S = contribution of a student

01

Influence of the venous outflow pattern on the accuracy of super-selective bilateral inferior petrosal sinus sampling in the diagnosis of ACTH-dependent Cushing's syndrome

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Background/Introduction
Variations in the venous outflow pattern of the inferior petrosal sinus into the jugular vein are frequently encountered. While bilateral inferior petrosal sinus sampling (BIPSS) is highly sensitive and specific distinguishing Cushing's disease (CD) from ectopic ACTH syndrome (EAS), accuracy in predicting the adenoma lateralization side still remains elusive.
In the present study, we aimed to invastigate on the influence of the outflow pattern in detecting the adenoma side using microcatheters preventing venous outflow diversion.

Methods
Single center follow-up study reviewing our prospectively maintained institutional database from June 1997 to January 2016. Patients with BIPSS met clinical and biochemical inclusion criteria of Cushing's syndrome (CS) with equivocal MRI findings. We evaluated demographics, laboratory, procedural, surgical and pathologic findings.

Results
BIPSS was performed in 38 patients (31 women, 7 men); age: 45 ± 15 years (mean ± SD; range 7–71 years). A central-to-peripheral gradient accurately distinguished CD from EAS in all but 3 patients. BIPSS predicted the correct lateralization of the adenoma with regard to the pathological finding in 22 (88%) patients with CD. Prediction was improved when the venous outflow was symmetric (100%) compared to asymmetric outflow (82%), though not significantly (p= 0.53). The sensitivity and specificity of BIPSS in detecting the correct ACTH-secreting source was 97% (95% CI, 83-99.9) and 60% (95% CI, 15-95), respectively. Remission was noted in 29 (82%) patients, 19 (54%) patients were cured from CS.

Conclusion
Detailed understanding of the different venous drainages is key to attain high catheterization success rates. Preventing venous outflow diversion by using microcatheters allows for accurate prediction of the adenoma side independent of the venous outflow pattern.

02

Ultra-Rapid BioChaperone® Lispro Ameliorates Postprandial Blood Glucose (PBG) Control Compared with Humalog in Subjects with Type 1 Diabetes Mellitus

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Background/Introduction
BioChaperone Lispro (BCLIS) is an ultra-rapid insulin lispro (LIS) formulation designed to better mimic the physiological timing of prandial insulin action.

Methods
In this double-blind cross-over study, 38 subjects with type 1 diabetes [mean±SD diabetes duration: 23±9 yrs; age: 44±13 yrs; BMI; 25±2 kg/m2; HbA1c: 57±10 mmol/mol (7.4±0.9%)] received a single subcutaneous dose (0.2 U/kg) of BCLIS or LIS at the start of a standardised liquid meal (600 kcal: 80 g carbohydrates; 25 g proteins; 20 g fat).

Results
Baseline blood glucose (BG) was controlled at 5.6 mmol/L. Compared to LIS, BCLIS exhibited a statistically significant higher early insulin exposure post-dosing (least square mean ratio [95% CI] AUC{0-30min}: 2.68 [2.18; 3.30]; AUC{0-1h}: 1.52 [1.37; 1.68]), a lower late exposure (AUC{2-8h}: 0.79 [0.72; 0.87]) and earlier time to early and late 50% Tmax (T{0.5 max early}: 0.63 [0.57; 0.71]; T{0.5 max late}: 0.85 [0.79; 0.91]) and Tmax (0.75 [0.69;0.83]). PBG was significantly better controlled after BCLIS than LIS, with a reduction of mean BG concentrations 1h (BG1h) and 2h (BG2h) after meal start of -2.3 and -1.5 mmol/L respectively and a decrease of incremental AUC{BG} over the 2 first hours (ΔAUC{BG 0-2h}) of 61%. The number of hypoglycaemic events after each medication was similar and there were no safety or local tolerance issues.

Conclusion
In conclusion, ultra-rapid BCLIS is more rapidly absorbed and improves postprandial glucose control in comparison to LIS.

03

F18–fluorocholine as PET tracer to localize parathyroid adenomas

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Background/Introduction
Successful preoperative imaging (e.g., concordant localization by neck ultrasound and scintigraphy) allows minimally invasive selective parathyroidectomy (MIP) in a majority of patients with primary hyperparathyroidism (PHPT). 18F-fluorocholine PET/MRI is currently under investigation as a novel imaging tool, especially for patients qualifying and willing to undergo parathyroid surgery where standard preoperative diagnostic localization procedures are discordant or even all fail to localize an adenoma.

Results
During the past three years, we (endocrinologists, working in four different hospitals) proposed 18F-fluorocholine PET/MRI to 17 patients (12 female; age 27-76, median 62 years) with PHPT (PTH range 60-266, median 128 ng/ml) and indication and consent for parathyroid surgery and negative parathyroid scintigraphy. In 2 of them, ultrasound revealed single candidate culprit lesions compatible with parathyroid adenoma (in retrospect, proven to be correct), in 15 of them, this was not the case. All patients consented to off-label imaging with 18F-fluorocholine PET/MRI, and in all of them, fluorocholine PET/MRI identified a single parathyroid adenoma. Focal tracer accumulation (SUVmax median 7.3, range 1.6-14.9) was found and helped to guide removal of parathyroid glands (weighing 0.06-1.1, median 0.5 g) by MIP in 15 patients and along with thyroidectomy in 2 patients with multinodular goiter. Interestingly, a preoperative ultrasound added with the knowledge of fluorocholine PET/MRI was not able to identify parathyroid adenomas in six patients (glands weighing 0.06-0.6, median 0.33 g). Surgery resulted in an intraoperative drop of PTH and subsequent normalization of serum calcium (albumin-corrected, range 2.11-2.47, median 2.32 mmol/l) in all patients.

Conclusion
Our limited experience with the exam does not allow a comment on the specificity but suggests improved sensitivity (compared with scintigraphy, apparently also with ultrasound) of 18F-fluorocholine PET/MR, particularly for the detection of small adenomas. It is an expensive but potentially helpful tool to localize the dominant source of PTH in difficult selected cases with PHPT where a targeted surgical approach (often MIP) is considered the treatment of choice.

04

Carbohydrate estimation supported by the GoCARB system in individuals with type 1 diabetes – a randomized prospective pilot study

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Background/Introduction
Quantification of carbohydrates (CHO) is essential to achieve satisfactory glucose control in type 1 diabetes (T1D). Accurate CHO counting however remains challenging. Patients may benefit from user-friendly approaches in CHO estimation. GoCARB is a computer-vision based system that provides users with CHO content estimation using pictures of served plated-meals. We present results of the first prospective clinical trial assessing the effects of GoCARB on glucose control in individuals with T1D treated by sensor-augmented insulin pump therapy (SAP).

Methods
Twenty adults with T1D on SAP (mean±SEM: age 35±14 years, HbA1C 7.5±0.6 %, duration of diabetes 17±10 years) were enrolled into this randomized prospective single-centre cross-over study. One week use of GoCARB was compared with conventional methods to estimate CHO intake. After a 2 week run-in period with a GoCARB training version (without automated CHO output), patients were randomly assigned to either one week of GoCARB use (GoCARB), followed by their individual CHO estimation (control) during a second week, or vice versa. During the GoCARB period, patients were provided with an automatically generated CHO suggestion.Translation of the suggested CHO amount into individual insulin meal bolus was at the patients' own discretion. Glycemic profile was assessed using CGM. Statistical analysis was performed on an intention-to-treat approach using paired comparison and general linear models with fixed and random effects.

Results
Percentage of time spent in hyperglycemia (>12 mmol/l) was significantly lower in GoCARB compared to control (15.0±2.0 vs. 18.2±2.1%, p=0.039). The postprandial iAUC over 180min was 205±28.8 mmol x min/l and. 270±39.6mmol x min/l for GoCARB and control, respectively (p=0.13). Percentage of time spent in hypoglycaemia (<3.5 mmol/l) was 2.3±0.8% in GoCARB and 2.6±0.7% in control (p=0.58). Mean glucose between the interventions were comparable (8.7±0.3 vs. 8.9±0.3 mmol/l,p=0.22). Percentage of time above,within and below target (3.9-10mmol/l) was 65.9±2.7%, 30.1±3.1% and 4.0±1.1% for GoCARB and 63.2±2.8%, 32.5±3.2% and 4.2±0.9% for control (p=0.19, 0.25 and 0.66, respectively). Glucose variability measured as standard deviation of sensor glucose, was significantly lower in GoCARB than control (3.0±0.1 vs. 3.2±0.2mmol/l, p=0.01). The mean number of daily CHO-containing meals was 4.4±0.6 and 3.8±0.5 during GoCARB and control, respectively (p=0.07). During GoCARB 47.2±4.1% of the meals were assessed using the software, accounting for 53.8±4.2% of recorded daily CHO intake. Insulin dose and bolus frequency did not differ between the interventions.

Conclusion
GoCARB use significantly reduced time spent hyperglycemic and glucose variability. GoCARB may provide a novel approach to reduce CHO counting burden with potentially beneficial effects on glucose control in T1D.

05

Glycemic control and hypoglycaemia - does time of day matter?

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Background/Introduction
Tight glycemic control has been the standard of care to prevent diabetes-related complications in type 1 diabetes (T1D). This however is currently limited by increased risk of hypoglycaemia, which may be mitigated by real-time CGM use. The differences in the risk of hypoglycaemia during different time periods of the day in well- and poorly controlled patients with T1D is currently not well understood. We aimed to assess the differences in hypoglycemia risk in two cohorts with differing baseline HbA1C levels, and its association with daytime and overnight periods.

Methods
Real-time CGM data from two multi-centre studies involving T1D adult patients on insulin pump therapy [Group1, n= 28 (HbA1C<7.5%) and Group2, n=30 (HbA1C≥7.5%)] were compared over a 2 week period. Comparative analysis was performed between and within groups for overall, daytime (0800 - midnight) and overnight (midnight - 0800) periods. CGM data was collected for mean glucose, time in target (3.9-10 mmol/l for overall and daytime, 3.9-8 mmol/l for overnight), time below and above target. Correlation between baseline HbA1C and time spent below target was also evaluated for overall, daytime and overnight periods.

Results
Baseline HbA1C was 6.8±0.8% and 8.4±0.6% for Group1 and Group2, respectively. Baseline demographics were otherwise comparable between groups, with the exception of total daily insulin dose (0.6±0.2 and 0.5±0.1U/kg, p=0.02). Mean glucose (8.1 vs. 8.9 mmol/l) and time above target (23.8 vs. 33.4%) were lower, and time within target higher (70.8 vs. 62.1 %), in Group1 compared to Group2 for all time periods (p<0.05 for each). Between groups, time spent below target in Group1 tended to be higher overnight compared to Group2 (median 5.7 vs. 3.4 %, p=0.05). Within groups, significantly increased time spent below target during overnight versus daytime (median 5.7 vs. 3.1 %, p=0.004) was observed in Group1. However, time spent below target in Group2 were comparable during daytime and overnight periods. An inverse correlation was found between HbA1C and time spent below target in the overall period when data from both groups were combined (r=-0.3, p=0.03), this correlation was more notable during the overnight period (r=-0.4, p=0.002).

Conclusion
Compared to patients with HbA1C≥7.5%, those with HbA1C<7.5% have a tendency to spend greater time below target overnight. In addition, these patients are also at greater risk of hypoglycaemia overnight than during the day. In spite of real-time CGM use, overnight hypoglycaemia still remains a challenge in well-controlled patients.

06

Metabolomic profiling during different exercise conditions in type 1 diabetes

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Background/Introduction
Exercise in type 1 diabetes (T1D) involves a complex interplay of exogenous insulin use, counter-regulatory response and changes in whole body insulin sensitivity. Intermittent high-intensity exercise (IHE) may be metabolically beneficial in T1D due to its glycaemic stabilizing effects. The effects of IHE on counter-regulatory hormones are well-understood, in comparison to changes of metabolites during the same. The aim of this study was to explore changes in metabolic profiles during IHE and iso-energetic continuous moderate intensity exercise (CONT) in T1D without prior insulin reduction.

Methods
Metabolic profiling was performed in 12 male patients with well-controlled T1D (mean±SD age 26.2±3.9 years, HbA1c 7.0±0.6%) who underwent 90 min of exercise at 50%VO2max with and without interspersed 10s supramaximal sprints (IHE and CONT) in a randomized cross-over design. Insulin and blood glucose levels were kept identical. Serum samples at baseline (0'), 80 min of exercise (80') and 120 min post-exercise (120') were assessed using ultra-high performance liquid chromatography coupled to high-resolution mass spectrometry (UHPLC-HR-MS). Findings from non-targeted measurements were validated by quantitative UHPLC-MS UPLC-QQQ for acylcarnitines and conventional immunoassays for purine metabolites. Multivariate analysis of targeted data consisted of PCA and OPLS or OPLS-DA using information from study groups (IHE, CONT) and time (0', 80', 120'). The statistical software R 3.1.2 was used for all statistical analysis.

Results
Non-targeted and targeted metabolomics analyses revealed significant exercise-induced changes in acylcarnitine profiles and purine metabolites. Purine metabolites (inosine, hypoxanthine and uric acid) were significantly higher during and after exercise in IHE when compared to CONT (p<0.05 for all), reflecting enhanced ATP turnnover. IHE led to significantly higher lactate compared with CONT (7.3±0.4 vs 2.0±1.2 mmol/l, p<0.001). Free fatty acids did not significantly differ. CHO oxidation was comparable during both interventions, however fat oxidation tended to be higher in IHE (2.8±0.2 vs 2.3±0.2 mg kg−1 min−1, p=0.13). Exercise-induced increase in acetylcarnitine (C2) was observed during both IHE and CON, however between interventions, levels were significantly higher during IHE during and after exercise (p=0.0004 and p=0.03). Medium chain (C6-C12) acylcarnitines increased during CONT (p<0.001), but not IHE. Long chain (C14-C18) acylcarnitines were comparable throughout the intervention period. Plasma insulin levels during IHE and CONT were 150.7±11.5 pmol/l and 148.5±15.1 pmol/l respectively (p=0.50).

Conclusion
Non-targeted and targeted metabolomics profiling suggest that eight 10-s sprints over 90 min compared to iso-energetic continuous exercise, increases ATP-turnover and beta oxidation flux in T1D. In spite of supraphysiological insulin levels, metabolic flexibility in T1D may still occur in certain exercise conditions. This highlights that IHE may be of potential benefit for exercise management T1D.

07

Nutritional Support Practices in Hematopoietic Stem Cell Transplantation Centers: A nationwide Comparison

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Background/Introduction
In 2009, international nutritional societies in Europe and the United States published practice guidelines on screening and nutritional support of patients undergoing stem cell transplantation. Little is known about how these guidelines are implemented in routine clinical practice. We performed a nationwide survey involving all transplantation centres with the aim of better understanding current practice patterns, differences between clinical practice and international recommendations as well as possible barriers to the use of nutritional therapy. Hopefully, the knowledge gained from this survey will contribute to the development of national practice guidelines in Switzerland.

Methods
We performed a qualitative survey including all clinical centres across Switzerland that offer allogeneic (n=3) or autologous (n=7) stem cell transplantation. We focused on in-house protocols pertaining to malnutrition screening, indications to initiate nutritional support, types of nutritional therapy available and provided, and recommendations regarding neutropenic diets.

Results
All centres offering allogeneic transplantation, and most of the centres offering autologous transplantation, had a malnutrition screening-tool in place, mainly the Nutritional Risk Screening (NRS 2002) tool. All centres provided nutritional support for patients. There is wide variation regarding start and stop of nutritional therapy as well as route of delivery, with 5 centres recommending parenteral nutrition (PN) and 5 centres recommending enteral nutrition (EN) as a first step. Although all centres offering allogeneic transplantation and about every other autologous transplant centre used a neutropenic diet, the specific recommendations regarding the type of food and food handling showed significant variation.

Conclusion
This Swiss nationwide practice survey found wide variation in the use of nutritional therapy in patients undergoing stem cell transplantation, with low adherence overall to current practice guidelines. Understanding and reducing barriers to guideline implementation in clinical practice may improve clinical outcomes. Close collaboration of centres will facilitate future research needed to improve current practice and ensure high quality of treatment. Furthermore, homogeneity of recommendations will improve patient's confidence and, enhance the credibility of caregiver recommendations

08

Nutritional parameters and clinical outcomes in patients with acute myeloid leukemia undergoing hematopoietic stem cell transplantation

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Background/Introduction
In acute myeloid leukemia (AML) patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT), there is uncertainty about the relation of nutritional parameters and clinical outcomes. Herein, we investigated associations of initial body mass index (BMI) and weight loss during HSCT on clinical outcomes in a well-characterised cohort of AML patients.

