucose tolerance up to 5 months. In contrast, mice orally treated with DEP developed impaired glucose tolerance and reduced insulin secretion, while insulin sensitivity was not affected. Oral DEP did not trigger systemic, adipose tissue or liver inflammation. However, in the lamina propria of the gut, oral DEP led to a specific loss of anti-inflammatory resident macrophages, shifting the balance of intestinal macrophages towards an inflammatory state.

Conclusion:
Exposure of DEP to the gut but not the lungs triggers impaired glucose tolerance. Reduced anti-inflammatory, resident macrophages in the lamina propria of the gut upon air pollution exposure suggests an immune-mediated mechanism. Our findings provide a new understanding of how environmental pollutants affect health, which is a crucial advance in preventing the worldwide disease burden of air pollution-induced diabetes.

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Reduced skeletal muscle protein turnover and altered local thyroid hormone metabolism in the adaptive thermogenesis that facilitates body fat recovery during weight regain

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Background/Introduction:
The recovery of body weight after weight loss is characterized by an accelerated rate of fat recovery (preferential catch-up fat) resulting partly from an adaptive suppression of thermogenesis. Although the skeletal muscle has been implicated as an effector site for such thrifty metabolism driving catch-up fat, the underlying mechanisms remain to be elucidated. We test here the hypothesis that this thrifty metabolism driving catch-up fat could reside in a reduced rate of protein turnover (an energetically costly 'futile' cycle) and in altered local thyroid hormone metabolism in skeletal muscle.

Methods:
Using a validated rat model of semi-starvation-refeeding in which catch-up fat is driven solely by suppressed thermogenesis, we assessed after 1 week of refeeding in refed and control animals the following: (i) in-vivo rates of protein synthesis in hindlimb skeletal muscles using the stable isotope flooding dose technique of incorporation of 13C-labeled valine in muscle protein, (ii) ex-vivo muscle assay of net formation of thyroid hormone tri-iodothyronine (T3) from precursor hormone, thyroxine (T4), and (iii) protein expression of muscle deiodinases (type 1, 2 and 3) using validated antibodies.

Results:
We show that after 1 week of calorie-controlled refeeding, the fractional protein synthesis rate was lower in skeletal muscles of refed animals than in controls (by 30-35%, $p<0.01$) despite no between-group differences in the rate of skeletal muscle growth or whole-body protein deposition - thereby underscoring concomitant reductions in both protein synthesis and protein degradation rates in skeletal muscles of refed animals compared to controls. These differences in skeletal muscle protein turnover during catch-up fat were found to be independent of muscle type and fiber composition, and were associated with a slower net formation of muscle T3 from precursor hormone T4, together with a significant increase (~50%) in muscle expression of deiodinase type 3 (which inactivates T3 and T4), and a decreased or unaltered expression of the T3-activating enzyme, deiodinase type 2.

Conclusion:
These results suggest that diminished skeletal muscle protein turnover, together with altered local muscle metabolism of thyroid hormones leading to diminished intracellular T3 availability, are features of the thrifty metabolism that drives the rapid restoration of the fat reserves during weight regain after caloric restriction. Such reduced energy cost of homeothermy persisting during weight regain has implication for the "metabolic adaptation" that facilitates obesity relapse, as well as for

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The impact of daily sugar sweetened beverage consumption on lipid metabolism in healthy men - a double-blind, randomized, controlled study

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Background/Introduction:
This study addresses the question whether a prolonged high-carbohydrate eucaloric diet rich in either fructose, sucrose or glucose exerts an effect on lipid metabolism in healthy men. This is a question of particular interest with regard to the discussion about potential health risks of high-carbohydrate and/or high-fructose diets and was not addressed by previous studies which do not discriminate between carbohydrate overfeeding and sugar type specific effects in this context.

Methods:
Subjects (n=94) consumed daily either sucrose, fructose or glucose containing beverages (80g/day) with their usual diet or abstained from SSB. They kept dietary records during the study for analysis by EBISpro nutrition software. After 6 weeks, hepatic fatty acid (FA) synthesis was measured by infusion of 13C-acetate and subsequent measurement of the incorporation of the 13C label into palmitate isolated from plasma very low density lipoprotein (VLDL)-triglyceride (TAG). At the same time, peripheral lipolysis represented as rate of appearance of glycerol was measured by D5-glycerol infusion. VLDL-TAG secretion rates were measured by labeling newly synthesized TAG with D5-glycerol. Whole body fat oxidation was measured by indirect calorimetry measurements and in an additional examination (week 5) plasma derived free fatty acid oxidation was evaluated by measuring breath 13CO2 enrichment during infusion of U-13C palmitate.

Results:
SSB consumption did not increase total energy intake. Consumption of beverages containing fructose increased fasting fractional secretion rates (FSR) of newly synthesized FA of the liver 2- fold compared to control (median FSR %/day: sucrose 20.8 (p=0.003); fructose 19.7 (p=0.026); control 9.1). In contrast, the same amounts of glucose did not change FSR (median of FSR %/day 11.0 p=0.322). Secretion of newly synthesized VLDL-TAG was not changed (median of FSR %/day: sucrose 15.9; fructose 14.4; glucose 20.7; control 18.9). Neither rates of peripheral lipolysis nor whole body fat and plasma fatty acid oxidation were altered.

Conclusion:
This findings support the thesis of an increased expression of hepatic lipogenic enzymes in response to a high-fructose diet. We conclude that a chronically high consumption of fructose increases the capacity of the hepatic fatty acid synthesis pathway even in a fasting state. We hypothesize that this adaptation will enhance fatty acid synthesis in acute situations when excessive substrate for fatty acid synthesis accumulates as after SSB consumption.

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How diet, physical activity and psychosocial well-being interact in women with GDM: An integrative review.

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Background/Introduction:
Gestational Diabetes Mellitus (GDM) is associated with future metabolic risks for the mother and her child. In addition, one-third of women with recent GDM develop postpartum depression. Given these adverse impacts of GDM on the health of the mother and her offspring, it is important to intervene on modifiable factors such as diet, physical activity, and psychosocial well-being. This integrative review therefore explored evidence on how these modifiable factors interact in women with GDM and their offspring, and how effective combined interventions are in reducing adverse impacts of GDM.

Methods:
A comprehensive search strategy included carefully selecting terms that corresponded to the domains of interest (diet, physical activity, and psychosocial well-being). The databases searched for articles published between 1980 and February 2018 were: CINAHL, PsycINFO, Embase, Pubmed and Cochrane. Studies that were included in this review were either observational or intervention studies that included at least two domains of interest. Articles had to at least report data on maternal outcomes of women with GDM. Articles that exclusively investigated women with type 1 or type 2 diabetes, pharmacological interventions, genetic, epigenetic, genomic and dietary supplement studies and animal research were excluded.

Results:
The search strategies identified 14'419 citations after excluding duplicates. After screening titles and then abstracts, 114 articles were selected for detailed evaluation of their full text, and 17 were included in this review: 2 observational and 15 intervention studies. The majority of studies demonstrated good quality upon assessment. Results from observational studies showed that psychosocial well-being (social support and self-efficacy) had a positive effect on physical activity and diet. Intervention studies always included diet and physical activity interventions, although none integrated psychosocial well-being in the intervention. These lifestyle interventions led to increased physical activity, improved diet and psychosocial well-being, reduced BMI and postpartum diabetes status and improved metabolic outcomes, while results for birth outcomes were inconsistent.

Conclusion:
This integrative review showed that diet, physical activity and psychosocial well-being interact in women with GDM. We recommend that future intervention studies integrate psychosocial well-being, as observational studies demonstrated the importance of social support and self-efficacy in adopting a healthy lifestyle following GDM diagnosis.

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The reduction of visceral adipose tissue after Roux-en-Y gastric bypass is more pronounced in patients with impaired glucose metabolism

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Background/Introduction:
Visceral adipose tissue (VAT) is associated with cardiometabolic risk factors and insulin resistance. Roux-en-Y gastric bypass (RYGB) surgery leads to improvement in type 2 diabetes and lowers the incidence of diabetes. However, the physiological mechanisms underlying the benefits of RYGB on glucose metabolism remain incompletely understood.

We aimed to evaluate the impact of RYGB on VAT, as measured by dual-energy X-ray absorptiometry (DXA), among three groups of patients stratified by their glucose tolerance before surgery.

Methods:
We enrolled 44 obese women from 2015 to 2017 in a prospective convenience sample within the RYGB clinical pathway. We measured plasma glucose, HbA1c in all patients at baseline and 12 months post-surgery, as well as 75-g OGTT in non-diabetic patients before surgery. Patients were categorized into normoglycemia (n = 21), impaired glucose tolerance (IGT, n = 18) and diabetes (n = 5) before surgery. Body composition was measured by DXA before and at 6 and 12 months after surgery.

Results:
The three groups had comparable mean age (mean 38.6 ± SD 9.9) and BMI at baseline (41.9 ± 4.3 kg/m2). After 12 months, overall weight loss and decrease in BMI after surgery were similar across groups. Total weight loss (35.1% ± 7.5) and excess weight loss (91.1% ± 25.1) were also similar.

Pre-surgery mean VAT was significantly higher in diabetes (2495 ± 616 grams) than in normoglycemia (1750 ± 617 grams, p = 0.02). The percentage of VAT to total body fat was significantly higher in diabetes (4.4% ± 0.9) compared to normoglycemia (2.9% ± 0.8, p = 0.003).

Twelve months after surgery, VAT loss was significantly greater among patients with diabetes (1927 ± 413 g) compared to normoglycemia (1202 ± 450, p = 0.009). While the VAT mass in proportion to the total fat mass before surgery was clearly larger in diabetes (4.4% ± 0.9) than in normoglycemia (2.9% ± 0.8, p = 0.002), this difference disappeared 12 months after RYGB with very similar proportions, calculated by VAT mass / total fat mass (2.33% ± 0.79 in diabetes vs. 2.28% ± 0.95 in normoglycemia, p = 0.91). In other terms, in proportion to the total fat mass, VAT loss was more pronounced in diabetes (-2.09% ± 0.60) than in normoglycemia (-0.63% ± 1.10, p = 0.002).

Conclusion:
RYGB leads to important VAT loss, and this loss is more prominent in patients with diabetes prior to surgery. As VAT is associated with insulin resistance, this reduction may account for the profound impact of this surgery on glucose metabolism.

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Remission in Diabetic Foot Infections: Duration of Antibiotic Therapy and Other Possible Associated Factors

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Background/Introduction:
Few studies have addressed the most appropriate duration of antibiotic therapy for diabetic foot infections (DFI).

Methods:
Using a clinical pathway for adult patients hospitalized for moderate to severe DFI, we conducted a cluster-controlled (at the patients' level) Cox regression model, assessing factors related to remission of infection, emphasizing antibiotic-related parameters.

Results:
Among1018 DFI episodes in 482 patients, we identified 392 had osteomyelitis, 626 soft tissue infections, 246 large abscesses, 322 cellulitis, and 335 necrosis; 313 cases involved revascularization. Patients underwent surgical debridement in 824 episodes (81%), of which 596 (59%) required amputation. The median total duration of antibiotic therapy was 20 days, with 25% given intravenously.
After a median follow-up of three years, 251 of the episodes (24.7%) were followed by ≥1 additional episode(s). Comparing those with and without additional episodes, risk of recurrence was lower in those who underwent amputation, had diabetes type I, or had revascularization. By multivariate analysis, risk of remission was inversely associated with having diabetes type I (hazard ratio [HR] 0.3, 95%CI 0.2-0.6). Neither duration of antibiotic therapy nor parenteral treatment affected risk of recurrence (HR 1.0, 95%CI 0.99-1.01 for both). Similarly, neither >3 weeks versus <3 weeks of therapy, nor >1 week of intravenous versus <1 week affected recurrence. Plotting of duration of antibiotic therapy failed to identify any optimal threshold for preventing recurrences.

Conclusion:
Our analysis found no threshold for the optimal duration or route of administration of antibiotic therapy to prevent recurrences of DFI. In view of the hazards of unnecessarily prolonged antibiotic therapy, these limited data support a shorter treatment duration for patients with DFI.

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Guiding ketogenic diet with breath acetone sensors

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Background/Introduction:
Ketogenic diet (high fat, low carb) is a treatment option for obesity and neurological diseases (e.g. refractory epilepsy). Therein, the level of ketosis needs to be regulated tightly to ensure effectiveness of the therapy. Measuring breath acetone, a volatile product of ketogenesis, could enable non-invasive monitoring of the ketotic status. Especially promising are hand-held and inexpensive breath acetone sensors for routine application in widespread populations.

Methods:
Tests included 11 subjects (5 women and 6 men) undergoing a 36-h ketogenic diet based on the John Hopkins protocol. Breath was analyzed every 3 h during daytime with a sensor chip based on Si-doped WO3 nanoparticles to selectively detect breath acetone and benchmarked with state-of-the-art quadrupole mass spectrometry. Capillary blood beta-hydroxybutyrate and glucose were measured in parallel.

Results:
The sensor recognized clearly increasing breath acetone concentrations during the ketogenic diet, in good agreement to quadrupole mass spectrometry ($R2 = 0.95$). Breath acetone reflected well the status of ketosis, as confirmed by parallel capillary blood β-hydroxybutyrate (Pearson's 0.78). Most interestingly, strong inter-subject differences were observed in response to the diet that were recognized accurately by the sensor.

Conclusion:
This portable breath sensor represents an easily applicable and reliable technology to guide ketogenic diet for potential application in the treatment of obesity or other medical conditions.

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Does Sleep Affect Weight Gain? Assessing subjective sleep and polysomnography measures in a population-based cohort study (CoLaus/HypnoLaus)

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Background/Introduction:
Mixed results regarding the effect of short and long sleep duration on weight gain exist. Few other sleep characteristics including obstructive sleep apnea and sleep fragmentation have been linked to weight gain. We prospectively investigated the effect of a range of sleep characteristics measured by questionnaire and polysomnography on weight gain in a population-based, middle-aged cohort.