Methods
We analysed data of the Basel stem-cell transplantation registry ("KMT Kohorte") including all patients with AML undergoing first allogeneic HSCT from 01/2003 to 01/2014. We used multivariable regression models adjusted for prognostic indicators (i.e., European Group for Blood and Marrow Transplantation (EBMT) risk score and cytogenetics).

Results
Mortality in the 156 AML patients (46% female, mean age 46 years) over the 10-years of follow-up was 57%. Compared to patients with a baseline BMI (kg/m2) of 20-25, a low BMI<20 was associated with higher long-term mortality (70% vs 49%, adjusted hazard ratio (HR) 1.97 (95%CI 1.04 to 3.71), p=0.036). A more pronounced weight loss during HSCT (>7% vs. <2%) was associated with higher risk for bacterial infections (52% vs 28%, odds ratio (OR) 2.8 (95%CI 0.96 to 8.18), p=0.059) and fungal infections (48% vs 23%, OR 3.37 (95%CI 1.11 to 10.19), p=0.032), and longer hospital stays (64 vs 38 days, adjusted mean difference 25.6 days (15.7 to 35.5), p<0.001).

Conclusion
In patients with AML, low initial BMI and a more pronounced weight loss during HSCT are strong prognostic indicators associated with lower survival and worse disease outcomes. Intervention research is needed to investigate whether enforced nutritional therapy / efforts (□) can reverse these associations.

09

The Circadian Rhythm of Copeptin

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Background/Introduction
Copeptin - a 39-amino acid glycopeptide comprising the C-terminal part of the AVP (Arginin Vasopressin) precursor (CT-proAVP) - was found to be a stable and sensitive marker for AVP release, the key hormone in water homeostasis. Copeptin shows identical changes during disordered water states as shown for AVP. Several studies have investigated copeptin as a prognostic marker of different acute diseases and as a diagnostic marker in disorders of water and salt homeostasis. However, to date no data of the normal circadian rhythm of copeptin in healthy subjects are available.

Methods
19 healthy volunteers aged 18 to 50 years, male and female, were studied in a prospective observational study. The mean age was 25.8 years, mean weight 70.7kg, mean BMI 22.7 kg/m2. Physical examination and medical history were normal, 4 women took regularly birth control pills. In all 19 participants blood samples for copeptin were taken in regular intervals of 30 minutes for 24 hours after a fasting period of minimum 8 hours. Every 3 hours blood samples were taken for sodium and osmolality. Cortisol was measured at morning after awekening and at midnight.

Results
The mean and median values of copeptin showed a detectable, but mild circadian rhythm, similar as described for AVP release, with a trend towards higher levels at night and early morning (7.5 ± 0.9 pmol/l) and lowest levels in the afternoon (2.3 ± 0.2 pmol/l). This finding was primarily observed in individuals with initial higher copeptin levels, whereas in individuals with lower basal copeptin levels no circadian rhythm was observed meaning that individuals with higher baseline copeptin levels showed significantly higher AUC (24h) values (R= 0.88, p<0.001).

In contrast, there was no significant correlation of copeptin values with sodium (R=0.04, p=0.62) and osmolality (R=-0.05, p= 0.55) during the 24 hours testing.

Conclusion
There is evidence for a circadian rhythm in copeptin release during 24 hours, however, of minor extent. These findings suggest that copeptin levels can be determined irrespectively of the time of the day.

10

FGF21 is a marker of pneumonia severity and outcome

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Background/Introduction
Fibroblast growth factor 21 (FGF21) is a hormone secreted by the liver in response to metabolic challenges such as starvation and exercise. It improves insulin sensitivity and has been shown to activate brown adipose tissue recruitment. Recently, it has been shown to be significantly elevated during severe sepsis and septic shock. No data are available about FGF21 levels in in more specific infections like pneumonia.

Methods
We measured FGF21 levels in serum samples of 151 patients with community-acquired pneumonia. FGF21 was measured by ELISA (R&D Technologies) and compared to pneumonia severity index (PSI), clinical variable at admission and outcome after a median of 6.9 ± 1.9 weeks. Levels of FGF21, procalcitonin (PCT) and C-reactive protein were log-transformed to achieve a normal distribution prior to linear regression analysis. Analysis of transformed variables was corroborated by rank tests of the untransformed data. Results are given as median, unless otherwise stated.

Results
FGF21 levels at admission were correlated with PSI, R^2=0.2248, p<0.0001. Further, they discriminated well between PSI classes (Kruskal Wallis test p<0.0001). Procalcitonin (PCT) levels at admission were also associated with PSI scores, however the correlation was lower than that of FGF21, R^2=0.1477, p<0.0001. FGF21 also performed better than PCT as a discriminatory marker of non-severe (PSI class I-III) vs. severe (PSI class IV-V) pneumonia: FGF21 levels were 170 pg/ml (PSI class I-III) vs. 522 pg/ml (PSI class IV-V), p<0.0001, respectively. Median PCT values were 0.1960 ng/ml vs. 0.5938 ng/ml. The area under the ROC curve to discriminate the severity of pneumonia was 0.7296 (p<0.0001) for FGF21 vs. 0.6760 (p=0.0002) for PCT. Accordingly, patients who had a favourable outcome had significantly lower FGF21 level than those with an unfavourable outcome, 293 pg/ml vs. 741 pg/ml, p=0.0006.

Conclusion
FGF21 serum levels can be used as a prognostic marker of pneumonia severity comparing favorably to PCT.

11 S

Early experience with the thyroid imaging and data reporting system (TIRADS) in the workup thyroid nodules

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Background/Introduction
The thyroid imaging reporting and data system (TIRADS), which systemically assesses grey scale echographic features of thyroid nodules to assign them to 5 distinct categories has been shown to have a high sensitivity and negative predictive value for thyroid cancer.

Methods
All patients referred for the workup of thyroid nodules between May 2015 and June 2016 that underwent FNAB were prospectively investigated and clinical, echographic, cytological and if available histological data were collected. The nodules were classified with regard to their grey scale echographic pattern according to the TIRADS system: TIRADS 2,3: absence of hypoechogenicity or high risk echographic features (marked hypoechogenicity, irregular or lobulated margins, taller than wide shape, microcalcifications), 4A: hypoechogenicity with no high risk features, 4B: 1-2 high risk features, 5 >= 3 high risk features. All patients with TIRADS 3 nodules > 2 cm, TIRADS 4A nodules > 1 cm and TIRADS 4B,5 nodules > 5 mm underwent FNAB. Cytological results were reported according the Bethesda system and a diagnostic hemithyroidectomy or follow-up within 6 months was suggested for BIII and IV nodules and immediate diagnostic or total thyroidectomy was suggested for BV and 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
148 thyroid nodules were biopsied in 126 patients (96 females, 30 males; median age 55 years, range 23-82). 36% were incidentalomas, 31% manifested with clinical symptoms,11% were detected clinically and 22% during targeted thyroid imaging. 49% of the patients had a palpable nodule. 43% presented with a solitary nodule. The median size of the biopsied nodules was 21 mm (range 8-72). High risk echographic features were detected in 14% (taller than wide), 18% (lobulated or irregular margins), 9% (marked hypoechogenicity) and 9% (microcalcifications). Overall, 4% were assigned to the TIRADS 2, 29% to the TIRADS 3, 39% to the TIRADS 4A, 24% to the TIRADS 4B and 4% to the TIRADS 5 category. A final diagnosis of malignancy was made in 2% of the nodules assigned to TIRADS 3, 7% assigned to 4A, 8% assigned to 4B and 33% assigned to 5. The sensitivity and PPV of a benign echographic pattern (TIRADS 2,3) to predict a benign cytological (Bethesda II) and finally benign outcome were 45 and 69% and 35 and 98%, respectively. The prevalence of indeterminate (Bethesda III,IV) and likely malignant (Bethesda V, VI) cytological results was 14 and 0% in the TIRADS 2,3 category. The sensitivity and PPV of a high risk echographic pattern (TIRADS 4B,5) to predict a cytological and final malignant outcome were limited to 66 and 14% and 50 and 12%.

Conclusion
The presence of a benign echographic pattern (TIRADS 2,3) ist highly predictive of a benign cytological and final outcome and FNAB may be safely withheld in these nodules. FNAB is recommended to guide the further workup in all other nodules. In contrast to the literature, the presence of 1-2 high risk echographic features does not markedly increase the malignancy risk in our population.

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Lipoid CAH - A rare cause of adrenal insufficiency

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Background/Introduction
StAR (steroid acute regulatory protein) is a key enzyme for the intracellular transport of cholesterol to the mitochondrium in endocrine organs (e.g. adrenal gland, ovaries, testes) and thus essential for the synthesis of all steroid hormones. More than 30 mutations are described so far. Clinical phenotype varies strongly, but may be grouped in classic lipoid CAH (LCAH) where all steroidogenesis is disrupted and non-classic LCAH, which resembles the FGD phenotype affecting predominantly adrenal function. Classic LCAH is characterized by early and maybe life-threatening manifestation of adrenal insufficiency with fatal electrolyte shifts and 46,XY disorder of sex development in males as well as lack of pubertal development in both sexes. Non-classic LCAH manifests generally later and as an adrenal deficiency phenotype only; although life-long follow-up of gonadal function is warranted.

Methods
Case report

Results
We present the cases of a 26 year old female patient and her 28 year old brother. Both were diagnosed with primary adrenal insufficiency in early life, at birth and two years of age respectively. At the time of diagnosis, the female patient presented with hyperpigmentation, elevated ACTH (1500ng/L) and low cortisol levels (149 nmol/L). Electrolytes and vital parameters were normal. As her brother was diagnosed with primary adrenal insufficiency two years earlier, she was put on hydrocortisone and fludrocortisone replacement therapy directly. Over the years hydrocortisone and fludrocortisone doses were repeatedly adjusted due to elevated ACTH-levels and elevated blood pressure. Upon review of the case, consanguinity was found in the family. Genetic analysis for familial glucocorticoid deficiency (FGD) due to MC2R or MRAP mutations was negative. Further genetic analyses revealed a homozygous mutation in the StAR gene (c.562C>T, p.Arg188Cys) in both siblings. A heterozygous carrier state was found in both parents.

Conclusion
We describe the homozygous mutation c.562C>T in the StAR gene as a cause of adrenal insufficiency diagnosed at very young age.

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To Be or Not To Be … Male

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Background/Introduction
Pats. with Klinefelter Syndrome (KS) have elevated morbidity and mortality due to several reasons. Yet, there is no connection between KS and male-to-female sex change.

Case
A 74-year old man was sent for endocrine work-up prior to surgery due to gynecomastia. The patient had lived as a man-to-woman transgender for many years. He was told not to qualify for a transgender surgical approach when he was 55 years old. He took estradiol substitution for several years, but by age 60 after developing recurrent severe pulmonary embolism he stopped substitution. After that he lived "asexual" and bilateral, non-painful gynecomastia developed. Gonadal examination revealed small testes, bilateral Gynecomastia (Tanner IV) and signs of chronic venous insufficiency. The biochemical analyses showed hypergonadotropic hypogonadism with otherwise normal values. The molecular analyses revealed a 47XXY Karyotype. Osteodensitometry showed low peak bone mass. We started topical testosterone replacement and calcium/vitamin D3 substitution.

Discussion
KS affects about 1 in 660 men, but remains often undetected with only about 25% of patients receiving the correct diagnosis. Age at diagnosis is around 35. The phenotype is thought to be linked to non-inactivated genes from the extra X-chromosome, but alternative mechanisms are possible. The excess morbidity and mortality may be explained by endocrine dysfunction and diseases of the cardiovascular and of respiratory systems. Only few studies have examined the association of KS and transsexuality. One study found an association of gender dysphoria with KS. Yet, no significant increase in KS was reported in previous studies looking at men–to-female transgender populations. Still, this hypothesis has to our knowledge not systematically been investigated to make firm conclusions.

Conclusion
Thus, in patients with male-to-female sex change, further work-up towards KS should only be envisaged if there is additional clinical suspicion – such as small testes or hypergonadotropic hypogonadism as found in our case.

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A case report of pembrolizumab-induced painless autoimmune thyroiditis

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Background/Introduction
Immunotherapy targeting checkpoint inhibitors is associated with endocrine immune-related adverse events (irAE) including hypophysitis and thyroiditis. Thyroiditis induced by pembrolizumab, a monoclonal antidody targeting programmed cell death 1 (PD 1), is a well recognized irAE, yet its clinical and imaging features remain poorly characterized. We describe here a comprehensively investigated case of pembrolizumab-induced painless autoimmune thyroiditis.

Methods
Case report of a 53-year-old woman with metastatic ovarian cancer who presented with thyrotoxicosis two weeks after starting pembrolizumab 2 mg iv qw3.

Results
Routine thyroid test monitoring performed 18 days after starting pembrolizumab showed overt hyperthyroidism with both FT4 and FT3 levels twice the upper limit of normal. The titer of thyroid peroxidase antibodies (AbTPO) were weakly positive before pembrolizumab was started and increased concurrently with hyperthyroidism. TSH receptor antibodies were negative. A neck ultrasound showed 2 nodules without increased vascularity or suspicious features. A F-18-FDG-PET/CT scan performed 9 days after hyperthyroidism diagnosis, as part of the oncologic follow-up, showed a diffuse high thyroid uptake. A Tc-99m thyroid scan showed diffusely low uptake, consistent with destructive thyroiditis. Pembrolizumab was continued.The thyrotoxicosis resolved spontaneously after approximately 2 months, and was followed by hypothyroidism requiring levothyroxine replacement. At the latest follow-up (3 months), hypothyroidism did not resolve.

Conclusion
Hyperthyroidism induced by pembrolizumab may be secondary to autoimmune thyroiditis associated with mild and self-limiting thyrotoxicosis in most cases. Thyroid scintigraphy may be helpful for making the diagnosis especially in the setting of thyrotoxicosis with coexisting nodules. Underlying mechanisms are still unknown but pretreatment baseline positive AbTPO could be a predictive factor, thus it is reasonable to include their measurement in the pretreatment laboratory tests.

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Comparison of 1mg versus 2mg Dexamethasone Suppression Test in obese individuals

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Background/Introduction
Whether the gold-standard 1mg dexamethasone suppression test (DST) should be replaced by a 2mg DST in obese patients to reduce false-positive test results for Cushing's syndrome (CS) has not been investigated in larger cohorts. We compared the 1mg vs 2mg DST in obese patients.

Methods
Primary endpoint was the comparison of serum cortisol levels after 1mg vs 2mg DST in 54 patients with a BMI >30kg/m² and at least one additional feature of the metabolic syndrome. Secondary endpoints were comparison of salivary cortisol and ACTH levels, respectively.

Results
Median serum cortisol levels after 1mg DST and 2mg DST were not different in obese patients (28nmol/l (20; 36) vs 28nmol/l (20; 38), p=0.53). Salivary cortisol was 8.2nmol/l (4.7; 11.7) after the 1mg DST vs 6.7nmol/l (4.2; 9.5) after the 2mg test, p=0.09. ACTH levels were higher after the 1mg DST compared to the 2mg DST (10.0pg/ml (7.6; 10.7) vs 5.0pg/ml (5.0; 5.1), p<0.0001). The false positive rate after the 1mg DST was 14.8% (n=8) and was reduced to 11.1% (n=6) after the 2mg DST. All non-suppressors (n=8) had type 2 diabetes and most of them took a medication interacting with cytochrome P450 3A4 (CYP3A4).

Conclusion
In obese individuals the 2mg DST was not better than the 1mg DST with regard to serum cortisol levels. However, in some patients, particularly with poorly controlled diabetes or medication interacting with CYP3A4 and without adequate suppression after the 1mg DST, the 2mg DST may reduce the false-positive rate for CS.

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Efficacy and Safety by Baseline HbA1c with Once Weekly Dulaglutide in AWARD Programme

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Background/Introduction
Dulaglutide (DU), a once weekly GLP-1 receptor agonist, was studied in the AWARD clinical trial program in adult patients (pts) with T2D and demonstrated significant HbA1c reduction and potential for weight loss. Our aim was to evaluate the efficacy and safety of DU 1.5mg and DU 0.75mg in T2D pts by baselineHbA1c <69mmol/mol (%) or ≥69mmol/mol (8.5%).

Methods
We conducted a post-hoc analysis on AWARD-1 to 6 and 8 at 6 months.

Results
Across 7 studies, 55 to 82% of the DU-treated pts had a baseline HbA1c <69mmol/mol (8.5%) and 18 to 45% had a baseline HbA1c ≥69mmol/mol (8.5%). The ranges of HbA1c reductions with baseline HbA1c <69mmol/mol (8.5%) and ≥69mmol/mol (8.5%), respectively, were: DU 1.5mg: -7.32mmol/mol (-0.67%) to -13.66mmol/mol (-1.25%) and -13.34mmol/mol (-1.22%) to -25.91mmol/mol (-2.37%); DU 0.75mg: -5.79mmol/mol (-0.53%) to -11.70mmol/mol (-1.07%) and -14.98mmol/mol (-1.37%) to -23.94mmol/mol (-2.19%). The HbA1c reduction from the pooled analysis was greater in pts with baseline HbA1c ≥69mmol/mol (8.5%) than pts with baseline HbA1c <69mmol/mol (8.5%), respectively: DU 1.5mg: -20.33mmol/mol (-1.86%) and -11.15mmol/mol (-1.02%); DU 0.75mg: -19.13mmol/mol (-1.75%) and -9.07mmol/mol (-0.83%). DU treatments were well tolerated among baseline HbA1c subgroups.

Conclusion
Across the AWARD program, DU 1.5mg and DU 0.75mg demonstrated significant HbA1c reduction in both subgroups with an acceptable safety profile. Compared to pts with baseline HbA1c <69mmol/mol (8.5%), pts with baseline HbA1c ≥69mmol/mol (8.5%) had greater HbA1c reduction.

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18-Fluorocholine-Positron Emission Tomography/Computerized Tomography for the localization of hyperfunctioning parathyroid tissue in patients with sporadic primary hyperparathyroidism and negative/equivocal conventional imaging techniques

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Background/Introduction
The essential prerequisite for focused parathyroidectomy in patients with primary hyperparathyroidism (pHPT) is proper localization of all hyperfunctioning parathyroid tissue. Sensitivity of conventional imaging modalities (ultrasound, 99mTc-sestamibi scintigraphy/SPECT/CT [sestamibi-SSC]) is influenced by different factors (i.e. adenoma size/weight and position) and decreases in the presence of a multinodular goiter (MNG). Therefore a considerable percentage of patients with pHPT will have negative or equivocal localization studies before surgery. Recently published studies have shown equal or even superior detection rates of 18F-Fluorocholine-PET/CT (FCH-PET/CT) compared to conventional imaging. The aim of our study was to evaluate the utility of FCH-PET/CT for preoperative localization in a patients with pHPT and negative or equivocal sestamibi-SSC and/or ultrasound.

Methods
Between 2014-2016 a total of 24 patients with pPHT and negative/equivocal conventional imaging was referred for FCH-PET/CT at our institution. In the analysis, we included those (n=14) who had surgery and a histopathologic workup of the lesions. FCH-PET/CT imaging results were compared with the exploration of the intraoperative situs and the histopathologic examination.

Results
13/14 patients demonstrated no tracer uptake with sestamibi-SSC, 4 patients had an equivocal sonographic lesion, a MNG was present in 43% (6/14). In 12/14 patients hyperfunctioning parathyroid tissue was identified correctly by FCH-PET/CT (12 true-positive, 1 false-negative, 1 false-positive; per-patient sensitivity 92.3% [95%-CI 63.9-99.8]). 19 lesions were resected (12 true-positives, 3 false-negatives, 1 false-positive and 3 true-negatives; per-lesion sensitivity 80% [95%-CI 51.9-95.7]). All patients were classified as having surgical success according to a decrease of intraoperative PTH of ≥50%and normalization of postoperative serum calcium levels.

Conclusion
Despite a high prevalence of multinodular goiter, diagnostic accuracy of FCH-PET/CT in our patient group was excellent. Therefore FCH-PET/CT is a promising new imaging tool in patients with pHPT and negative/equivocal conventional imaging techniques.

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Iron metabolism in patients with Graves' disease

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Background/Introduction
Iron metabolism is influenced by thyroid hormones. Smaller studies and case reports demonstrated hyperferritinemia in hyperthyroid patients that normalized after achieving euthyroid state. Hepcidin plays a crucial role in iron homeostasis by lowering iron levels through binding and down-regulating Ferroportin 1 (FPN1). Both ferritin and hepcidin are acute phase proteins and are up-regulated in acute and chronic disease states (i.e. anemia of chronic disease) by – amongst other factors – different cytokines (e.g. IL-6, IL-1ß). To date the exact mechanisms of thyrotoxicosis-associated hyperferritinemia remain unclear, apart from inflammatory factors a direct influence of thyroid hormones must be hypothesized. No data about hepcidin in patients with hyperthyroidism exist. Therefore the aim of this study was:

a) To study ferritin- and hepcidin-levels and other parameters of iron metabolism (e.g. transferrin) in patients with hyperthyroidism and after achieving euthyroid function.
b) To investigate potential mechanisms by measuring inflammatory parameters and cytokines.

Methods
We prospectively studied patients with hyperthyroidism due to Graves' disease (GD). Persons with hepatopathy, alcohol abuse, known/treated iron deficiency, neoplasia, chronic renal insufficiency and infections were excluded. Laboratory parameters were longitudinally assessed at diagnosis of GD (T0) and after reaching euthyroid function (T1) by antithyroid therapy with carbimazole or propylthiouracil and compared between T0/T1 and in smokers/non-smokers using regression analysis.

Results
A total of 31 patients (22 female, 9 male; mean age 48 years; range 26-82) was studied, 12/31 were smokers. Baseline (T0) median fT4/fT3 and interquartile range (IQR) were 35.3 (26.7-51.9)/13.8 (9.0-23.1) pmol/l. Compared to smokers, non-smokers had significantly higher median fT4- and fT3-levels at T0 (43.8 [27.6-65.1] vs. 28.4 [21.6-39.8] pmol/l, p=0.014; 17.6 [9.0-27.6] vs. 11.4 [8.9-17.2] pmol/l, p=0.028, respectively). Compared to T0, Transferrin increased significantly at T1 (2.6 [2.4-2.8] g/l vs. 2.3 [2.1-2.5], p<0.001). Median ferritin- and hepcidin-levels decreased significantly after achieving euthyroid function (156.0 [63.0-262.0] vs. 80.0 [38.0-141.0] µg/l, p<0.001); 9.0 [6.5-17.1] vs. 5.9 [4.3-7.6] ng/ml, p<0.001 respectively). Compared to smokers, non-smokers had significantly higher ferritin-levels at T0 (232.0 [93.0-298.0] vs. 129.3 [55.0-209.3] µg/l, p=0.029) whereas no difference in hepcidin-concentrations between these two groups could be detected. A positive correlation between hepcidin and ferritin was found at T0 (r=0.5926, p=0.001) and T1 (r=0.6226, p<0.001). Levels of inflammatory markers (hsCRP, procalcitonin) and cytokines (IL-6, IL-1ß, TNF-α) remained unchanged at T0 and T1 respectively.

Conclusion
- Hyperthyroidism is characterized by dynamic changes in iron metabolism that resemble those during other acute or chronic disease states: High ferritin-/hepcidin- and low transferrin-levels.
- During thyrotoxicosis and compared to smokers, non-smokers had higher fT3-, fT4- and ferritin-values suggesting – together with the fact that inflammatory markers/cytokines remained unchanged – a fT4-/fT3-dependent mechanism of hyperferritinemia.

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A novel mutation of DAX-1 (NR0B1) in a boy with X-linked adrenal hypoplasia congenita

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Background/Introduction
DAX-1 (NR0B1) plays a key role in adrenal and reproductive development. It interacts with other nuclear receptors; however, its exact biological role remains unclear. In men most patients with X-linked adrenal hypoplasia congenita (AHC) present with acute adrenal failure.
To date DAX-1 mutations have been found in more than 100 families or patients with X-linked AHC.

Results
We report the case of a 2.5-year-old boy who presented with a history of recurrent vomiting and progressive hyperpigmentation of the skin over 6 months. Finally, acute adrenal failure with salt loosing crisis was diagnosed and treated accordingly. Family history revealed sudden death of 3 brothers of the mother during infancy. Direct sequencing of PCR fragments amplified from genomic DNA of the patient revealed the presence of a novel hemizygous nonsense mutation, c.870C>A in Exon 1, leading to the formation a premature stop codon.

Conclusion
In any child presenting with isolated vomiting acute adrenal failure has to be assessed. Furthermore, this report shows a novel DAX-1 mutation and underlines the importance of genetic confirmation of the diagnosis to counsel the family and prevent other fatal outcomes.

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Value of Octreoscan and 18F-FDG-PET for Clinical Prognosis of Patients with Neuroendocrine Neoplasms

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Background/Introduction
Despite the existence of biological markers of aggressiveness, the clinical course of gastro-entero-pancreatic (GEP) neuroendocrine neoplasms (NEN) remains difficult to predict. Discrepancies between imaging data generated with 111In-pentetreotide scintigraphy (SRS) and 18F-FDG-PET could reflect the degree of cellular de-differentiatio

Methods
NEN patients with both types of studies were identified retrospectively from the SwissNET database, which started collecting information on Swiss NEN patients since 2008. Progression free survival (PFS) and overall survival (OS) were assessed depending on functional imaging results. Correlation between histological grading (according to the WHO 2010 classification) and functional imaging status was also assessed.

Results
We identified 31 patients with both imaging studies, either on the primary tumour site (21/31) or for metastases (21/31). Median follow-up was 25 months (range: 1-94). 21 patients had a mestatic disease at diagnosis and 11 had died at follow-up. 7/31 were NET G1, 16/52 were NET G2 and 8/26 were NEC G3. Only 18F-FDG PET status almost reached statistical significance ($p = 0.054$) with histological grading. Progression free-survival was significantly poorer in the 18F-FDG positive group (n=21), with a median time of 8 months, compared to 51 months in the negative group (n=10) ($p=0.04$). SRS status was not found to be predictive of survival nor progression.

Conclusion
These data demonstrate the poorer prognostic conferred by positivity at 18F-FDG-PET imaging in this cohort of patients.

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Nutrient intake and dietary habits in adults with type 1 diabetes using image-based dietary records

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Background/Introduction
Despite the focus of nutrition in type 1 diabetes (T1D) self-management, little is known about dietary habits and macronutrient distribution in these patients.Dietary recommendations have shifted from strict meal plans towards flexible dietary choices in line with general nutritional recommendations. Image-based dietary records provide a novel tool to evaluate dietary intake and alleviate the burden associated with food diary-based data acquisition.We examined the dietary habits, macronutrient distribution and compliance with dietary guidelines in adults with T1D on sensor-augmented pump therapy.

Methods
Eleven adult participants (age 35±11 years, duration of diabetes 16±8 years , HbA1C 7.6±0.5 %, BMI 25.8 kg/m2, male:female ratio=7:4) were asked to record images of their dietary intake using a smartphone device over a 2 week period. These records were referenced against a validated nutritional software (Prodi 6.0) and assessed for macronutrient distribution (carbohydrate, fat and protein content), total daily intake of calories, fiber, pure fructose and monunsaturated and polyunsaturated fats. Contextual factors including meal type (breakfast, lunch, dinner, or snack) was recorded.

Results
Meals were consumed on average 5 times per day. Carbohydrate, protein and fat contributed on average 60 %, 20 % and 20 % respectively, to total daily energy intake. This macronutrient distribution was comparable for all meal types. Average CHO content of breakfast, lunch, dinner and snacks were 36.4 g (SD: 9.6), 38.1 g (SD: 8.1), 42.3 g (SD: 10.1), and 24.5 g (SD: 5.9). Dinner (30 %) contributed the most to daily energy intake (breakfast: 27 %, lunch: 26 % and snacks: 17 %). Daily dietary fiber intake was notably low (9.7 g) and below recommended intake level (20-30 g). The recorded daily dietary fat intake was 37 g, of which 17 g was unsaturated (monounsaturated 11.4 g ,polyunsaturated 5.8 g). Pure daily fructose consumption was negligible (4.5 g).

Conclusion
More than half of total daily calorie intake in this cohort of T1D patients was attributable to carbohydrate consumption. Total daily consumption of fiber was below dietary recommendations. Studying dietary records of T1D patients may help understand dietary habits and its potential effect on glucose outcomes. Potential under-reporting of dietary intake by some patients suggests that results need to be interpreted with caution, and more studies are needed to determine reliability of the same.

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Reasons for Different Patterns of Basal Insulin Persistence After Initiation Among People with Type 2 Diabetes Mellitus (T2DM)

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Background/Introduction
People with T2DM who initiate basal insulin therapy often interrupt or stop therapy soon after initiation. This study assessed reasons for different persistence patterns (continuers, interrupters, discontinuers) among insulin-naïve people with T2DM who initiated basal insulin therapy within the prior 3 to 24 months.

Methods
An online survey was completed by 942 respondents from the United States (N=154), France (137), Germany (131), Spain (150), United Kingdom (131), Brazil (156), and Japan (83), identified from the Harris Panel and third party panels. Continuers were defined as patients with no gaps of ≥7 days in basal insulin treatment within the first 6 months after insulin initiation. Interrupters interrupted basal insulin for ≥7 days within the first 6 months after initiation and since restarted basal insulin. Discontinuers stopped using basal insulin for ≥7 days within the first 6 months after initiation and had not restarted basal insulin by the time of the survey. Multiple responses were possible when selecting reasons for reach specific pattern (continuation, discontinuation, interruption). Responses were weighted to give equal representation of each country.

Results
Continuers were older than interrupters and discontinuers: 46, 37 and 38 years, respectively ($p<.05$). Lower proportions of continuers and discontinuers were men: 62% and 58% vs interrupters:78%; $p<.05$. Reasons for continuing basal insulin were improved glycaemic control:71%; improved physical feeling:48%; belief that insulin is best for reducing risk of complications:45%; instruction by physician/healthcare provider(HCP) to continue:35%; improved emotional wellbeing:33%; and convenience of insulin relative to other diabetes treatments:30%. Major reasons for interruption were weight gain:44%; hypoglycaemia:33%; pain from injections:28%; fear of potential side effects of insulin:25%; assessing whether diabetes could be managed without insulin:23%; inconvenience of using insulin:21% and instruction by physician/HCP to stop:20%. Major reasons for discontinuation were weight gain:38%; hypoglycaemia:31%; pain from injections:27%; sense that diabetes could be managed without insulin:27% and instruction by physician/HCP to stop:26%. Benefits of basal insulin motivated continuers. Experienced or potential side effects were major factors for interruption/discontinuation. HCP instruction was often a reason for continuing/stopping/restarting therapy.

Conclusion
Persistence on basal insulin is often influenced by HCP actions, and understanding patient experiences that affect persistence may help clinicians increase persistence to therapy in T2DM.

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Clinical and radiological features of rare adrenal tumors.

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Background/Introduction
Adrenal tumors are found in 4-8% of abdominal scans. The common differential diagnosis includes (non)-functioning adenomas, pheochromocytomas, myelolipomas, metastases and primary adrenal carcinomas. Specific contrast enhanced CT and MR imaging characteristics have been found useful to distinguish benign from malignant lesions and a thorough biochemical workup is necessary to exclude hormone-secreting tumors. Rare, usually non-functioning lesions may present with nonspecific imaging findings and a correct diagnosis may be difficult to obtain preoperatively. We analysed the clinical, biochemical and radiological characteristics of adrenal neoplasms not belonging to these common categories in order to increase the awareness of these rare tumors and facilitate a correct preoperative diagnosis.

Methods
Case Study

Results
Between 2000 and 2016, 121 patients underwent adrenalectomy for unilateral hormone secreting or suspected malignant adrenal masses at our institution. The final diagnosis included non-functioning adenomas (29%), pheochromocytomas (26%), cortisol- and aldosterone producing adenomas (20%), metastases (11%), adrenocortical carcinomas (7%), myelolipomas (2%) and rare etiologies (5%). The latter comprised 2 leiomyosarcomas and 1 angiosarcoma, ganglioneuroma, neurofibroma and ecchinococcus cyst. The clinical, biochemical and radiological features of the rare lesions are described.

Conclusion
Rare lesions, including ganglioneuromas, neurofibromas and ecchinococcus cysts, may mimic malignant adrenal pathologies. Some typical radiological features can help to distinguish these benign entities from adrenal malignancies and may guide the surgical approach.