Methods:
Cohort of 5064 subjects, of which 2550 (47.3% men, 56.9 ±10.3 years) had data for subjective sleep characteristics and 1422 (49.4 men, 57.6 ±10.4 years) had data on polysomnography. Multivariate logistic regressions were performed to assess the effect of sleep characteristics on a ≥5 kg weight gain during a median follow-up of 5.3 years.

Results:
In both study sample 12% of the subjects gained ≥5kg. Multivariable analyses showed poor sleep quality [as assessed by Pittsburgh sleep quality index: Odds ratio (OR) and 95% confidence interval (CI): 1.08, CI 1.04-1.12)]; high risk of sleep apnea [as measured by Berlin questionnaire: 1.46 (1.08-1.99)], percentage of sleep spent under 90% oxygen saturation [1.02, (1.01-1.03)] and autonomic arousal duration [1.85, (1.06 - 3.23)] has an effect on ≥5kg weight gain over 5 years. However, high risk of sleep apnea, percentage of sleep spent under 90% oxygen saturation and autonomic arousal duration were no longer significant in sensitivity analyses.

Conclusion:
With the exception of sleep quality, no sleep characteristic had a robust effect on weight gain. Future studies should confirm the effect of sleep quality on weight gain and investigate underling mechanisms.

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Postprandial hypoglycemia with anakinra and empagliflozin in patients after bariatric surgery – The Hypo-BEAR study

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Background/Introduction:
Postprandial hypoglycemia after bariatric surgery is characterized by a pronounced glycemic rise after carbohydrate ingestion and an exaggerated hyperinsulinemic response. Recent studies have shown that IL-1β contributes to the postprandial stimulation of insulin, and bariatric surgery affects the gut flora and associated inflammatory response. Furthermore, inhibition of the SGLT2 may reduce excessive glucose increase. Therefore, we investigated whether inhibition of IL-1β with the IL-1 receptor antagonist anakinra and/or inhibition of SGLT2 with empagliflozin reduces postprandial hypoglycemia after bariatric surgery.

Methods:
In total, 12 subjects with confirmed postprandial hypoglycaemia after bariatric surgery will be included in this placebo controlled, double-blind, randomized, cross-over proof-of-concept study. Subjects received on each of the 3 study days either empagliflozin p. o. or anakinra s. c. along with the respective placebo or double placebos. Three hours after injection (anakinra or placebo) and two hours after ingestion of the oral study medication (empagliflozin or placebo) a mixed-meal-test was performed with assessment of hypoglycemia. Glucose, insulin, c-peptide and inflammatory parameters (leukocytes, CRP, IL1-Ra, IL6) will be assessed aside of clinical parameters (Edinburgh hypoglycaemia scale, mini mental status test, Sigstad score, Stanford sleepiness Scale) and compared in a mixed model analysis.

Results:
Up to now, 12 participants were included in the study and the last two subjects will finish the study period within the next weeks. Since the study is blinded, no preliminary conclusions can be drawn. However, differences in glucose profiles between the study visits and the appearance of hypoglycemic episodes at the study dates are apparent. Thus, we expect to see effects due to the study interventions.

Conclusion:
The aim of the study is to test whether empagliflozin or anakinra may influence and/or even prevent postprandial hypoglycemia in patients after bariatric surgery. We expect to present data from this trial in November this year.

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Comparative lipidomic analysis of human skeletal muscle and visceral adipose tissue biopsies derived from lean, obese and type 2 diabetic individuals

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Background: Type 2 diabetes (T2D) is characterized by both impaired insulin secretion and insulin resistance. Chronically increased plasma lipids, as induced by obesity, further promote this phenotype as the excessive accumulation of toxic lipid metabolites in peripheral organs, including adipose tissue and muscle contributes to insulin resistance. In particular, chronic ER stress and lipid-mediated SERCA inactivation participates in the pathogenesis of obesity-induced insulin resistance in insulin-sensitive tissues. We therefore aimed to investigate the lipidomic signatures of obesity and T2D in human in skeletal muscle and visceral adipose tissue.

Methods: Human tissue biopsy samples were obtained from lean, obese and obese/type 2 diabetic human skeletal muscle (N=67) and visceral adipose tissue donors (N=37). Adipose biopsy samples were taken from the same donors that were also subjected to muscle biopsy, and compared across subjects in each group, and among the groups. Lipid extracts were prepared using a modified MTBE extraction protocol and direct infusion tandem mass spectrometry was performed for the identification and quantification of phospho- and sphingolipid lipid species.

Results: Our results show that the ratio of phosphatidylcholine to phosphatidylethanolamine (PC/PE), which critically impacts ER homeostasis and SERCA activity is increased upon obesity and T2D in human skeletal muscle (lean vs obese, *p=0.03;* lean vs T2D *p=0.008*), but remains unchanged in human visceral adipose tissue. Moreover, obesity and T2D have a profound effect on the fatty acid composition of muscle phospholipids leading to significantly higher levels of saturated fatty acids (SFAs) and mono-unsaturated fatty acids (MUFAs) but only modestly impact adipose tissue phospholipids. In contrast sphingolipids were not highly affected in human skeletal muscle but were strongly altered in visceral adipose tissue upon obesity and T2D due to an increase in dihydroceramides and a decrease in glycosylceramide and sphingomyelin levels. The mitochondria-specific lipid cardiolipin was decreased upon obesity and T2D in human skeletal muscle, reflecting the more sedentary lifestyle of obese/T2D donors (lean vs T2D *p=0.022*).

Conclusion: This comparative analysis between lipidomic profiles from muscle and adipose tissue biopsies derived from non-obese, obese and T2D donors supports the hypothesis that tissue specific lipid metabolic changes occur in both skeletal muscle and adipose tissue upon obesity and T2D. These tissue-specific lipid changes might promote the development of type 2 diabetes through lipid-mediated chronic ER stress and inhibition of SERCA activity in human muscle as well as through adipocyte inflammation and accumulation of the diabetes susceptibility biomarker dihydroceramide in visceral adipose tissue.

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SwissHPN-II Study: Intermediate Results after One Year Focused on Catheter and Related Complications

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Background/Introduction:
Incidence of home parenteral nutrition (HPN) in Switzerland is about 4/a per 1 million inhabitants. Although necessary, no representative national registry exists up to now to compare and evaluate treatments with other countries and healthcare systems. This SwissHPN-II study in adults implements a first, smaller, prospective study from 2013/2014 (SwissHPN-I) [1] to get a robust national registry.This study aims to characterize adult Swiss HPN patients, their underlying diseases, HPN indications and complications, and living conditions. This intermediate analysis focusses on PN catheters and related complications, including regimen after half of the study period.

Methods:
Data from a questionnaire filled every 6 months by the patient and their treating physician of 50 patients (52% women) were analyzed.

Results:
Hickmann (58%), Port-a-Cath (34%), and PICC (8%) are the used central venous catheters. Except one, all patients were provided with commercial multi-chamber all-in-one nutritional admixtures from home care services. Half of the patients manage HPN administration themselves or with help of family members. Most prevalent underlying diseases are cancer (30%), Crohn's disease (14%) and bariatric surgery (12%). Mechanical and infectious catheter complications were experienced by 38% and 36% of the patients, respectively. Catheter thrombosis occurred in 16% of the patients.

Conclusion:
The increased patient's number (+50%) compared to SwissHPN-I gives a representative picture of the adult SwissHPN cohort. Oncologic patients account for only one third. Mechanical and infectious catheter-related complications affected almost every third, thrombosis every sixth studied patients. More comprehensive data will be presented after the study completion.

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Consensus Paper on Safe Refeeding Protocol in Anorexia Nervosa Patients

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Background/Introduction:
Anorexia nervosa (AN) patients are at high risk for developing refeeding syndrome (RFS) when starting refeeding. The hormonal and physiological changes occurring in AN have a great influence on metabolic response in the early replenishment phase. The aim of this study is to provide a consensus based on current literature regarding risk factors, clinical manifestations, preventive and therapeutic methods as well as appropriate monitoring of RFS in AN patients.

Methods:
We searched EMBASE and MEDLINE following the systematic literature review of Friedli et al., focussing on RFS in AN patients, excluding case reports and reviews. We extracted data based on a predefined case report form.

Results:
Of 4477 potential abstracts, 28 articles a total of 2471 patients were included in the evaluation (one interventional trial). Based on the results, a protocol about management of RFS will be worked out as a consensus in a network of opinion leaders.

Conclusion:
The opinion of several international experts in the field will be presented as a consensus supported protocol in terms of prevention, management and monitoring of RFS in AN.

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Prevalence and relevance of vitamin D deficiency in malnourished patients: secondary analysis of a prospective trial

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Introduction
Vitamin D deficiency is an under diagnosed medical condition. Several studies found associations of low vitamin D levels and increased mortality, reduced quality of life and other adverse outcomes. Whether vitamin D deficiency also contributes to adverse outcomes in malnourished patients remains unclear.

Methods
We conducted an observational study to examine the association of vitamin D status and outcome in malnourished patients on different adverse clinical outcomes. 25(OH)D levels were measured in malnourished adult patients upon hospital admission and follow-up data was assessed 30 and 180 days after admission. The primary endpoint was 180-day mortality, secondary endpoints were 30-day mortality, length of hospital stay (LOS), Barthel's index and quality of life (QoL).

Results
We included a total of 828 malnourished patients with 346 (41.8%) having normal vitamin D status (≥ 50nmol/l) and 482 (58.2%) having insufficient vitamin D levels (<50nmol/l).
We found an association between vitamin D deficiency and increased 180-days mortality for the overall malnourished population OR=1.42 (95%CI 1.03-1.94, p=0.031). This association was stronger in subgroup analysis limited to patients with no vitamin D substitution (OR=1.86(95%CI 1.20-2.88, p=0.006)) and less pronounced if patients received any form of vitamin D substitution (OR= 1.03 (95%CI 0.65 – 1.64, p=0.899)).

Conclusion
We found a high prevalence of Vitamin D deficiency in the population of malnourished patients and a negative association with long-term mortality. The effect was somewhat offset when substitution of Vitamin D was started upon hospital admission suggesting that patients may benefit from screening and treatment if vitamin D deficiency is detected. Further prospective studies are needed to verify this hypothesis.

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The impact of stress exposure and physiological stress levels on body composition in children at preschool age

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Background/Introduction: The theoretical model of allostatic load (McEwen, 1998) presumes that severe stress exposure influences health outcomes through a cascade of changes of physiological stress responses, which are negatively influencing health outcomes. There is evidence for this cascade in adults, but little is known for children especially at preschool age. The aim of the study was to investigate this cascade of stress exposure, physiological stress responses and body composition in a longitudinal setting within the preschool age period.

Methods: A total of 555 healthy children aged 2-6 years were assessed at baseline and 12 months later in their childcare center and at home. Assessment included parental questionnaires on stress exposure (life events, family conflicts and socioeconomic status (SES), physiological measures of the child including salivary cortisol, salivary alpha amylase and heart rate variability at home (diurnal patterns) and during an acute stress task; and measures of body composition (BMI, body fat).

Results: Low SES was directly related to higher BMI and body fat over the two assessment time points. There was no other such relationship for any other stressor (all p-values >0.05). Physiological responses did not mediate the relationship of stressors and body composition in this healthy sample (all p-values > 0.05).

Conclusion: The cascade of stress exposure, physiological stress responses and body composition cannot be proven in healthy children with moderate stress exposure. Risk conditions might be multifactorial and stress exposure such as low SES might be one among many factors impacting on body composition at that age and be mediated through factors such as lifestyle habits. More detailed results and information will be presented at the conference.

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Targeting Intestinal Macrophages as a Potential Therapeutic Option in Metabolic Disease

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Background: Preliminary evidence suggests an inflammatory state of intestinal macrophages (iMϕ) in obesity. However, the contribution of distinct iMϕ subpopulations in high fat diet (HFD)-induced obesity – especially glucose metabolism – is still unknown. The aim of our study is to assess the role of iMϕ subpopulations in mediating glucose intolerance in obese mice.

Methods: IMϕs were isolated from C57BL/6, germ-free or CCR2-/- mice fed a HFD or control diet and characterized by flow cytometry. Macrophages were depleted dose-dependently by the oral CSF-1R inhibitor BLZ945 (50, 100, 200 µg/g/d) or specifically in the colon by intrarectal injections of clodronate liposomes (500 µg every other day) and correlated to glucose tolerance.

Results: Inflammatory iMϕs increased within one week and up to three months of HFD feeding, which preceded adipose tissue inflammation. Two mouse models protected from metabolic disease – germ-free and CCR2-/- mice – exhibited 10-fold lower inflammatory iMϕ numbers compared to WT, suggesting that iMϕ numbers are linked to glycemic control. Indeed, dose-dependent depletion of macrophages resulted in gradual improvements in fasting glucose, glucose tolerance and insulin levels. Moreover, after gut-specific depletion of iMϕs fasting glycemia and glucose tolerance were significantly improved, highlighting a direct causal link between iMϕs and glucose metabolism.
Conclusion:
HFD increases inflammatory intestinal macrophages before adipose tissue inflammation. Mouse models protected from metabolic disease and dose-dependent depletion of macrophages show that lower iMϕ numbers are linked to improved glucose metabolism. In addition, gut-specific targeting of inflammatory iMϕs restores glycemic control, emphasizing a novel therapeutic approach to treat HFD-induced metabolic disease.

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Two different variants of Short Stature Homeobox-Containing gene (SHOX) mutation in the same family

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Background/Introduction:
Deficiency of the short stature homeobox-containing (SHOX) gene is a potential etiology of short stature in children. The phenotypic spectrum of SHOX deficiency, caused by haploinsufficiency of the SHOX-gene and inherited in a pseudo-autosomal dominant manner, is highly variable, even within the same family, ranging from nonspecific short stature to Leri-Weill dyschondrosteosis (LWD). Short stature, mesomelia and Madelung deformity define the classic clinical triad in LWD. SHOX deficiency can be caused either by single nucleotide variants or deletions encompassing the SHOX coding region and/or the enhancer region regulating SHOX expression.
We describe two brothers (21-month and 4-year old) with short stature and disproportion. Both children had an unremarkable past medical history. Family history was notable for several individuals with short stature. The parents presented both with short stature, but the father was proportioned, while the mother showed stigmas indicating

Methods:
Multiplex Ligation-dependent Probe Amplification (MLPA) of the PAR region on Xp22.32 and Yp11.32 containing the coding region and 5' and 3' flanking sequences of the SHOX gene was performed using the MRC-Holland kit P018-G1 according to the manufacturer's instructions.