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Backdoor Androgen Producing Enzymes Are Expressed in Some Pediatric Adrenal Cortex Tumors

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Background/Introduction
Children suffering from adrenocortical tumors (ACT) often present with clinical signs of virilization and precocious puberty, while signs of Cushings may be mild or even overlooked. This is due to high tumoral androgen production, of which dihydrotestosterone (DHT) is the most potent natural androgen. Recent work revealed two pathways for DHT biosynthesis, namely the classic and the alternative, backdoor pathway. In this alternative pathway, DHT is produced from 17-hydroxyprogesterone without the intermediacy of testosterone, using enzymes that are largely specific to the backdoor path.
Ongoing work of our group revealed evidence that the backdoor pathway may contribute to the hyperandrogenic phenotype in PCOS women. Moreover it has been shown that the virilization in 21-hydroxylase deficiency is related to DHT production via the backdoor pathway. However, whether the backdoor pathway plays a role in the virilization observed in pediatric ACT remains to be established and was subject of this study.

Methods
Seven children (aged 8 month to 17 years, 6 females and 1 male) suffering from androgen producing tumors were investigated. Clinical and biochemical characteristics (including broad urinary steroid profiling in two) were assessed. All tumors were characterized in depth by (immune)histochemical and genetic methods including immunostaining for protein expression of backdoor pathway enzymes.

Results
We describe two adrenal adenomas, four carcinoma and one ovarian steroid-cell tumor. All tumors produced large amounts of androgens. Immunohistochemical studies comparing the seven cases showed a very diverse pattern of protein expression of steroid enzymes involved in androgen synthesis of the classic and backdoor pathway. In comparison to normal, specifically localized and defined adrenal enzyme expression, tumors expressed single backdoor pathway enzymes either at high or low levels. Every tumor presented with a unique profile.

Conclusion
Excess DHT production via the backdoor pathway may cause severe virilization in some cases of pediatric ACT, but ACT may also produce big amounts of androgens rather through the classic pathway or both. We found no general pattern in this pilot study looking at 7 ACTs; also no difference between adenomas and carcinomas. Overall, this suggests that enhanced androgen production in pediatric ACTs is the result of deregulated steroidogenesis at multiple possible levels of the system. Every single ACT patient is therefore unique, and this makes pediatric ACT treatment very difficult.

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Endocrine Cause of Lower Limb Paresis

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Background/Introduction
Primary adrenal insufficiency (Addison's disease) leads to a defect in adrenal secretion of both glucocorticoids and mineralocorticoids. Clinical signs and symptoms are highly variable making diagnosis difficult. We report upon a patient with primary adrenal insufficiency presenting with paresis as initial symptom of disease.

Methods
Case report, tertiary referral hospital

Results
A 49 year old male patient presented to the emergency department of our hospital. He complained of lower back pain and moderate weakness of his proximal lower limbs. Imaging studies of the lumbar spine (X-ray/MRI) did not reveal suspicious lesions. In a routine laboratory testing extreme hyperkalemia of 8.7 mmol/l was detected. ECG showed typical disturbance of repolarization. The patient was admitted to the intensive care unit for cardiac monitoring and lowering of potassium levels.

As kidney function was only moderately impaired an endocrine workup was ordered. Serum sodium was low at 130 mmol/l, and the patient suffered from metabolic acidosis. Plasma aldosterone level was low at 97 pmol/l despite marked simultaneous hyperkalemia. The basal serum cortisol was also low at 65 nmol/l and rose to a maximum of 128 nmol/l one hour after injection of 1-24-ACTH (SynACTHen®), establishing the diagnosis of primary adrenal insufficiency. This was later corroborated, by a markedly elevated level of endogenous ACTH. The patient's symptoms completely subsided after substitution of hydrocortisone and normalization of serum potassium levels. Imaging of the adrenals and laboratory testing excluded hemorrhage or tuberculosis as cause of the adrenal failure. A diagnosis of autoimmune adrenal insufficiency was made.

Conclusion
Extreme hyperkalemia and consecutive disorders of neuromuscular transmission can be the presenting sign and symptom of adrenal insufficiency.

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Fibroblast Growth Factor-21 in clinical islet transplantation

Author/Address of institution
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Background/Introduction
Fibroblast Growth Factor-21 (FGF-21) is a metabolic regulator that increases islet insulin content and glucose-induced insulin secretion in diabetic animals. The aim of this study was to determine the correlation between donor FGF-21 levels and islet isolation and transplantation outcomes.

Methods
We have measured serum FGF-21 levels in 189 pancreas donor sera immediately before organ procurement. We had follow-up data in recipients of 67 islet transplantation procedures at 1, 6, and 12 months. We arbitrarily divided donors in two groups according to FGF-21 levels, with the median value as cut-off (FGF-21≥1500 pg/ml: N=33; FGF-21<1500 pg/ml: N=34).

Results
Donor FGF-21 levels were independent of age, gender, body mass index, cause of death or duration of ICU stay. At the end of the isolation procedure, higher donor FGF-21 level was associated with higher islet equivalent number (IEQ) in the mantled islet layers (i.e. endocrine/exocrine ratio of 10 to 50%) median 64'889 vs. 26'542 IEQ, p=0.003. Pancreas weight before and after digestion, islet size, total IEQ before and after purification were independent from FGF-21 levels. Recipients of islets from donor with FGF-21 ≥1500 pg/ml vs. <1500 pg/ml had insulin-independent rate of 21.9% vs. 20.6 at 1 month), 40.0% vs. 21.4% at 6 months, and 28.0% vs. 19.2% at 12 months (p value not significant for all time points).

Conclusion
FGF-21 levels correlated with higher IEQ in the mantled islet layers. Donors with the highest FGF-21 levels showed a trend toward higher insulin-independence rates at 6 and 12 months post transplantation. In conclusion, high FGF-21 levels may correlate with strong endocrine/exocrine cohesion and high islet functional reserve.

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The Tryptophan/Serotonin Pathway is associated with severity and predicts outcomes in pneumonia: results of a longterm cohort study

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Background/Introduction
Tryptophan (TRY) is an essential amino acid. There are two metabolic pathways in the breakdown of TRY. About 95% of TRY is metabolized via the Kynurenine (KYN) pathway. The rate-limiting enzymes are tryptophan 2,3-dioxygenase (TRYD) localized in hepatic tissue and indoleamin 2,3-dioxygenase (IDO) in extrahepatic tissue. IDO is inducible by interferon-γ and thus the rate-limiting enzyme during infections. The 5-HT pathway is catalyzed by the tryptophan hydroxylase (TRYH), whereat less than 5 % of TRY is metabolized by this pathway.
During infection, an increase in enzyme activity of IDO has been reported leading to a shift in pathway from tryptophan-serotonin to tryptophan-kynurenine. These adaptations in serotonin metabolism are thought to play a role in the immune-defense but data regarding outcome are lacking. We therefore investigated associations of tryptophan/serotonin pathway and adverse clinical outcomes in a cohort of patients with community-aquired pneumonia (CAP).

Methods
A total of 268 CAP patients from a previous Swiss multicenter trial were prospectively followed for a median of 6.1 years. Tryptophan, serotonin and kynurenine plasma levels were measured by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). We used linear and cox regression models to investigate associations between baseline metabolites levels and all-cause mortality.

Results
A total of 10.4% of patients had an adverse clinical outcome within 30 days and 45% died within 6 years of follow up. After adjusting for confounders, IDO levels were strongly associated with short term adverse outcome (adjusted OR 9.1 (95%CI 1.4 to 59.5), p=0.021). At long-term, Kynurenine and IDO were associated with mortality (HR 1.9 (95%CI 1.0 to 3.5), p=0.040), which after multivariate adjustment no longer remained significant.

Conclusion
In patients hospitalized for CAP, a breakdown from TRY to KYN by induction of IDO activity was found and IDO activity was an independent predictor for severity and adverse outcome. In contrast, no increase of the serotonin pathway of TRY could be observed.

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Evaluation of Adrenal Crisis and Preventive Measures in Patients with Primary and Secondary Adrenal insufficiency in Switzerland

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Background/Introduction
Adrenal insufficiency (AI) may be a dangerous clinical condition leading to significant morbidity or mortality in situations with inadequate glucocorticoid replacement therapy. Preventive education is critical in order to prevent adrenal crisis (AC). The frequency of AC, and the quality of preventive measures in order to avoid AC are ill defined in Switzerland. We, therefore, prospectively assessed all patients with primary (pAI) and secondary AI (sAI). Main outcome measures included the number of adrenal crisis experienced since the diagnosis of AI (excluding the AC that lead to the diagnosis), potential risk factors leading to AC and the therapeutic modalities of AC, as well as the presence of an emergency card, daily oral medication with spare pills and emergency kit (hydrocortisone and syringes for i.m. injection of cortisone).

Methods
All adult patients with pAI and sAI who attended the Division of Endocrinology, Diabetology and Metabolism at the Inselspital in Bern between May and June 2016 were included in a questionnaire-based interview. People with iatrogenic AI and adrenogenital syndrome were excluded from the study.

Results
Forty-three patients were assessed. Forty complete datasets were available for interim-analysis. Seven had pAI and 30 sAI. The age was 49.7±17.0 (years, mean ±SD), the duration of AI was 9.0±8.4, (years; range 0.08 - 37.2). Nine Patients (23%) experienced an AC. There were 18 AC in a total of 358.7 years of disease resulting in 5.0 AC per 100 disease years, less than in Germany (6.3/100 years of disease). Three patients with AC had pAI, 6 had sAI. Six patients experienced 1 AC, one patient with 3, one with 4 and one with 5 AC. Medical confirmation of AC was available in 13 AC. Fifteen of 18 crisis lead to hospitalisation, 3 were treated by the GP. Relatives or friends did not treat AC. People with pAI were not significantly at higher risk for an AC compared with sAI. Reasons for AC were: 27.8% no reason remembered by patient, 16.7% gastroenteritis and 11.1% malcompliance, misapprehension or influenza and 5.6% physical effort, radiation therapy, common cold or unknown infection. 93% of the patients kept an emergency card, 82.5% carried it with them. The oral medication was available in 62.5 at the consultation, 57.5% of the patients carried spare pills and 17.5% had an emergency kit available as described above.

Conclusion
1) The incidence of AC in educated patients is still high, but less frequent than recent data from Germany.

2) In most of the cases AC results in a short hospitalisation.

3) Although a substantial number of patients with AI carried their emergency card with them, oral emergency medication was not immediately available in nearly half of the patients

4) There is a need to improve the education of patients with AI in Switzerland.

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Subjective and Objective Knowledge of Patients with Primary and Secondary Adrenal Insufficiency

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Background/Introduction
Adrenal insufficiency (AI) is a dangerous clinical condition leading to significant morbidity or mortality in situations with inadequate glucocorticoid replacement treatment. Preventive education is critical in order to prevent adrenal crisis (AC). Recent studies indicate that the knowledge of patients with primary and secondary adrenal insufficiency (AI) is insufficient. We, therefore, prospectively assessed all patients with primary (pAI) and secondary AI (sAI). Main outcome measures were self-experienced level of knowledge (subjective assessment of knowledge) and questions concerning modalities of cortisone replacement therapy and dose adjustments in different clinical situations (objective assessment of knowledge).

Methods
All adult patients with pAI and sAI who attended the Division of Endocrinology, Diabetology and Metabolism at the Inselspital in Bern between May and June 2016 were included in a questionnaire-based interview. People with iatrogenic AI and adrenogenital syndrome were excluded from the study. Subjective assessment of knowledge incuded a grading scale with a self-estimation about education/information status. Objective assessment included adapted questions from Harsch et al (Part A: modalities of cortisone replacement therapy) and Fleming et al; Repping Wurts et al. (Part B: cortisone dose adjustement in different clincial situations). Part A comprised 8 correct answers with a total of 21 points and in part B a total of 7 correct answers were possible.

Results
Forty-three patients were assessed and 40 datasets were available for interim-analysis. Seven patients had pAI and 30 sAI. The age was 49.7±17.0 (years, mean ±SD), the duration of AI was 9.0±8.37 (years, mean ±SD, range 0.08 - 37.2). There was no significant difference with regard to subjective or objective knowledge between patients who experienced an AC compared to patients without AC. Subjective knowledge: 17.5% considered themselves as being very well informed, 72.5% as well informed and only 9.5% as badly informed or very badly informed. Objective knowledge: The total correct answers of part A were 2.9±1.4 (mean ±SD, range 1-6) and the total points were 12.3 ±3.8 (mean ±SD, range 3-20). The total correct answers in part B were 3.8±2.1 (mean ±SD,range 0-7). Correct answers of part A and B together were 6.7±3.3 (mean ±SD, range 1-13.0). Nobody answered all questions correctly. In part A there was a significant improved knowledge in patients with pAI compared to patients with sAI. Females scored significantly better in part B. Higher education level resulted in a significantly better score. In the analysis of 4 different quartiles of age and of disease duration, lower disease duration and lower age were significantly associated with better scores in part A and B together.

Conclusion
1) There is a clear mismatch between subjective knowledge and objective assessment of knowledge in patients with pAI and sAI. Thus, objective evaluation of knowledge should be performed.

2) Based on these preliminary data, a particular care for instruction (ore re-instruction) should be given to patients with sAI, male patients, older patients, patients with a longer duration of disease and less-well educated patients.

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Improving chronic disease management for patients with type 2 diabetes in primary care

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Background/Introduction
The aim of this project was to improve the care for diabetes type 2 (T2DM) patients in a primary care team of 4 physicians through the implementation of the criteria for 'good disease management diabetes' which were developed by the Diabetes Disease Management Working Group of the SGED. The aforementioned eight NCQA/ADA Diabetes Recognition Program based criteria were adjusted for the Swiss clinical setting and are measured with a scoring system (max score = 100). Main aspects of diabetes care such as number of diabetes-related consultations; lifestyle recommendations; examination of eyes, kidney function and feet and also diagnostic criteria (HbA1c; blood pressure; lipids) each receive an individual weighting
which adds into total score. Both, the evaluation criteria, as well as the required performance to reach the cutoff values for each measured parameter are used as targets for the care of a patient population and not for single patients.

Methods
Patients were selected via the search criteria 'any patient with at least a single HbA1c measurement > 6.4% since 2011 in our group practice in the Achilles©/Axonlab software and identified patients were manually confirmed by cross-checking the patient records. The patient baseline was established in 2013 with intervention period follow-up in 2014 and 2015. Inclusion criteria: Diagnosis of T2DM and start of intervention in the first quarter of the analysed calendar year. Patients were excluded if they had received care in our medical office for less than 9 months of the observed calendar year (e.g. change to external physician; death). Data were analysed with an Excel spreadsheet developed by QualiCCare and a score was calculated for the total cohort and for the subcohorts of each physician.

Results
65 patients were included at baseline and for the two intervention years 2014 and 2015 78 and 88 patients were included respectively. 62% of the patients were males with an average BMI of 31.9kg/m2 and an average age of 62 years. A significant improvement was achieved in all individual criteria except from the criterion 'BMI <25kg/m2 or appropriate lifestyle advice'. The total baseline score for the practice team was 30 (range 30-43) in 2013 and increased to 48 (range 10-63) in 2015. In 2013, the target scores for the criterion 'number of control visits' and the two 'LDL' criteria were met. In addition to this also the target values for the three criteria HbA1c <7.5; HbA1c <8.0 and nephropathy screening were reached in 2015. From 2013 to 2015 the average HbA1c was reduced by -0.27 HbA1c % points and BMI was decreased by -0.8kg/m2.

Conclusion
It was possible to improve 7 out of 8 diabetes care scoring criteria with a small intervention in our primary care practice. The biggest gaps to the target values remained in the areas lifestyle intervention; blood pressure control and foot examination. It may be assumed that the positive impact on the reduction of HbA1c and BMI could have resulted from the implementation of the scoring criteria into our daily routine in itself. In future, it would be desirable to develop a practice software application which could calculate the scores automatically.

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Benefit of adjunct corticosteroids for community-acquired pneumonia in diabetic patients

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Background/Introduction
We have recently shown that adjunct prednisone shortens time to clinical stability (TTCS) in patients with Community-Acquired Pneumonia (CAP). Considering the hyperglycaemic effects of prednisone, there are concerns about the efficacy and safety of this therapy for diabetic patients with CAP. The objective was to evaluate whether diabetes and/or hyperglycaemia on admission has an influence on the effect of corticosteroids on outcome in a well-defined cohort of patients with CAP.

Methods
This is a preplanned subanalysis of a prospective randomized, double-blind placebo-controlled multicentre trial. Patients aged 18 years or older with CAP were randomized to either 50 mg prednisone for 7 days or placebo. The primary endpoint was TTCS, secondary endpoints were length of stay, mortality, duration of antibiotic treatment, CAP complications and new insulin requirement at day 30. Furthermore, we analysed whether these endpoints are influenced by a glycaemic dysregulation during study time.

Results
Twenty per cent of 727 patients treated per protocol had diabetes mellitus (n=66 in the prednisone, n=72 in the placebo group). Adjunct prednisone shortened TTCS in diabetic patients (HR 1.65 (95%CI 1.16, 2.35), p=0.007) with no evidence for effect modification by diabetes in interaction analysis (p=0.44). No difference was found in other clinically relevant endpoints. Although adjunct prednisone was associated with glycaemic dysregulation, this did not translate into worse clinical outcomes in both groups with no difference in secondary endpoints.

Conclusion
The benefit of adjunct prednisone in CAP patients is also valid for patients with diabetes or admission hyperglycaemia. Hyperglycaemia in diabetic patients or due to adjunct prednisone did not have a negative effect on outcome.

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Improved Glycaemic Control and Weight Loss with Once Weekly Dulaglutide versus Placebo, Both Added to Titrated Daily Insulin Glargine, in Type 2 Diabetes Patients (AWARD-9)

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Background/Introduction
This double-blind, 28-week study compared once weekly GLP-1 receptor agonist dulaglutide (DU) 1.5mg and placebo when added to titrated once daily insulin glargine (±metformin), in type 2 diabetes patients with inadequate glycaemic control (HbA1c ≥53mmol/mol [≥7.0%] and ≤91mmol/mol [≤10.5%]).

Methods
Patients (N=300; mean baseline characteristics: age 60.4 years; HbA1c 68mmol/mol (8.4%); BMI 32.7kg/m2; glargine dose 39U [0.42U/kg]) were randomised (1:1) to DU 1.5mg, or placebo; glargine was titrated to fasting plasma glucose target (3.9–5.5mmol/L); primary objective was HbA1c change from baseline at week 28 tested for superiority.

Results
At week 28, DU 1.5mg resulted in significantly greater reductions vs placebo in HbA1c; least squares (LS) mean change from baseline [SE]: -15mmol/mol [1](-1.4% [0.09]) vs -8mmol/mol [1](-0.7% [0.09]), respectively;P<0.001, and FSG (LS mean change from baseline [SE]: -2.5mmol/L [0.23] vs -1.6mmol/L [0.23] respectively;P<0.001). Body weight decreased with DU 1.5mg and increased with placebo (LS mean change from baseline [SE]: -1.9kg [0.30] vs +0.5kg [0.30];P<0.001). Hypoglycaemia rate (plasma glucose ≤3.9mmol/L and/or symptoms) was 7.69 and 8.56 events/patient/year for DU 1.5mg and placebo, respectively(P=0.488); severe hypoglycaemia events were(n): DU 1.5mg(1), placebo(0). A statistically greater increase in glargine dose was observed with placebo vs DU 1.5mg (LS mean change from baseline [SE]: 25.9U [2.3] vs 12.8U [2.3];P<0.001). Nausea and diarrhoea were more common with DU 1.5mg (12.0%, 11.3%) vs placebo (1.3%, 4.0%).

Conclusion
Once weekly DU 1.5mg compared to placebo, both add-on to titrated daily glargine, resulted in better glycaemic control and weight loss without significantly increasing the risk of hypoglycaemia.

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Rapid onset of ketoacidosis following treatment with a sodium-glucose-transporter 2 inhibitor in a patient with diabetes secondary to previously unrecognized acromegaly

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Background/Introduction
Diabetic ketoacidosis has been described as a rare complication of acromegaly and may be observed in 1% of affected patients. The well described direct lipolytic effects of growth hormone, resulting in increased availability of free fatty acids (FFA) for hepatic ketogenesis, is an important pathogenetic event. More recently, ketoacidosis has been identified as an important complication of sodium-glucose-transport-protein 2 (SGLT2) inhibitors. Increased pancreatic glucagon secretion, impaired renal ketone body clearance and an increase in FFA concentrations secondary to decreased insulin requirements are likely precipitating factors. We report a case of rapid onset severe ketoacidosis within two days after starting empagliflozin in a presumably type 2 diabetic patient with unrecognized acromegaly.

Methods
Case Report

Results
A 52-year-old man with a diagnosis of type 2 DM established five years earlier presented to the emergency room with increasing dyspnea since several hours. Two days before, empagliflozin had been added to the preexisting regimen of metformin, sitagliptin and gliclazid because of insufficient glucose control (HbA1c 9.6%) during a routine follow-up with the general practitioner. This was followed by an immediate and distinct loss of appetite accompanied by thirst, polyuria and dyspnea.

Upon arrival in the ER a diagnosis of diabetic ketoacidosis (blood glucose 26 mmol/l, pH 6.96, anion gap 24.7 mmol/l, urine ketones +++, normal lactate) was made. A gradual metabolic improvement was observed during the subsequent treatment with i.v. fluids, potassium and insulin in the ICU, although high doses of insulin (130 U per day) were needed even after the acid-base status had been controlled.

Guided by the remarkable appearance with several acromegaloid features the patient reported the need for bigger shoe sizes and impossibility of wearing the wedding ring since five years on direct questioning. Moreover, he noticed a muffled speech and periodic bifrontal headache since several months. The diagnosis of acromegaly was confirmed by increased serum concentrations of IGF-1 (111.10 nmol/l; range 6.89 – 30.68 nmol/l) and growth hormone (18.6 ug/l; range < 3.0 ug/l) with no evidence for a deficiency of the remaining pituitary axes. A sellar MRI scan revealed a 12 mm intrasellar pituitary macroadenoma. Glucose control was achieved with multiple daily insulin injections. Endoscopic transsphenoidal surgery was performed 4 weeks later and the patients diabetes was controlled with dietary measures upon discharge

Conclusion
SGLT2 inhibitors, through their intrinsic effects on ketone body metabolism, may precipitate ketoacidosis in patients with active acromegaly. We suggest that their use is contraindicated in patients with diabetes secondary to uncontrolled growth hormone excess.

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Effects of the SGLT2-inhibitor Empagliflozin on healthy volunteers with artificial SIADH – a placebo-controlled double blind crossover study

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Background/Introduction
The Syndrome of inappropriate antidiuresis (SIADH) is the predominant cause of hyponatremia and its therapy options are unsatisfying. SGLT2-inhibitors have become a valuable treatment option for type 2 diabetes by increasing glucose excretion in the urine with concomitant osmotic diuresis.
We therefore hypothesized that SGLT2-inhibitors could be a novel treatment option in patients with SIADH.

Methods
We developed an artificial SIADH model by administration of desmopressin i.v. and excessive hydration. After the initial oral volume load and administration of desmopressin, the study drug Empagliflozin 25mg or Placebo respectively was given in random order. The main outcomes were the area under the curve (AUC) of the serum sodium concentration, diuresis, urinary glucose and sodium excretion. The outcome measures were obtained 2-8 hours after administration of the study drug.

Results
14 healthy volunteers (64% males), BMI 23.1kg/m2 (±2.4), age 28.6 years (±9) were included. Baseline serum sodium level was 140mmol/l (±1.4). Serum sodium concentration was similar under Empagliflozin compared to Placebo (Difference of AUC 0.2, CI -7.38;6.98, p=0.96). Empagliflozin led to a significantly increased diuresis (579.3ml ±194.8 vs 367.3ml ±158.8; p=0.001) and glucosuria (74.18mmol ±22.3 vs 0.12mmol ±0.04; p<0.0001). Natriuresis was slightly higher under treatment with Empagliflozin (83.3mmol ±42 vs 64.4mmol ±41.1; p=0.078).

Conclusion
In healthy volunteers with induced SIADH, Empagliflozin had no effect on serum sodium concentration but increased urinary glucose excretion and diuresis. Possibly, the lack of effect on sodium levels despite an increased diuresis might be explained by the short observation period.

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Incidence and major characteristics of gestational diabetes mellitus with the new IADPSG criteria: updated data of the Cantonal hospital of Fribourg

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Background/Introduction
The International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria replace the Carpenter and Coustan (C&C) criteria in a Cantonal Hospital in Switzerland since 2011. These new criteria propose a one-step screening test with a lower glucose concentration threshold and abandon the category of gestational glucose intolerance (GGI). The aim of this study is to assess the incidence of gestational diabetes mellitus (GDM) and birth major complications in the population of the Cantonal Hospital of Fribourg. Results are compared with the data of a previous study done in the same hospital and using the C&C criteria.

Methods
We conducted a retrospective study of all pregnant women screened for GDM between the January 1st 2014 and December 31st 2015. Clinical data of the GDM women and their offspring were collected and analyzed from the screening test until the postpartum OGTT control test. We compared these data to women without GDM and their offspring as controls. At least the results are compared with a previous study concerning pregnant women screened in 2004-05.

Results
Of 502 pregnant women included, 159 women (31.7%) were diagnosed for GDM; 132 (83%), 18 (11.3%) and 9 (5.7%) women were diagnosed at fasting, at 1-hour and 2-hour after glucose challenge respectively. There was an increase of GDM incidence comparing with C&C criteria (4.8% of GDM and 2.6% of GGI). Mean age for GDM women was 30 years old and 29 years old for non GDM women (p= 0.04). Our population of GDM women was significantly younger comparing to the previously study (p=0.0223). Mean BMI before pregnancy was higher for GDM women compared to non GDM women (25.6 vs 23.7 kg/m2, p=0.0002). Fifty-nine GDM women (37%) needed insulin-treatment. The proportion of women treated for GDM decreased in the current study (37% in current study vs 70% in previous study, p=0.0233). Proportion of caesarean section was not significantly different with 33.6% of GDM women vs 28% for non GDM women (p=0.226). Proportions of preeclampsia, premature delivery, symptomatic newborn's hypoglycemia and obstetrical trauma were not significantly different in the two groups. The rate of persistent impaired glucose tolerance was not significantly different between the current and the previous study (16% of GDM women in current study vs 18% in previous study, p=0.85).

Conclusion
Our results show a significant increase in GDM incidence more than four times in a same population with the new IADPSG criteria. The proportion of insulin-treated women decreases by almost half most likely because the new criteria include women with a less severe GDM. The proportion of birth complications is unchanged.

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Analysis inpatient blood glucose monitoring – how does it help the clinician?

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Background/Introduction
Optimal blood glucose control in hospitalized patients is challenging. Inpatient glycemic excursions and variability may be related due to underlying illness, heterogeneous patient population and limited infrastructure and support. The aim of this analysis was to assess inpatient glucose control at a university hospital and identify areas which may benefit from further input to improve quality of delivered care for inpatient glucose management.

Methods
Blood glucose values from hospitalized patients within the year 2014 which were assessed using either central laboratory or point of care methods were included in the analysis. Inpatient status was defined by a minimum of two blood glucose measurements on two subsequent days. Diabetes in hospital was defined as random venous glucose ≥11mmol/l or HbA1C≥6.5%. Mean glucose and glucose variability as well as distribution within the following glycaemic ranges were assessed. Coefficient of variation (CV) per patient was calculated to assess glucose variability. In wards with >5'000 measurements, the ratio between high and low glucose variability patients was calculated. All analyses were performed in the R programming language (R Core Team, 2016).

Results
Over a period of 12 months, 234'444 samples (72% point of care samples, 28% central laboratory samples) were obtained from inpatients across various specialty wards (both critical and non-critical care). Mean age was 64±16 years (52% male, 48% female) and 73.7% of the collected samples came from patients fulfilling the diagnosis of diabetes in hospital. Those with diabetes in hospital were older (66±14 vs 60±19 years) and had higher mean glucose (9.2±3.7 vs 6.6±1.5 mmol/l). 74.2% of overall inpatient glucose measurements were within the acceptable range (4-10mmol/l). 24.2% and 3.2% were in the hyperglycaemic (>10mmol/l) and severe hyperglycemic range (>16.7 mmol/l) respectively. Hypoglycaemia (<4mmol/l) was observed in 1.6%, and severe hypoglycaemia (<2.2mmol/l) in 0.1%. Notable differences were seen in glucose variability across the wards. Five wards with >5'000 measurements had high to low within patient variability ratios >10, i.e. more than 10 times as many patients with glucose CV>20% compared to those with low glucose variability (CV<20%).

Conclusion
Analysis of inpatient blood glucose monitoring may identify high variability of glucose levels across different hospital wards. This in turn may support inpatient diabetes team to focus on subpopulations of inpatients who could benefit from optimisation of inpatient glucose control. Limitations include mixture of critical and non-critical care patients in this analysis. Separate analysis of these two cohorts will be needed to ascertain quality of care within each inpatient setting.

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The role of KIAA2022 in the pancreas and its contribution to monogenic diabetes

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Background/Introduction
Whole exome sequencing of a patient with mental retardation and autoimmune antibody-negative diabetes identified a truncating mutation (R218X) in the KIAA2022 gene. The KIAA2022 gene encodes a large protein of 1516 amino acids, which has no functional motifs or significant homology with other known proteins. Initially, KIAA2022 was linked to X-linked mental retardation. It is shown that KIAA2022 mRNA is expressed in mouse brain, particularly during the late embryonic and perinatal stages of development. The expression generally drops in the adult brain. In this study we determine the role of KIAA2022 in the pancreas and its contribution to monogenic diabetes.

Methods
The ethics committee of the Geneva University Hospital approved the study. Whole exome capture sequencing was performed using the Illumina HiSeq instrument. The healthy parents and the affected child (trio) were sequenced. Saenger sequencing confirmed the identified variant. KIAA2022 mRNA and protein expression analysis was done by qRT-PCR and immunohistochemistry at different stages in murine and human islets and pancreas with a commercially available antibody (Atlas). We used the INS-1E cell line for in vitro studies. In vivo knock down studies were performed in the zebrafish by injecting 8 ng KIAA2022 specific morpholino antisense nucleotides. This approach caused a reduction of 80%, which we assessed by qRT-PCR.

Results
We confirmed mRNA and protein expression of KIAA2022 in murine and human islets and pancreas by qRT-PCR and immunohistochemistry. The expression in the human islets was higher than in the exocrine tissue. KIAA2022 partially co-stained with insulin in pancreatic sections. In vitro experiments using INS-1E cells showed that KIAA2022 is highly expressed in the midbody during cytokinesis.

The in vivo knock down studies in zebrafish lead to a decrease of the beta cell mass by 40% compared to wild type. The beta cell expansion rate was assed by culturing zebrafish embryos with and without glucose, which revealed that KIAA2022 kock down lead to a 30% decrease of the expansion rate in comparison to the control group.

Conclusion
Our data indicate that KIAA2022 is expressed in pancreatic islets. In vitro experiments using INS-1E cells suggest that KIAA2022 may play a role in cell division. In vivo KIAA2022 knock down experiments lead to a decrease of the beta cell mass and glucose-induced expansion rate, which may underlie the diabetic phenotype.

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Bovine colostrum: a panacea?

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Background/Introduction
Inherited and acquired lipodystrophies are metabolic disorders characterized by a varying degree of body fat loss and secondary metabolic abnormalities such as insulin resistance diabetes mellitus, hypertriglyceridemia and hepatic steatosis. Consumption of bovine colostrum has been reported to reduce blood glucose and triglyceride levels in type 2 diabetic patients.

Results
A 31 year old woman with congenital partial lipodystrophy and diabetes mellitus presented to our outpatient clinic for a routine control. Diabetes mellitus was diagnosed 12 years ago, and is treated with insulin glargine, insulin lispro, metformin and pioglitazone. Self-monitoring blood glucose measurements demonstrated capillary glucose levels mostly within the target range and HbA1c was 6.1%. Clinical examination showed a normal weight (53 kg, BMI 22.3 kg/m2) cardially compensated, normotensive patient with the typical pattern of adipose tissue distribution.

Later on the same day, we received a query from our central lab regarding the lipid profile of the patient. An acute hypertriglyceridemia (fasting triglyceride 19.4 mmol/l) was reported and a possible drug interference that did not allow the assessment of the cholesterol levels. On previous ex-aminations, the patient always had normal triglyceride values. Factors contributing to increased insulin resistance or hypertriglyceridemia (i.e. medicaments, ethanol consumption, significant weight gain) were absent. Further inquiry revealed a self-initiated consumption of bovine colostrum in the previous weeks. After discontinuation of the colostrum consumption the triglyceride values returned to normal.