Results:
SHOX gene analysis revealed a known heterozygous ~47, 5 kb deletion in the 3'-flanking region (probes L25091-L24249) in the mother and the older child, whereas a novel duplication in the SHOX 5'-flanking sequence (probes L24430-L20651) was found in the father and the younger child. This duplication has not been described previously, but likely influences the regulation of SHOX protein expression.

Conclusion:
Short stature can be caused by different SHOX gene mutations and there is no established correlation between the severity of phenotype and the underlying pathogenic variant. The penetrance of SHOX deficiency is high, and it's clinical expression highly variable, even in the same family. Phenotypic characteristics become more pronounced with age and are more severe in females. All the more it was a surprise to find two different SHOX gene variants in two short siblings.

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Nutritional Assessment in Patients Affected by Cystic Fibrosis (NACYFI study)

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Background/Introduction:
Cystic fibrosis (CF) patients are at nutritional risk. One of the main pathologic issues is viscous mucus blocking pancreatic ducts, leading to reduced production of pancreatic enzymes. Therefore, maldigestion and consequently malabsorption occurs, particularly of fats and liposoluble vitamins, resulting in steatorrhoa, vitamin deficiencies and subsequently malnutrition. We aimed to determine the prevalence of malnutrition and investigate the nutritional status of an adult Swiss CF cohort.

Methods:
We contrasted CF patients with healthy controls regarding nutritional status and dietary habits in an observational cohort study. Assessment was based on nutritional risk screening (NRS-2002), dietary habits (7-day food record), body composition (bioelectric impedance analysis, anthropometrics), resting energy expenditure (REE; indirect calorimetry), and physical/mental function (SF-36v2®).

Results:
Nineteen patients (13 men, median age 32 years) and 15 controls (8 men, median age 52 years) were included. Eight patients (42%) were at nutritional risk (NRS-2002≥3). According to ESPEN guidelines, 8 (42%) patients were malnourished. Energy intake per kg body weight was significantly higher in patients (p=.015). No significant differences arose in REE (p=.451) and estimated energy requirements (p=.202). Energy balance is +648 kcal in patients and +57 kcal in controls (p=.176). Patients' body fat-free mass percentage (p<.001) was significantly higher and BMI (p=.027) and physical/mental health scores (p<.001) were significantly lower.

Conclusion:
Malnutrition is highly prevalent in this CF cohort (47%). Energy intake and body weight are highly discrepant in patients. In clinical practice, energy requirements of CF patients are approximately twice the Harris-Benedict estimation and adequate intake of pancreatic enzyme substitution is crucial.

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Ketogenic diet and its evidence based therapeutic implementation in endocrine diseases: a literature review

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Background/Introduction:
Ketogenic diets (KD) have been in clinical use for treatment of therapy-resistant epilepsy in children since the 1920. Implementation of KD in other target populations is increasingly being discussed (i.e. oncology, endocrinology). In this literature review, we assessed the efficacy of KD for the treatment of metabolic disorders such as type 2 diabetes mellitus (T2DM) and polycystic ovary syndrome (PCOS).

Methods:
We searched MEDLINE and EMBASE focussing on efficacy of KD in T2DM and PCOS, excluding case reports.

Results:
A total of 271 studies for T2DM and 81 for PCOS were identified, of which 16 (8 RCT, 8 interventional studies) and 12 studies (6 RCT, 6 interventional studies) were included in the analysis. Restriction of carbohydrates without energy restriction leads to significant weight loss in most studies. In case-control studies with T2DM, KD significantly reduced HbA1c-levels compared to reference diet. Fasting blood glucose levels were significantly lowered by KD across almost all studies. Moreover, positive effects of KD on insulin resistance and lipid blood profile were observed in several but not all studies. Of the 28 included studies, diet-induced ketosis was biochemically confirmed in two studies only ketosis. Inconsistency among studies mainly relate to quantity and quality of dietary fats in KD and regimes of reference diets.

Conclusion:
Although preliminary evidence supporting clinical benefits of KD in T2DM and PCOS exist, study results are highly heterogenic, what makes a general recommendation difficult. To evaluate efficacy, safety and usability of KD in T2DM and PCOS, further well-designed studies are needed.

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Effects of Relaxation on Cortisol and Obesity in Adolescents - a Randomised Controlled Study.

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Introduction:
Lack of impulse control and impaired stress regulation may explain the development of obesity and its challenging therapy, already in youth (Nederkoorn 2007). To improve self-regulation of overweight adolescents and subsequently their weight status, we tested, whether a biofeedback relaxation exercise decreases stress and whether relaxation services implemented in a novel Smartphone App supported intervention have effects on stress and weight outcomes.

Methods:
First 6 months' data in 30 adolescents with BMI >P.90 of an ongoing 12-month randomized controlled study are being reported. Patients try to relax over two minutes through a breathing exercise while observing in real time their arousal level measured as skin conductance with NeXus-10. Cortisol in blood as stress marker is measured before and after this exercise, at start, 3, 6 and 12 months. During the intensive phase of 6 months, 17 patients of the intervention group (IG) are equipped with a smartphone and a specially designed chat App with game character, which encourages them through a virtual coach to achieve daily activity or relaxation challenges and earn virtual rewards. While 13 patients of the treatment as-usual group (CG) have monthly visits on site during the intensive phase, IG has only four visits. Beside BMI and BMI Standard Deviation Score (SDS), adjusted for age and sex, clinical parameters and stress questionnaires (TICS) are being assessed at start, 6 and 12 months.

Results:
Age (13.6 years, 11-17), mean BMI (29.5±3.7kg/m^2), mean BMI SDS (2.5±0.5 SD) and cortisol levels (median 217, 109-434mmol/L) were similar in both groups at start. In the IG, cortisol levels decreased after the biofeedback session by 30% (p<0.01) after 3 and 30% after 6 months (p<0.01). The CG exhibited a significant cortisol decrease by 36% (p<0.01) at start and 39% after 3 months (p<0.01). After 6 months there was a trend in Cortisol reduction in the CG by 35% (p=0.051). No long-term changes of cortisol were observed. BMI SDS was stabilized in the IG (Δ BMI SDS -0.08) while decreased significantly in the CG (Δ BMI SDS -0.4, p=0.01) after 6 months. So far, no consistent correlations between changes in BMI SDS and cortisol during therapy were found.

Conclusion:
Electrodermal biofeedback reduces acute stress hormone levels in obese adolescents, an age group with difficulties managing emotions and can be a valuable tool in obesity therapy. The long-term effects of biofeedback therapy on chronic stress and BMI are currently under investigation.

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Mild Impairment of Mitochondrial OXPHOS Promotes Fatty Acid Utilization in POMC-Neurons and Improves Glucose Homeostasis in Obesity

Author/Address of institution:
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Background/Introduction:
Hypothalamic proopiomelanocortin (POMC)-expressing neurons are important central regulators of glucose- and energy homeostasis. Mitochondrial oxidative phosphorylation (OXPHOS) and substrate utilization critically regulate the function of hypothalamic POMC-expressing neurons. However, upon high-fat diet (HFD) feeding, mitochondrial network complexity and dynamics are impaired in POMC neurons, causing decreased excitability in these neurons.