Conclusion
Bovine colostrum is a popular health product for the enhancement of the immune system and for body empowerment. Its health promoting effects have also been linked to a reduction in blood glucose, cholesterol and triglyceride levels in type 2 diabetics. An analysis of its fat components showed high levels of cholesterol as well as high-carbon-number triglycerides. Patients with inherited or acquired lipodystrophies have defective adipocyte differentiation and regulation. The congenital/inherited forms in particular are linked to gene mutations that interfere with the adipocyte maturation (PPRAG/FPLD3, AKT2/FPLD4) or the adipocyte apoptosis (LMNA/FPLD2). Distorted adipocyte function and lipid storage may lead to further increase in blood lipid levels after consumption of fat-rich products, which also explains the laboratory findings in this case.

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The degree of TSH suppression of autonomously functioning thyroid nodules is correlated with their stiffness at real-time elastography.

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Background/Introduction
Real time elastography (RTE) has increased the sensitivity of ultrasound (US) and improved the selection of thyroid nodules at risk of malignancy. However, sparse data on RTE assessment of autonomously functioning thyroid nodules (AFTN) exist. Here, we investigated the potential role of RTE in AFTN. Specifically, the correlation between serum thyroid hormones and RTE score, as well as other clinical and ultrasound features, was analyzed.

Methods
Patients with AFTN identified during the period from 2015 September to 2016 June were enrolled and underwent 123I-TS, US, RTE and serum evaluation. The association between suppressed TSH and patient's age, nodule's size, US presentation and RTE scoring was analyzed by Odds Ratio (OR) in univariate and multivariate fashion.

Results
A number of 33 subjects with single (n=31) or multiple (n=2) AFTN were enrolled. Median age of 63 yrs, median size of 2 cm, and suppressed TSH levels in 24% of cases were found. Those nodules classified at high risk underwent FNAC and cancer was excluded. At RTE evaluation, a 46% of AFTN had a hard/anelastic appearance, 23% was soft and 31% had intermediate elasticity. Hard-anelastic (i.e. RTE III) AFTN had TSH significantly lower than the other RTE groups. At univariate analysis only hardness at RTE and larger size were significantly associated with TSH <0.10 mIU/L and RTE III had the highest OR. The multivariate analysis demonstrated that RTE III was an independent risk factor for suppressed TSH.

Conclusion
AFTN may have variable elasticity at RTE examination, being hard score associated with lower/suppressed TSH. As mentioned in ATA guidelines, the stiffness should not change the nodule risk stratification at conventional US. For clinical practice, the presence of AFTN should be considered in patients with hard lesions within a goiter to avoid a unhelpful and potentially confusing biopsy.

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Interleukin-1 antagonism decreases cortisol levels in obese individuals

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Background/Introduction
Increased cortisol levels in obesity may contribute to the associated metabolic syndrome. In obesity, the activated innate immune system leads to increased interleukin (IL)-1β, which is known to stimulate the release of adrenocorticotropin hormone (ACTH). We therefore hypothesised that in obesity IL-1 antagonism would result in downregulation of the hypothalamo-pituitary-adrenal (HPA) axis, leading to decreased cortisol levels.

Methods
In this prospective intervention study we included 73 patients with obesity (BMI >30kg/m2) and at least one additional feature of the metabolic syndrome. The primary endpoint was change in morning cortisol from baseline to after the administration of the IL-1 receptor antagonist (anakinra/Kineret®, total dose 3x100mg). Secondary endpoints were effects on salivary cortisol and ACTH.

Results
Median morning serum cortisol levels (nmol/l) decreased significantly after IL-1-antagonism (from baseline 452 to 423, absolute difference -38.7, 95%CI -64 to-13.4, p=0.0019). Similar effects were found for salivary cortisol levels (-2.8, 95%CI -4.4 to -1.3, p=0.0007), ACTH levels (-2.2, 95%CI -4.2 to -0.1, p=0.038), systolic blood pressure (-5.2, 95%CI -8.5 to-1.8, p=0.0006) and heart rate (-2.9, 95%CI -4.7 to-1.0, p=0.0029).

Conclusion
IL-1 antagonism in obese individuals with features of the metabolic syndrome leads to a decrease in serum cortisol, salivary cortisol and ACTH-levels along with a reduction in systolic blood pressure and heart rate. IL-1 antagonism could thus be a novel treatment option to improve cortisol levels and associated comorbidities in obesity.

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Unilateral adrenalectomy guided by adrenal venous sampling in primary bilateral macronodular adrenal hyperplasia

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Background/Introduction
Bilateral macronodular adrenal hyperplasia (BMAH) is a rare cause of endogenous cushing's syndrome (CS; <2%). It typically presents with modest cortisol secretion in the 5th and 6th decade with a female preponderance. Mutations in ARMC5 have been described in up to 50% of familial and spontaneous cases and it may be associated with several genetic syndromes. Adrenocortical cortisol secretion may be secondary to the presence of aberrant G-protein coupled receptors and autocrine ACTH-secretion. Specific pharmacological treatments eventually succeed to control cortisol secretion if aberrant receptors are present and bilateral adrenalectomy is the standard approach for the remaining cases. In patients with mild hypercortisolism, unilateral adrenalectomy may result in long-term control of hypercortisolism while avoiding the sequelae of adrenal failure.

Results
A 47-year old perimenopausal woman was referred for suspected CS because a 13 kg weight-gain in 6 months, newly diagnosed hypertension leading to hypertensive crisis and generalized edema. On examination, she presented hypertensive (176/100mmHg) with visceral obesity and supraclavicular fat pads. A diagnosis of ACTH-independent CS was established after serum cortisol failed to suppress after overnight dexamethasone (1 mg, 352 nmol/l), urinary free cortisol was slightly elevated (157 µg/24h, normal <136 µg/24h) and ACTH was undetectable (<5.0 ng/l).The subsequent MRI showed bilateral nodular adrenals with the largest nodule measuring 21 x 41 mm on the right side, indicating a diagnosis of BMAH.
To test for aberrant adrenal hormone receptor mediated cortisol production we measured serum cortisol during a posture test (angiotensin II, vasopressin, catecholamines, ANP etc.), a mixed meal test (gastrointestinal hormones: GIP, GLP etc.) and following i.v. glucagon, TRH, vasopressin and metoclopramide with no evidence for a medically treatable condition. Finally, gonadotropin suppression following long-acting goserelin-acetate failed to correct the hypercortisolism.
Because of the biochemically relatively mild hypercortisolism (24h-FUC < 2fold ULN) a decision to proceed with unilateral adrenalectomy was made. To establish whether there was a preferential unilateral cortisol secretion it was measured during bilateral adrenal venous sampling and corrected with adrenal venous plasma metanephrines to account for a potentially lateralized venous drainage. With this approach, a preferentially right-sided (2:1) cortisol secretion was demonstrated and guided a laparoscopic right adrenalectomy.
Following surgery, the patients well-being improved impressively and she was able to resume her previous work while she lost 5 kg. The previously severe hypertension is well controlled despite the reduction of antihypertensives. 24h-FUC returned to the normal range while serum cortisol still failed to adequately suppress after overnight dexamethasone. A close clinical and biochemical follow-up has been scheduled.

Conclusion
Unilateral adrenalectomy is a successful approach in patients with BMAH with mild hypercortisolism if extensive testing for aberrant G-protein receptors fails to identify a medically treatable cause. Adrenal-venous sampling may guide to predominant unilateral cortisol secretion and thereby improve the long-term success of an initially unilateral surgical approach.

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Islet beta cell deletion of the IL-1Receptor Antagonist impairs insulin secretion

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Background/Introduction
Activation of the IL-1 system is implicated in low grade inflammation and beta cell dysfunction during obesity and Type 2 Diabetes (T2D). The IL-1 system is particular in its inclusion of the endogenous receptor antagonist IL-1Ra, which is elevated systemically in obesity and T2D, but decreased in islets from tissue sections of T2D patients, pointing to an imbalance of IL-1beta and IL-1Ra within islets. We aim to understand the functional role of islet local IL-1Ra and to chronically increase IL-1 action within islets in vivo.

Methods
We produced beta cell and myeloid cells specific IL-1Ra knockout mice and evaluated glucose metabolism and insulin secretion of normal and high fat diet (HFD) fed littermate mice by GTTs. Markers for beta cell identity, inflammation and cell proliferation were assesed from ex vivo isolated and from cultured islets by qPCR. Islet area and proliferation was determined by immunohistochemistry. The function of isolated islets was evaluated by glucose stimulated insulin secretion assays. IL-1Ra was measured by ELISA.

Results
Beta cell specific but not myeloid cells specific IL-1Ra knockout reduced islet IL-1Ra expression and resulted in impaired islet function in isolated islets. Glucose stimulated insulin secretion was reduced in normal and obese beta cell specific IL-1Ra ko mice at all ages. Glucose tolerance of beta cell specific IL-1Ra ko mice was impaired after 4 weeks of HFD while myeloid cells specific ko mice remain normal. Both, beta cell and myeloid cells specific obese IL-1Ra ko mice had similar circulating IL-1Ra concentrations compared to their wildtype controls. Beta cell specific IL-1Ra knockout mice displayed a reduced islet area and an increased proportion of small islets. There was no reduction in beta cell identity genes and no increase in caspase 3, inflammation and iNOS gene expression. However, there was a reduction of proliferation associated genes KI67, cyclinA, cyclinD and E2F1 along with reduced insulin and KI67 double positive cells.

Conclusion
These findings provide evidence for the functional importance of beta cell specific IL-1Ra expression and suggest that in vivo the chronic increase of the ratio of IL-1beta to IL-1Ra directly reduces insulin secretion. Downregulation of proliferation genes in islets may underly the altered islet morphology and beta cell dysfunction. Further, in obesity myeloid cell derived IL-1Ra does not appear to regulate glucose homeostasis and is not the source of elevated circulating IL-Ra.

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Functional and molecular adaptation of intestinal L-cells in mice under high fat diet is associated to the preservation of alpha and beta-cell function and to normoglycemia.

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Background/Introduction
Type 2 diabetes is characterized by insulin resistance as well as alterations of insulin (beta-cell), glucagon (alpha-cell) and GLP-1 (intestinal L-cell) secretions. The aim of the study is to identify molecular and functional alterations of proglucagon cells and their roles in diabetes.

Methods
Transgenic mice (expressing the fluorescent protein Venus in proglugacon-expressing cells) were submitted to a 16 weeks control Low Fat Diet (LFD) or to a High Fat Diet (HFD). 3 groups were defined at the end of the study according to glycated hemoglobine : LFD (3,90±0,05%) ; HFD mice with impaired glucose tolerance (I-HFD) (4,00±0,04%) and HFD hyperglycemic mice (H-HFD) (4,9±0,10%). The molecular and functional aspects are studied in vivo and ex vivo on alpha and L-cells purified by FACS.

Results
I-HFD and H-HFD mice have the same weight gain, hyperinsulinemia, and insulin resistance. However, insulin secretion stimulation after an oral glucose load is maintained in I-HFD but strongly altered in H-HFD. I-HFD mice are principally characterized by intestinal L-cells molecular and functional adaptations. In response to glucose gavage, GLP-1 secretion is strongly increased (Fold=6.97+/-1.54 for LFD vs 44.86+/-7.93 for I-HFD) while the regulation of glucagon is preserved. Glucagon and PC1/3 genes are increased in L-cells as well as GLP-1 content. By contrast H-HFD mice exhibit dysfunctional alpha-cells, with an abolished response to glucose. Beta and L-cells numbers are increased without improvement of their function. Administration of the GLP-1R antagonist Exendin9-39 to I-HFD mice before a glucose gavage induces alterations of glucagon secretion without changes of insulin and reduces glucose tolerance (AUC=275.06+/-61,47 for I-HFD vs 699.38+/-112.03 mmol/l X min for I-HFD treated Ex9-39) leading to an increase of glycated hemoglobin when chronically administered (3.73+/-0.08 for I-HFD vs 3.95+/-0.06 % for I-HFD treated Ex9-39).

Conclusion
These results highlight the crosstalk between endocrine L-cells and pancreatic islets and show that a compensatory adaptation of L-cells is implicated in the preservation of glucose homeostasis through the control of pancreatic alpha cell function.

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Overweight and obesity in the canton of Vaud: past prevalence and projected incidence

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Background/Introduction
Over the last decades, obesity has become a major public health problem. Its worldwide prevalence has more than doubled since 1980. The World Health Organization reported in 2014 that 600 million adults were obese and 41 million children under the age of 5 were overweight or obese. These global figures need to be tackled at the local level, since understanding regional problem is needed to face our future challenges. To address this question, we aimed to project the likely prevalence of overweight and obesity in Vaud canton in the next 25 years.

Methods
Data from the Enquête suisse sur la santé, a survey conducted every five years since 1992 by the Swiss Federal Office of Public Health, have been used. Data are collected via telephone interviews or self administrated questionnaires from 21'500 subjects over the age of 15 living in private households. It questioned 1748 people in the canton of Vaud . Self-reported height and weight are used to calculate BMI. Using the assumptions of the arithmetic linear change model, the rate of increase in the prevalence of obesity between 1992 and 2012 was calculated. A projection of the future prevalence of obesity was made.

Results
In 2012, the prevalence of overweight (BMI > 25 kg/m2) in the Vaud canton was 36.5%. Prevalence of obesity (BMI > 30 kg/m2) was 9.64%, representing 60'000 persons. Obesity affected 1.39% of the population under 40 and 8.26% of the population aged 40 and over, among which 2.9% are 65 and over. By 2040, assuming a constant prevalence rate, there will be an increase in the number of obesity cases of 26% which corresponds to 79'500 persons. Using the arithmetic linear change observed in Switzerland between 1992 and 2012, the projection is an increase of 100% translating into 136'100 obese subjects in 2040. Effective growth rate of obesity from 2016 to 2040 should be between 16'500 cases (minimum) and 69'500 cases (maximum) depending on the uncertainty about the effective prevalence increase over this period.

Conclusion
Projection of overweight and obesity trends are important for the planning of future health policies.Obesity is a worldwide major issue nowadays but it is also a regional challenge that we have to face. The prevalence of obesity in Switzerland is low compared with other countries like the US. Nevertheless, obesity prevalence is constantly increasing in our region and projections are not reassuring. It is essential to limit this trend and prevention should be intensified.

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Exosome-mediated transfer of microRNAs from immune cells to β-cells contributes to type 1 diabetes development

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Background/Introduction
During type 1 diabetes development, lymphocytes infiltrating the pancreatic islets cause β-cell dysfunction and death. Beside cytokines, lymphocytes release small vesicles called exosomes containing microRNAs that can be transferred in active form to recipient cells. Since during insulitis β-cells and T cells are brought in close proximity and microRNAs are important regulators of β-cell functions, we hypothesized that an exosome-mediated transfer of microRNAs from T lymphocytes to β-cells may contribute to the death of the insulin-secreting cells in the initial phases of type 1 diabetes.

Methods
To test this novel concept, exosomes were isolated from the culture media of Jurkat T cells or T effector cells of NOD mice, a well known model of type 1 diabetes. After analysis of their microRNA content, the exosomes were used to study the transfer of microRNAs from T cells to β-cells and to investigate their functional impact. Blockade of miR-142-3p and miR-142-5p in vivo was achieved by injecting an Adeno Associated Virus expressing, under the control of the insulin promoter, a transcript containing multiple binding sites for these microRNAs.

Results
We observed that two T-cell specific microRNAs, miR-142-3p and miR-142-5p, are highly upregulated in pancreatic islets of NOD mice during pre-diabetic insulitis. The increase of these microRNAs was not caused by the presence of pro-inflammatory cytokines released by lymphocytes, but resulted from an exosome-mediated transfer. Indeed, exposure of islet cells to T cell exosomes led to a rise in the level of miR-142-3p and miR-142-5p and caused apoptosis of β-cells but not of α-cells. This effect could be prevented by inhibiting the action of these microRNAs and was reproduced by direct overexpression of miR-142-3p or miR-142-5p in β-cells. To verify the relevance of this phenomenon in type 1 diabetes development, pre-diabetic NOD mice were injected with a viral construct capable of blocking specifically the microRNAs of interest in β-cells. Inactivation of miR-142-3p and miR-142-5p in β-cells led to a significant decrease in the incidence of type 1 diabetes in NOD.