Methods:
Mice with POMC neuron-specific apoptosis-inducing factor (AIF) and mitochondrial pyruvate carrier (MPC)-1 deficiency were generated using the Cre-lox system and metabolically phenotyped upon control diet or HFD feeding, using insulin- and glucose tolerance tests, hyperinsulinemic-euglycemic clamps, indirect calorimetry (phenomaster system), leptin sensitivity tests and reactive oxygen species (ROS)-detection in POMC neurons in vivo. Mitochondrial dynamics in POMC neurons were assessed using electron microscopy and POMC-neuron activity was assessed via perforated patch-clamp recordings from synaptically isolated neurons. Mitochondrial OXPHOS and ROS formation was evaluated using an AIF-deficient hypothalamic cell line via Seahorse-technology and FACS analysis.

Results:
Here, we demonstrate that inactivation of AIF in POMC-neurons results in a slightly impaired mitochondrial respiration chain complex I activity. This mild impairment in mitochondrial OXPHOS decreases POMC-neuron activity in lean mice, but prevents HFD-induced inhibition of POMC-neurons in obese animals. AIF-deficient POMC-neurons exhibit restored mitochondrial morphology and an increased ability to utilize fatty acids (FAs) for mitochondrial respiration and ROS-formation, enabling their increased firing activity upon HFD-feeding. Overall, AIF-deficiency in POMC neurons results in improved leptin- and insulin-sensitivity as well as increased thermogenesis and restored glucose metabolism in obesity. Consistent with a role for altered fuel usage in this process, also POMC-Cre-dependent deletion of the mitochondrial pyruvate carrier (MPC)-1, which transports the critical complex I substrate pyruvate into the mitochondrial matrix, also protects from HFD-induced glucose intolerance.

Conclusion:
Collectively, partial impairment of mitochondrial respiration shifts substrate utilization in POMC-neurons from glucose to FAs, restoring their firing properties in obesity and improving obesity-associated deteriorations in systemic glucose- and energy metabolism, pointing to the therapeutic potential for mild complex I inhibition in hypothalamic neurons for the treatment of obesity and obesity-associated insulin resistance.

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Hyperammonemic encephalopathy – a rare but life-threatening complication after bariatric surgery

Author/Address of institution:
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Background:
Roux-en-Y gastric bypass (RYGBP) is the most commonly performed bariatric weight loss procedure. Despite its well described favorable effects on obesity and its co-morbidities lifelong follow-up is required to identify and appropriately manage surgical, nutritional and metabolic complications of the procedure. More recently, hyperammonemic encephalopathy in the absence of liver disease has been identified as another potential life-threatening condition associated with the procedure.

Case presentation:
Within a six months period we identified hyperammonemic encephalopathy in 3 female patients who had undergone a so-called distal RYGBP 10-11 years previously. All three patients presented with multiple micronutrient deficiencies and severe protein malnutrition and their history was remarkable for long-term poor dietetic management and psychiatric comorbidities.
All patients developed signs of the refeeding syndrome and progressive neurological deterioration including generalized epilepsy in one patient after high-protein supplementation had been started. An extensive clinical, neurological and biochemical workup revealed severe hyperammonemia with no evidence for underlying liver disease. The management of our patients included the immediate withdrawal of any enteral and parenteral protein supply, supplementation of citrulline and arginine, and alternative pathway therapy with sodium-benzoate to remove ammonium. With this approach, mental status improved gradually and ammonium levels normalized within a few days. Plasma ammonium levels remained normal after the gradual introduction of dietary proteins thereafter. An extensive biochemical work-up failed to detect yet unrecognized mild urea-cycle defects, organic acidurias and fatty acid oxidation disorders. However, very low plasma concentrations of several urea-cycle intermediates such as citrulline were detected during the acute phase of the episodes.

Conclusion:
Hyperammonemic encephalopathy should be recognized as a novel, rare but life-threatening complication of RYGBP. The condition may occur in patients with severe malnutrition receiving protein supplementation. A functional impairment of the urea-cycle due to the deficiency of several substrates of the pathway, possibly as a consequence of the severe malnutrition, is a likely pathogenetic event. Early and aggressive treatment of the hyperammonemia including alternative pathway therapy to remove ammonium via the kidneys and supplementation of arginine and citrulline to restore urea-cycle function are recommended and may allow a favorable outcome.

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Individualized nutritional support in medical inpatients at nutritional risk: a randomized clinical trial

Author/Address of institution:
1) Philipp Schuetz, 1) Rebecca Fehr, 1) Valerie Baechli, 1) Martina Geiser, 1) Manuela Deiss, 1) Filomena Gomes, 1) Alexander Kutz; 2Pascal Tribolet, 2) Thomas Bregenzer, 3) Nina Braun, 3) Claus Hoess, 3) Vojtech Pavlicek, 3) Sarah Schmid, 4) Stefan Bilz, 4) Sarah Sigrist, 4) Michael Brändle, 4) Carmen Benz, 5) Christoph Henzen, 5) Silvia Mattmann, 6) Robert Thomann, 6) Claudia Brand, 7) Jonas Rutishauser, 8) Drahomir Aujesky, 8) Nicolas Rodondi, 8) Jacques Donzé, 10) Zeno Stanga*, 1) Beat Mueller*
1) Kantonsspital Aarau, Aarau, 2) Spital Lachen, 3) Kantonsspital Münsterlingen, 4) Kantonsspital St.Gallen, 5) Kantonsspital Luzern, 6) Bürgerspital Solothurn, 7) Kantonsspital Baselland, 8) Inselspital, Bern University Hospital,

Background/Introduction:
Guidelines recommend use of nutritional support during hospital stays of medical patients at risk for malnutrition. However, the supporting evidence is limited, and there is growing concern about possible negative effects of nutritional therapy during acute illness on recovery and clinical outcome.

Methods:
In a pragmatic, investigator-initiated, open-label, multicenter trial in eight Swiss hospitals, we randomly assigned 2088 medical inpatients at nutritional risk (Nutritional Risk Screening [NRS] score ≥3 points) to receive protocol-guided individualized nutritional support to reach protein and energy goals (intervention group) or standard hospital food (control group). The composite primary endpoint included all-cause mortality, intensive care admission, non-elective hospital readmission, major complications and decline in functional status at 30 days.

Results:
During the hospital stay, 78% of intervention group patients reached energy and protein goals according to the protocol. By 30 days, 232 of 1015 patients (22.9%) in the intervention group reached the composite primary endpoint compared to 272 of 1013 (26.9%) control group patients (adjusted odds ratio 0.79 [95%CI 0.64 to 0.97], p=0.023). In the intervention group, there were lower rates of death (73 patients [7.2%] vs. 100 patients [9.9%], adjusted odds ratio 0.65 [95%CI 0.47 to 0.91], p=0.011) and functional decline (35 patients [3.7%] vs. 55 patients [6.0%], adjusted odds ratio 0.62 [95%CI 0.40 to 0.96], p=0.034).