Conclusion
Taken together, our results suggest that a subset of microRNAs carried by exosomes released by T cells is transferred in active form to β-cells triggering their apoptosis. Our results support the concept that the transfer of microRNAs constitutes a novel cell-to-cell communication mechanism contributing to β-cell failure in type 1 diabetes.

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Estrogens modulate glucose homeostasis by increasing glucagon-like peptide-1 secretion from L and alpha cells.

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Background/Introduction
Estrogens and their associated signaling pathways have known for several years a growing interest, and in particular regarding to their role in metabolism. In fact, clinical and experimental data highlight their beneficial impact on energy and glucose homeostasis. Indeed, their administration has been shown to reduce the risk of type 2 diabetes in several animal models but also in humans. This beneficial action is partly linked to protective effects on the endocrine pancreas. The aim of our study is to investigate the impact of estrogen on proglucagon producing cells, the alpha and L cells.

Methods
In order to characterize the direct impact of estrogens on proglucagon producing cells, we will use the transgenic "Gcg-Venus /Rip- Cherry" mouse model, characterized by the specific expression of Venus fluorescent proteins in proglucagon producing cells and Cherry in the insulin producing cells, allowing the isolation of pure cells after sorting by flow cytometry. To free ourselves from the estrogenic impregnation, "Venus / Cherry" adult female mice are ovariectomized (ovx), or sham operated. Next to identified direct effects of estrogens on proglucagon producing cells, alpha and L cells, from one week ovx mice are isolated and purified by FACS and treated or not during 48h with 17β-estradiol (E2, 10-8M). Then to confirm this effects in vivo "Venus / Cherry" adult female ovx mice, received an administration of 17β-estradiol (E2, 80µg/kg) for 48h.

Results
As expected, one week estrogenic deprivation has an effect in vivo on glucose homeostasis after 6 h of fasting. Indeed, the mice exhibit an altered response to glucose during an OGTT (2g/kg), with a significant increase in the glycemia's AUC. This effect is correlated to a decrease in insulin levels and an increase in glucagon. Furthermore, ovx mice presented a lower GLP-1 secretion in response to glucose than sham mice. Then to determine if E2 has a direct impact on proglucagon producing cells, we isolated pure α cells, or realised mixed intestinal cells cultures from the small intestine and treated them in vitro with E2 10-8M for 48h. The purified α cells showed no differences in term of proglucagon expression (mRNA), but we can see that estradiol influences de prohormone convertase expressions. This is correlated with a decrease in glucagon biosynthesis, and an increase in GLP-1 (in protein). Concordantly, we also observe an increase capacity of α cells to secrete GLP-1, and a decrease in glucagon's secretion. Furthermore, E2 treatment in small intestine explants, increased their GLP-1 secretary capacity. Next in vivo administration of E2 increases insulin and decreases glucagon pancreatic contents. Futhermore GLP-1 purified L cells content from E2 treated mice increases.

Conclusion
Our results demonstrate that the favorable action of estrogen on the carbohydrate homeostasis is partly due to its direct effects on proglucagon cells, by increasing GLP-1 biosynthesis and secretion. These results open the way to a better understanding of the mechanisms underlying the protective effects of estrogen for the prevention and treatment of diabetes.

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Vitamin D-dependent rickets type 1 caused by novel mutations in CYP27B1 affecting protein interactions with adrenodoxin.

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Background/Introduction
The mitochondrial CYP27B1 enzyme converts 25-hydroxyvitamin D3 to active 1,25-dihydroxyvitamin D3, playing a vital role in calcium homeostasis and bone growth. Similar to other cytochrome P450s in mitochondrion, CYP27B1 relies on adrenodoxin (FDX1) and adrenodoxin reductase (FDXR) for the supply of redox equivalents for its catalytic activity. Vitamin D-dependent rickets type 1 (VDDR-1) is a rare autosomal recessive disorder caused by mutations in CYP27B1. Here we are reporting two siblings presented with calcipenic rickets but normal 1,25-dihydroxyvitamin D3 levels.

Methods
The genetic analysis of CYP27B1 showed compound heterozygous mutations confirming VDDR-1. We studied wild type CYP27B1 and mutations H441Y and R459L by computational homology modeling, molecular dynamics simulations and functional studies using a luciferase-based two-hybrid assay.

Results
We created models of CYP27B1-FDX1 complex which revealed negative effects of mutations H441Y and R459L. Upon structural analysis, near-identical folds, protein contact areas, and orientations of heme/iron-sulfur cluster suggested that both mutations may destabilize the CYP27B1-FDX1 complex by negating directional interactions with FDX1. This system is highly sensitive to small local changes modulating the binding/dissociation of FDX1, and electron-transporting efficiency might change with mutations at the surface. Functional assays confirmed this hypothesis and showed severe loss of activity of CYP27B1 by both mutations. The patients were successfully treated with calcitriol.

Conclusion
This is the first report of mutations in CYP27B1 causing VDDR-1 by affecting protein-protein interactions with FDX1 that result in reduced CYP27B1 activities. Detailed characterization of mutations in CYP27B1 is required for understanding the novel molecular mechanisms causing VDDR-1.

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Beta cell-specific PC1/3 deletion promotes obesity and glucose intolerance in mice

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Background/Introduction
The peptide hormones insulin and amylin lower blood glucose and promote satiety, respectively. They are processed in pancreatic beta cells by prohormone convertases (PCs). PC1/3 loss of function mutations in humans have been associated with impaired glucose homeostasis and global PC1/3 knockout in genetic mouse models leads to severe birth defects due to disruption of various (growth) hormones, making it difficult to elucidate the role of specific hormones in the development and progression of this hormone-processing related metabolic disorder.

Methods
We generated a beta cell-specific, (tamoxifen) inducible PC1/3 knockout mouse (KO) and examined its body weight, food intake and glucose metabolism upon normal chow or high fat diet (HFD) feeding.

Results
KO mice were phenotypically indistinguishable from their non-transgenic littermates (WT) before tamoxifen-induced PC1/3 knockout. Upon tamoxifen administration, KO mice almost completely lost PC1/3 expression in their beta cells, showed a progressive increase in fasting plasma glucose and a prominent increase in food intake and body weight compared to their WT littermates. Four weeks after knockout-induction, glucose tolerance in vivo was severely impaired and inflammatory markers increased in islets isolated from KO mice. Proinsulin was increased 300-fold in KO vs WT plasma following glucose stimulation. While HFD feeding increased body weight and impaired gluocose tolerance in WT mice, KO mice fed a HFD did not display a worsened phenotype compared to KO mice fed a normal chow diet. Whether the phenotype can be rescued by insulin therapy is currently under investigation. We are also exploring the role of the satiety hormone amylin, as a lack of fully-processed amylin could explain the observed increase in food intake and subsequent body weight gain.

Conclusion
Lack of beta-cell expression of PC1/3 leads to increased body weight gain, glucose intolerance and islet inflammation, presumably due to lack of mature insulin and amylin.

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Anti-diabetic and anti-obesity activity of Caralluma adscendens var. gracilis and Caralluma pauciflora: in vitro experimental studies

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Background/Introduction
The plants fractions of Caralluma adscendens var. gracilis and Caralluma pauciflora were evaluated for their total phenolic content in relation to their antioxidant activity and inhibitory effect of starch and lipids digestive enzymes.

Methods
Total phenolic content, in vitro DPPH, α-glucosidase α-amylase and lipase assays were fallowed to evaluate activity.

Results
Among all fractions of C. adscendens var. gracilis and C. pauciflora, diethyl eather fractions showed highest phenolic content (36.23±1.51 mg of GAE/g DW, 28.21±3.61 mg of GAE/g DW), DPPH radical scavenging activity (27.96 ±3.45 µg/ml and 37.23±0.92 µg/ml). The inhibition of starch digestive enzymes α-glucosidase (59.13±1.31 µg/ml and 73.03±2.04 µg/ml), α-amylase (65.35±2.05 µg/ml and 89.42±2.41 µg/ml) and lipid digestive enzyme Lipase (41.91±3.51 µg/ml and 49.12±3.89 µg/ml) Significantly high in diethyl eather fraction compare to butanone and n-butanol fractions where the activity was nonsignificant compare to standards.

Conclusion
The present study provides the first evidence that these two plants (C. adscendens var. gracilis and C. pauciflora) are potent inhibitors of key enzymes in type 2 diabetes and obesity studies in vitro.

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Regulation of pancreatic islet circadian genes by microRNAs during postnatal beta-cell maturation

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Background/Introduction
Pancreatic islets possess self-sustained molecular clocks that produce circadian rhythms responsible for the optimization of glucose metabolism and beta-cell function, and whose disruption can contribute to diabetes development. Fully functional beta-cells undergo a postnatal maturation process involving expression changes of metabolic and cell cycle genes. We recently demonstrated that microRNAs contribute to these changes, which are required to achieve a mature phenotype. However, circadian rhythmicity and its mechanisms have never been addressed in the developing pancreas. In this study, we assessed the expression of circadian genes and its regulation by selected microRNAs in islets during postnatal development.

Methods
Circadian gene expression was measured by qPCR in islets of rats at different postnatal ages up to 3 months, and by in vitro bioluminescence recording in newborn (10-day-old) and adult (3-month-old) islets. The effect of miR-17-5p and miR-29b-3p on the expression of target circadian genes was assessed in newborn rat islets transfected with microRNA antisense or mimic oligonucleotides, and luciferase reporter assays were performed in INS cells to determine a direct effect.

Results
We observed major differences in the expression profile of core circadian genes throughout postnatal islet maturation. Furthermore, rhythmic expression of most of these genes was strikingly attenuated across the 12:12 light-dark cycle, while cell-autonomous rhythmicity was delayed in newborn islets compared to the islets of adult rats. At least part of these differences could be attributed to modifications in the level of microRNAs occurring during postnatal development. Indeed, reduced miR-17-5p and increased miR-29b-3p levels in newborn rat islets, which are able to improve the secretory phenotype of beta cells, directly or indirectly regulate the expression of key circadian genes such as Clock and Npas2, targets of miR-17-5p, and Per3, a target of miR-29b-3p.

Conclusion
Our data show that the rhythmic expression of circadian genes is not fully established in newborn islets, and suggest that microRNAs can contribute to the control of circadian rhythms during postnatal beta-cell maturation. Defects in this process may have long-term consequences on circadian physiology and islet function, favoring the manifestation of metabolic diseases.

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Beta-Klotho deficiency protects against obesity: a crosstalk between bile acids and microbiota

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Background/Introduction
Fibroblast growth factor 21 (FGF21) is a recently-identified hormone acting through FGF receptor 1 (FGFR1) and its obligate co-receptor Beta-Klotho (KLB) to stimulate energy expenditure and glucose uptake. Therefore, FGF21 is a promising drug candidate to treat obesity and insulin resistance. KLB is also the obligate co-receptor for FGF15/19-FGFR4 signaling which represses hepatic bile acid (BA) synthesis. Here, we hypothesis that Klb-/- mice are prone to diet-induced obesity (DIO).

Methods
Klb-/- and WT mice were fed with a normal chow diet or a high fat diet (HFD) (60% of calories from fat) before metabolic phenotyping, which includes body composition analysis, indirect calorimetry, tissue gene expression and histology, microbiota analysis, and blood dosage (including BA, metabolites and hormones).

Results
On chow diet, Klb-/- mice exhibited moderate modification in glucose homeostasis. In contrast, on HFD these mice are resistant to diet-induced obesity (DIO) due to increased energy expenditure and BAT activity. Beyond a derepressed BA synthesis, Klb-/- mice exhibit a specific change in circulating BA composition featured by upregulation of the classic (neutral) BA synthesis pathway at the expense of the alternative (acidic) BA synthesis pathway. This led to the overrepresentation of cholic acid (CA) and its microbiota-derivative deoxycholic acid (DCA), which stimulates the BAT thermogenic program. Blocking the bacterial conversion of CA to DCA with antibiotic (pharmacological approach) or concomitant deletion of membrane BA receptor TGR5 (genetic approach) reverses the phenotype, thus identifying the DCA/TGR5 axis as the main activator of thermogenesis in Klb-/- mice.

Conclusion
Our work demonstrates that 1) endogenous FGF21 signaling is not mandatory for resistance to DIO and 2) the change in production of primary and secondary BA potently impacts energy expenditure, conferring to microbiota a new regulatory role in the control of host thermogenesis. Therapeutic approaches targeting the FGF15-19/FGFR4/KLB pathway to selectively modulate BA pool composition could be valuable to treat metabolic disorders.

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CBX2.2 mutation as novel cause for 46, XY Disorder of Sex Development

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Background/Introduction
Sexual differentiation during early embryonic development is one of the defining moments of human life. The chromatin architecture regulator CBX2.1 has been identified as an essential transactivator for human male gonadal development. However, less is known about the second isoform CBX2.2. In this work, we try to elucidate the role of CBX2.2, taking advantage of the p.C132R mutation of CBX2.2 in a 46, XY patient with complete female phenotype and dysgenetic gonads.

Methods
DNA adenine methyltransferase identification and next-generation sequencing in the Sertoli-like NT2-D1 cells has been performed. Furthermore, the sequencing data and potential targets of CBX2.2 have been studied using Pathway Studio and Gene Expression Enrichement analysis. Potential candidates have been validated using qRT-PCR under overexpression of either WT or mutated CBX2.2.

Results
Over 1900 direct targets of CBX2.2 have been identified. These have been analyzed with the help of the gene pahtway software Pathway Studio and Gene Expression Enrichment. Finally, a subset of six candidate genes has been selected based on their influence on sex development: EMX2, MAK, HOXA13, WDR77, TWIST1 and BNC2. The influence of CBX2.2 on these targets was validated with the help of qRT-PCR. WT CBX2.2 increased the expression of EMX2, MAK, HOXA13, WDR77, TWIST1 and BNC2 by 3.2, 2.0, 2.1, 1.24, 1.3 and 1.35 - fold, respectively. In the mutant CBX2.2, this effect was significantly diminished for EMX2, MAK and HOXA13 and slightly decreased for TWIST1 and WDR77. Furthermore, the mutant CBX2.2 has also been shown to decreased the expression of the androgen receptor.

Conclusion
This study shows that the mutant CBX2.2 failed to regulate the expression of genes essential for sexual development leading to 46, XY DSD, most likely because of a defective expression of EMX2 in the developing gonad. Our study indicates a distinct function of the shorter form of CBX2 and by identifying several of its partners can impact our understanding of DSD pathogenesis and ultimately DSD diagnosis and management.

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Pro-inflammatory macrophages are attenuated by immune-modulatory effects of imatinib

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Background/Introduction
As an unexpected side effect, some patients treated with tyrosine kinase inhibitor (TKI) for chronic myeloid leukemia experience improved glycemic control. Reduced beta-cell apoptosis and insulin resistance have been postulated as underlying mechanisms. As TKIs were shown to influence the activation status of tumor-associated macrophages and leukemia cells, we hypothesize that TKIs shift macrophages from a pro- to anti-inflammatory phenotype, thus mediating improved glycemic control in metabolic disease.

Methods
For in vitro studies, peritoneal macrophages (PM) or bone marrow derived macrophages (BMDM) were isolated from mice and polarized in vitro to a pro- (M1; by LPS/ IFNγ) or anti-inflammatory (M2; by IL-4/ IL-13) phenotype in the presence or absence of imatinib (1µM). To test the effects of imatinib in vivo, mice were kept for 3 months on a high fat diet. Half of the group was treated with a single dose of the beta-cell toxin streptozotocin (130mg/kg) to induce diabetes. Mice were treated with oral imatinib (100mg/kg) or water during the last 3 weeks. Macrophage polarization was assessed by gene and protein expression of pro- and anti-inflammatory markers.

Results
Gene expression of the pro-inflammatory cytokines TNF-α and IL-6 was down-regulated in M1-macrophages upon imatinib treatment when compared to untreated M1-controls in both PC and BMDM. Interestingly, these changes were not found in non-polarized or M2-activated macrophages. M2-typical makers Mrc1, Mgl2 and Chil3 were up-regulated in M1-polarized PM upon treatment with imatinib. In vivo, we observed a down-regulation of TNF-α, IL-6 and hexokinase 2 in peritoneal cells in imatinib-treated obese and diabetic mice.

Conclusion
Pro-inflammatory macrophages are attenuated by immune-modulatory effects of imatinib, which might be useful as a treatment option in patients with inflammation-mediated insulin resistance.