Conclusion:
Among medical inpatients at nutritional risk, use of individualized nutritional support during the hospital stay increased daily energy and protein intakes, and improved important clinical outcomes including survival as compared to standard hospital food.

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

Authors: Sophia J Wiedemann[1], Erez Dror[1], Daniel T Meier[1], Leila Rachid[1], Friederike Schulze[1], Stéphanie Häuselmann[1], Marc Stawiski[1], Josua Wehner[1], Theresa Rohm[1], Philipp Carter[1], Marianne Böni-Schnetzler[1], Marc Y Donath[1]

Affiliations/Adress of Institution:[1]Clinic of Endocrinology, Diabetes and Metabolism University Hospital Basel, Basel, Switzerland and Department of Biomedicine, University of Basel, Basel, Switzerland.

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

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

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

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

Schweizerische Gesellschaft für Endokrinologie und Diabetologie
Société Suisse d'Endocrinologie et de Diabétologie
Società Svizzera d'Endocrinologia e Diabetologia
Societad Svizra d'Endocrinologia e Diabetologia

An die Mitglieder der SGED
Aux membres de la SSED

Baden, Oktober/octobre 2018

EINLADUNG ZUR ORDENTLICHEN GENERALVERSAMMLUNG 2018
INVITATION À L'ASSEMBLEE GENERALE ORDINAIRE 2018

Ort/Lieu Bern, Inselspital, Auditorium Rossi
Datum/Date Donnerstag/jeudi, 15. November 2018, 17.30 – 19.00

TRAKTANDEN / ORDRE DU JOUR

1	Begrüssung / bienvenue	F. Pralong
2	Protokoll der GV vom 16.11.17 / procès verbal de l'AG du 16.11.17**	F. Pralong
3	Bericht des Präsidenten / rapport du président	F. Pralong
4	<u>Statutenänderung / Révision des statuts***:</u> • Verlängerung der Amtszeit des Präsidenten auf 4 Jahre • Statutenänderung der Praktizierenden Endokrinologen, Diabetologen • Prolongation de la présidence à 4 ans • Changement des statuts de la section des praticiens	F. Pralong
5	Sponsoringboard 2017-2018 / Sponsors 2017-2018 Neues Konzept ab 2019 / nouveau concept à partir de 2019	F. Pralong S. Bilz
6	Jahresrechnung 2017 / comptes annuels 2017** Rechnungsrevision / rapport du réviseur** Budget 2019 / budget 2019	S. Bilz
7	<u>Bericht aus den Sektionen, Kommissionen und Arbeitsgruppen / rapports des commissions et groupes de travail</u> <u>Sektionen/sections</u> SKED (ex FED), SEDC (ex PES) SGPED, SSEDP <u>Arbeitsgruppen</u> ASEMO Forschung / recherche Working Group Disease management diabetes / QualiCCare (2017/18)	 M. Faulenbach V. Schwitzgebel K. Laederach C. Dibner E. Christ

Schweizerische Gesellschaft für Endokrinologie und Diabetologie
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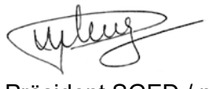
Società Svizzera d'Endocrinologia e Diabetologia
Societad Svizra d'Endocrinologia e Diabetologia

	Interdisziplinäre Diabetologie / IDW (2017/18) Diabetischer Fuss / pied diabétique (2017/18) Andere <u>Kommissionen intern / commissions internes:</u> KWFB: Weiter- und Fortbildung / formation continue, formation postgraduée • Fortbildungsprogramm / programme formation continue • Weiterbildungsprogramm / programme formation postgraduée (accréditation) <u>Kommissionen extern / groupes de travail externes:</u> FMH 2017/18 DV & Aerztekammer, AD & chamber des médecins Swiss DRG Tarmed/Tarvision DIAfit (2017/18)	M.Faulenbach B. Peter S. Thalmann E. Christ E. Christ F. Pralong P. Elsässer M. Laimer
8	Tagungen / Réunions 2019 FOSPED: 04.04.2019 Biel/Bienne Herbsttagung: 14./15.11.19 Berne	 M. Faulenbach M. Christ-Crain
9	Wahlen Vorstand / Elections comité • Prolongation présidence F. Pralong pour une année • Prolongation Mirjam Christ-Crain (wissenschaftliches Komitee) • Neuwahlen/nouveaux membres: Felix Beuschlein & Marc Donath Wahl der Revisionsstelle: Hüsser & Gmür Baden-Dättwil Verabschiedung / Adieux	F. Pralong
10	Neue Mitglieder / nouveaux membres** Austritte-Todesfälle / Démissions-Déces	F. Pralong
11	Varia	F. Pralong

François Pralong



Präsident SGED / président SSED

** liegt an der Jahresversammlung auf / disponible lors de la réunion annuelle
*** siehe Anträge auf den Folgeseiten / voir propositions sur les pages suivantes

Mitgliederversammlung vom 15 November 2018

Traktandum 4 Statutenänderung

Aktuelle Statuten	**neu**
Art. 17.7 Die Amtsdauer als Vorstandsmitglied kann für den Kassier und für den Präsidenten während seiner Amtsdauer um 2 Jahre verlängert werden. Die Amtsdauer des Präsidenten ist jedoch auf 3 Jahre beschränkt. Der Präsident bleibt nach seinem Rücktritt noch während eines weiteren Jahres als past president im Vorstand.	… Die Amtsdauer des Präsidenten ist auf 4 Jahre beschränkt. …
Art. 19.1 Die Sektion der freipraktizierenden Endokrinologen (FPES) wird durch ein internes Reglement geregelt, das die Statuten der Gesellschaft respektiert. Das Reglement der Sektion muss von der Generalver-sammlung der Gesellschaft gebilligt werden. Die Sektion ist ökonomisch unabhängig von der Gesellschaft.	Die Sektion für Klinische Endokrinologie und Diabetologie (SKED) … (Namensänderung)

Vorschlag verabschiedet an der Vorstandssitzung vom 29. August 2018 in Bern. Die gesamten Statuten finden Sie auf unserer Homepage (www.sgedssed.ch)

Ihre Notizen:

Assemblée générale du 15 novembre 2018

Ordre du jour, point 4, révision des statuts

Status actuels	**nouveau**
Art. 17.7 Pour le trésorier et le président, durant l'exercice de leurs fonctions, la durée du mandat en tant que membre du comité peut être prolongée de 2 ans. La durée du mandat du président est toutefois limitée à 3 ans. Après la fin de son mandat, le président reste dans le comité encore une année en tant qu'ancien président.	… la durée du mandat du président est limitée à 4 ans. …
Art. 19.1 La Section des endocrinologues praticiens (SEP) est régie par un règlement interne qui respecte les statuts de la Société. Le règlement de la section doit être approuvé par l'assemblée générale de la Société. La section est économiquement indépendante de la Société.	La section d'endocrinologie et de diabétologie clinique (SEDC) (changement de nom)

Proposition approuvée par le comité lors de sa séance du 29 août 2018 à Berne. Les statuts complets sont téléchargeables depuis notre site internet (www.sgedssed.ch)

Vos notes:

Galadinner mit Preisverleihung / Dîner de gala avecattribution des prix

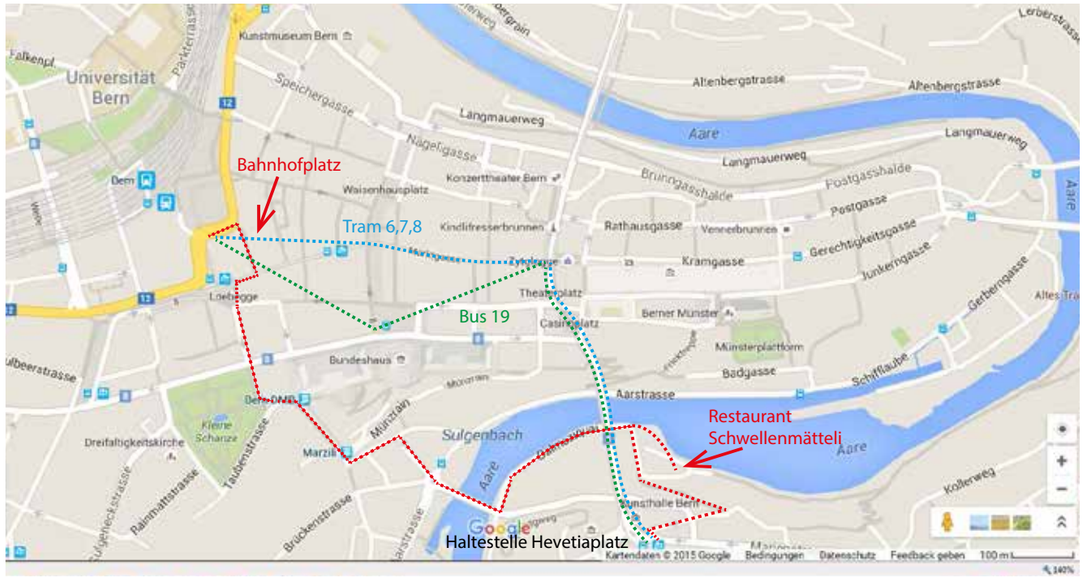
Datum / *Date:* Donnerstag, 15. November 2018 / *jeudi 15 novembre 2018*

ab 19.30 Uhr / *dès 19.30 h*

Ort / *Lieu:* **Restaurant Schwellenmätteli (Event Lounge)**
Dalmaziquai 11, 3000 Bern 13
Telefon 031 / 350 50 01
Telefax 031 / 350 50 02
info@schwellenmaetteli.ch
www.schwellenmaetteli.ch

Programm/*e:* Apéro für junge Mitglieder ab 18.30 Uhr

Apéro ab 19.30 Uhr / *apéritif dès 19.30 h*
Nachtessen um 20.00 Uhr / *dîner à 20.00 h*



Wegbeschreibung:

zu Fuss ab Bahnhofplatz: ● ● ● ● ●
↱ auf Bahnhofplatz, ↱ auf Bubenbergplatz/Spitalgasse, ↰ auf die Christoffelgasse, ↰ Richtung Taubenstrasse, Fussgängerunterführung, ↗ auf Taubenstrasse, ↑ weiter auf Bundesrain, ↰ auf die Weihergasse, ↱ auf Gasstrasse, ⟲ im Kreisverkehr dritte Ausfahrt (Dalmazibrücke), ↰ auf Dalmaziquai.

mit Tram ab Bahnhof: ● ● ● ● ●
bis Haltestelle Helvetiaplatz. Tram 6 Richtung Worb Dorf, Tram 7 Richtung Bern Ostring, Tram 8 Richtung Bern Saali.

mit Bus ab Bahnhof: ● ● ● ● ●
bis Haltestelle Helvetiaplatz. Bus 19 Richtung Bern Elfenau

Zu Fuss ab Helvetiaplatz: ● ● ● ● ●
Anschliessend zu Fuss ↑ Marienstrasse, ↖ weiter auf Marienstrasse, ↱ Englische Anlagen, ↖ Richtung Dalmaziquai, ↑ weiter auf Dalmaziquai.

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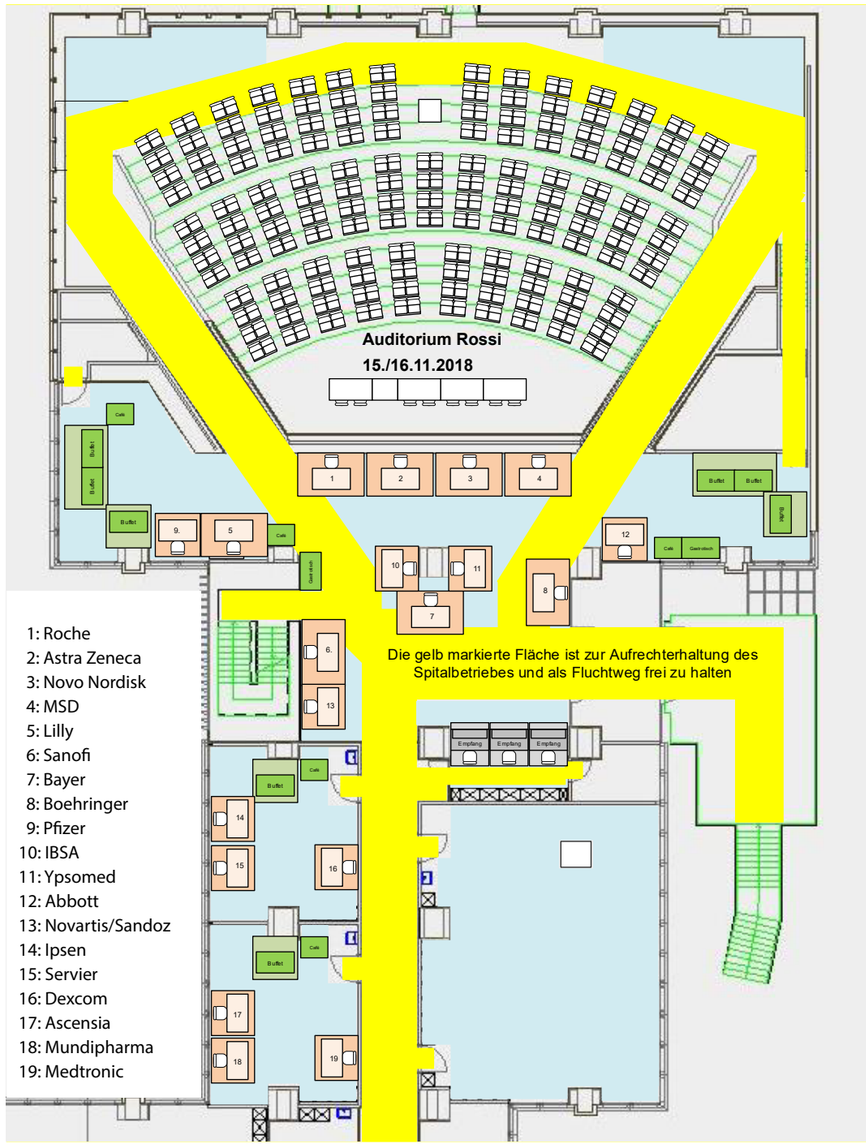

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