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Potentially modifiable predictors of adverse neonatal outcomes in pregnancies complicated by gestational diabetes

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Background/Introduction
In Switzerland, the prevalence of GDM is around 10%. Maternal treatment modality influences clinical decisions such as the timing of labor induction, neonatal glucose monitoring and early feeding. However, data are lacking and controversial. The aim of the study was to identify simple clinical predictors of (adverse) neonatal outcomes that are potentially modifiable.

Methods
This prospective cohort study included 232 singleton pregnant women that presented with gestational diabetes (GDM) in the GDM unit of a tertiary hospital clinic between 4/2012 and 3/2016 for whom we had neonatal clinical data and who gave informed consent. Investigated predictors included BMI before pregnancy, gestational weight gain, results of the oral glucose tolerance test (oGTT), treatment modality, fetal estimated weight by ultrasound (US) at 33 ± 1.6 weeks and glycated hemoglobin (HbA1c) at the end of the pregnancy. Neonatal outcome variables included BMI, macrosomia (birthweight > 4kg), hypoglycemia (glycemia <2.5 mmol/l) and hospitalisation in a neonatal unit. Data were analysed using linear or logistic regression analysis adjusting for sex and gestational age at birth.

Results
Mean age ± SD was 33.5 ± 5 years, BMI before pregnancy was 26.4 ± 5.2 kg/m2 and weight gain during pregnancy 13.1 ± 6.1 kg. 49.8% of the women were treated with insulin, 6.8% with metformin and 3.4% with both. HbA1c at the end of the pregnancy was 5.6 ± 0.4%. The mean gestational age at birth was 38.9 ± 1.8 wks and the rate of cesarian delivery 39%. Birth weight was 3261.1 ± 576.7 g and BMI 13.6± 1.6 kg/m2. 7% had macrosomia, 12% hypoglycemia and 10.1% were transferred to a neonatal unit.
Significant predictors of increased neonatal BMI were maternal BMI before pregnancy and gestational weight gain, US-estimated weight and HbA1c at the end of the pregnancy. Weight gain and US-estimated weight also predicted macrosomia (all p<0.05). Hypoglycemia was predicted by the 1h and 2h values during the oGTT and neonatal hospitalisation by the 1h values during oGTT and inversely by US-estimated weight (all p<0.05). Maternal treatment did not predict any of the neonatal outcomes (all p=NS).

Conclusion
Weight-related and metabolic parameters, but not the treatment modality, predicted adverse neonatal outcomes. HbA1c at the end of pregnancy might represent a novel and simple clinical predictor.

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The impact of the childcare environment on physical activity and BMI in preschool children (SPLASHY)

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Background/Introduction
Understanding environmental determinants in preschool years is primordial in tackling childhood obesity. The childcare (CC) environment can influence young children's physical activity (PA) behaviour and obesity. The aim of the study is to examine the impact of the CC environment on PA and BMI in preschool children.

Methods
84 CC were invited to participate in a Swiss Preschool's Health study (Splashy). CC environment was evaluated through a modified Nutrition and Physical Activity Self-- Assessment for Child Care (NAP SACC) questionnaire (1). Based on the Ecological model of health behaviour proposed by Sallis et al. (2), 5 domains were used for selection and categorisation of 33 variables in addition to age and sex: demographic/biological, psychological/cognitive/emotional, behavioural, socio--cultural, and physical environment. PA was measured using accelerometers which were worn at least 10 h/day over a week. Analyses were performed using total PA (TPA) and BMI Z--score (WHO criteria) as the main outcomes.

Results
476 preschool children (mean age 3.9±0.7 yrs;; 251 boys and 225 girls, 18% overweight, 5% obese) participated in the study. Mean TPA was 621.5±153.6 counts per minutes. Children attended CC for 2.9±1.1 days/week. Using 5 different imputed datasets and multiple regression and penalized regression analyses, we identified the following significant robust predictors for TPA: age (positive), sex (negative), number of age classes within one CC group (demographic/biological;; positive), and the less robust predictors were staff PA participation (behavioural, positive) and PA professionals intervening at CC (socio-- cultural, positive). Respective robust predictors for BMI were: age (negative), sociocultural region (positive), and being excluded by peers in CC (psychological/cognitive/emotional, positive), and less robust predictors were vegetables served at CC (behavioural, negative), a "healthy nutrition" label at CC (socio--cultural, negative), nutritional staff education (socio--cultural, positive), and CC total surface area (physical environment, positive).

Conclusion
CC environment can influence overall PA and BMI, but the respective predictors differ.

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Whole blood transcriptome changes in response to the intake of fermented and non-fermented dairy products

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Background/Introduction
Fermented dairy products have been widely promoted for their diverse health benefits. The impact of these foods on health is influenced by product composition that is modified by the external fermenting bacteria community and the unique microbiota of the host organism. To explore the early physiological changes in response to these products, we have used a multi-omic approach including gene expression evaluated in whole blood.

Methods
Fourteen healthy young men (age 24.6 ± 4.7 years, BMI 21.8 ± 1.8 kg/m²) were enrolled in a twelve-week randomised cross-over study to investigate the short-term impact of a fermented compared to a non-fermented dairy product on selected physiological parameters. Yoghurt containing the probiotic Lactobacillus rhamnosus GG and milk acidified with gluconic acid (control) were tested by acute, postprandial tests, completed over six hours (800g unique dose) and by a two-week 'chronic' test phase (400g/day). At the end of the chronic test phase fasting assessments were completed. In addition to classical clinical parameters, whole blood samples were collected for transcriptomic analysis for seven subjects using PAXgene Blood RNA Tubes. RNA was extracted with PAXgene Blood miRNA kit (Qiagen), assessed for quality with Nanodrop and Bioanalyzer platforms, before RNA sequencing was completed (Illumina HiSeq). Gene expression changes were evaluated by differential analysis (Limma) to be followed by over-representation analysis (ORA) and Gene Set Enrichment Analysis (GSEA).

Results
Differential analyses revealed significant responses in individual gene expression levels after the acute intake of either acidified milk (1 gene different, padj. <0.05 ; 164 genes different, p<0.01) and probiotic yoghurt (5 genes different, padj. <0.05 ; 242 genes different p<0.01). In addition, for those genes that were significantly altered in the postprandial phase of one condition, significant differences were detected between the two products (5 genes different, padj.<0.05; 52 genes different p<0.01). ORA and GSEA analyses are currently in progress.

Conclusion
Transcriptomic analysis of whole blood appears to be a sensitive method to observe the different responses to postprandial and short-term impact of fermented compared to non-fermented dairy product intake. The integration of these analyses with metabolomic and metagenomic data is planned to explore the physiological pathways that are regulated by the ingestion of fermented and non-fermented dairy products.

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Long term weight changes in obese patients after gastric bypass surgery; able to predict it ?

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Background/Introduction
Obesity is a major public health issue. It is a complex multifactorial disease often complicated by type 2 diabetes, hypertension or dyslipidemia. Bariatric surgery, including Roux-en-Y gastric bypass (RYBG), allows an average loss of 60-75% of the excess weight that is accompanied by a significant improvement of co-morbidities. However, there is a large inter-individual variability in the long term weight maintenance. Indeed, up to 20% of operated patients are unable to maintain their initial weight loss, raising the question of the potential existence of predictive factors of long term success.

Methods
This study was conducted on a retrospective cohort of patients operated by the same surgical team since 1999. 200 subjects were stratified according to their weight at 2 years after RYGB and compared in a case-control manner (100 pairs), where the cases were the patients who had lost the least weight after surgery, and the controls were the patients having lost the most. The 200 subjects were matched for age, sex and preoperative BMI. Pre-operative metabolic co-morbidities as well as socio-demographic data were then collected and analyzed.

Results
Pre-diabetes, hypertension (HTA) and hypertriglyceridemia were more prevalent pre-operatively in the cases than in the controls (59.3%, 58.2% and 76% respectively). When combining the parameters, the association of hypertension with prediabetes, or with hypertriglyceridemia, was found much more prevalent in the cases than the controls (66.7% and 83.3%, respectively). Further, the association of any three co-morbidities among pre-diabetes, diabetes, sleep apnea syndrome (SAS), HTA, and dyslipidemia was also more prevalent in the cases than in the controls. In contrast, there was no difference in the prevalence of SAS, dyslipidemia (all types) and hyperuricemia between the two groups. Finally, demographic factors such as being married or single, having children or not, being or not immigrated, having or not a secondary education seemed not to be predictive.

Conclusion
In this preliminary retrospective study, the presence of pre-diabetes, hypertension or hypertriglyceridemia before the intervention was associated with a worse weight outcome at two years after RYGB. However, the validity of these parameters as predictive factors of the outcome of bariatric surgery will have to be tested prospectively, before definitive conclusions can be made. If confirmed, these data could help reshape the indications and contra-indications for bariatric surgery.

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Treatment challenges for type 1 diabetes after Roux-en-Y gastric bypass

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Background/Introduction
The global epidemic of obesity does not spare patients with type 1 diabetes (T1DM) but until now no consensus exists regarding the role of bariatric surgery for the these patients. We describe here a patient illustrating the challenge of controlling T1DM after Roux-en-Y gastric bypass (RYGB). In light of our experience and according to the existing data in the literature, we propose explanations about the discrepant results reported on glycemic control in T1DM patients after bariatric surgery.

Methods
Case report: At the time of surgery, the patient was a 28 year-old woman weighing 141 kg for 167 cm (BMI 50.6 kg/m2). She had been put on metformin 6 months before the intervention because of T2DM (HbA1c 7.8%). Nine months after surgery, her HbA1c decreased to 5.7% without treatment. Eighteen months after surgery, she had lost 80% of excess weight and fasting glucose was 4.7 mmol/l. Five years after surgery she experienced further weight loss of 10 kg and was diagnosed with T1DM (anti-GAD auto-antibodies strongly positive). Insulin therapy was initiated and various continuous glucose monitoring were performed as her insulin treatment was modified (prandial insulin at meal time, after the start of the meal, before the start of the meal). Due to difficulties in getting optimal glucose control without hypoglycemia, we decided to start continuous subcutaneous insulin infusion using a sensor-augmented insulin pump with automated insulin suspension and her glycemic control improved.

Results
Discussion: Although weight outcomes after bariatric surgery are similar between patients with type 1 and type 2 diabetes, glycemic control may not necessarily improve in T1DM primarily because of the increased variability in post-prandial glucose concentration after RYGB. This results in an incongruity between glucose rate absorption and exogenous insulin kinetics. Published data on this topic are conflicting for various reasons. First, there are differences between diabetes therapies offered in case reports (timing for prandial insulin injection and use of insulin pump). Antibodies status and/or c-peptide levels are not reported in some cases reporting a very favourable HbA1c evolution, leaving some doubts about the precise diagnosis of diabetes type. In the reviews written on this topic, different bariatric operations are considered. However, sleeve gastrectomy results in a much lower post-prandial glucose peak than RYGB.

Conclusion
The marked and sustained weight loss consistently observed after bariatric surgery is not sufficient to expect improved glycemic control in T1DM. Reaching optimal glycemic control remains challenging because of the complex kinetics of post-prandial glucose absorption after RYGB. Insulin pump therapy with automated insulin suspension to avoid post-prandial hypoglycemia should be offered to such patients. A careful pre-operative evaluation for specific types of diabetes mellitus is essential.

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Posture allocation and obesity management: Is the heterogeneity in the energy cost of standing related to spontaneous weight-shifting behaviour?

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Background/Introduction
Due to the obesity and cardiometabolic risks associated with sedentary behaviour, there is interest in methods to increase low-intensity physical activity. In this context, it is a widely-held belief that altering posture allocation can modify energy expenditure (EE) to impact upon weight regulation and health. Put simply, we burn more calories when we are standing than when we are sitting. However, in reality, this is not the case, as we have recently shown the existence of two distinct phenotypes pertaining to the energy cost of standing – with the majority (~80%) of individuals having no sustained increase in EE during steady-state standing relative to sitting comfortably.

Here we investigated whether or not these two distinct phenotypes (so called "energy savers" and "energy spenders") could be related to patterns of spontaneous "weight-shifting" (WS), ie., the redistribution of body weight from one foot to the other in order to minimise discomfort or maintain postural balance.

Methods
Using indirect calorimetry to measure EE in a total of 44 young adults during sitting followed by 10 min of standing on a dual-balance system (i.e. with each foot on a separate weighing balance), we examined in subgroups:
(i) EE and spontaneous WS patterns, analysed by Fast Fourier Transformation (FFT);
(ii) EE during spontaneous WS vs experimentally-induced WS, and;
(iii) EE during spontaneous WS vs intermittent leg/body displacement.

Results
FFT analysis showed a negative relationship between EE and spontaneous WS, with individuals who showed a sustained increase in EE during steady-state standing relative to sitting ("energy spenders") exhibiting less variation and smaller amplitude in the spontaneous WS frequency domain. Whilst the experimentally-induced WS resulted in an increased EE of on average 11% (range: 0%-25%), intermittent leg/body displacement increased EE to >1.5 times resting EE (i.e., 1.5 METs) in all participants.

Conclusion
These studies revealed distinct spontaneous WS signatures, with those who expended more energy during standing ("energy spenders") showing less WS. They also underscore the fact that leg/body displacement, rather than standing alone, is needed to increase EE above the currently defined threshold for sedentary values (i.e. above 1.5 METS).

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Increased Inflammatory Intestinal Macrophage Subsets after High Fat Diet

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Background/Introduction
Intestinal macrophages (iMΦ) can be divided into different subpopulations (P1-P5). Blood monocyte-derived macrophages are believed to sequentially give rise to "inflammatory" (P1, P2), intermediate (P3) and resident iMΦ (P4, P5). Our aim is to assess the potential role of iMΦ in mediating inflammation in metabolic disease in the context of acute and chronic high fat consumption.

Methods
IMΦ were isolated from small (SI) and large intestine (LI) and characterized as P1-P5 by flow cytometry. For acute food intake, all groups were fasted over night. Refed mice had access to high fat diet (HFD) for 30 min, 2 h or 4 h after fasting. For chronic food intake, mice were fed a normal diet (chow) or HFD for up to one month.

Results
The majority of iMΦ subpopulations in the SI and LI of chow fed mice consists of the resident subset P5 (SI 48.4±2.6%; LI 50.8±4.9%). With acute food intake, the inflammatory monocyte marker Ly6C had higher geometrical mean fluorescence intensity (MFI) in inflammatory subsets P1 and P2 as compared to the fasted state, while P1-P5 proportions were unchanged. In contrast, after one week of HFD, proportions of P1 and P2 significantly increased (LI 4.0 and 9.7-fold), while P4 and P5 decreased (LI 12.4 and 1.6-fold, respectively) when compared to fasted chow diet. This was also true after two weeks and one month of HFD. Interestingly, one week of HFD followed by one week of chow diet reversed the effect of increased "inflammatory" P1 and P2 iMΦ subsets.

Conclusion
In summary, with normal diet the majority of iMΦ in the SI and LI consists of the resident macrophage subset designated as P5. While with acute high fat intake only the MFI of the inflammatory marker Ly6C in P1 and P2 increases, with chronic consumption of HFD the proportions of the subpopulations P1 and P2 increase, whereas P4 and P5 decrease. This switch of iMΦ towards inflammatory subsets is reversible by switching back to normal diet. The changes observed towards an inflammatory pattern of iMΦ could potentially connect HFD with systemic inflammation seen in metabolic disease.

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Inhibition of Interleukin-1beta improves glucose tolerance in pregnant C57BL/6 mice

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Background/Introduction
Pregnancy is a state of physiological insulin resistance and glucose intolerance. It is believed that this insulin resistance is needed to increase the glucose supply of the growing fetus. As a reaction, the mother produces more insulin. There is evidence that insulin resistance during pregnancy is caused by placental hormones, such as placental growth hormone or placental lactogen. The placenta also produces cytokines like TNFalpha, IL-1beta and IL-6, which are known inducers of insulin resistance in adipose tissue and liver. We aim to investigate the role of IL-1beta in glucose metabolism during pregnancy.

Methods
10-14 week old female C57BL6/N were subjected to timed mating. After confirmation of pregnancy on day 7.5, we treated mice with a murine blocking anti-IL-1beta antibody or vehicle. On day 13.5 of pregnancy we performed glucose-, insulin- or pyruvate tolerance tests. On day 14.5, we sacrificed the mice to obtain blood and tissue. We measured IL-1beta in the plasma using mesoscale assays and investigated AKT phosphorylation status of liver-, muscle- and parametrial adipose tissue extracts.

Results
The plasma levels of IL-1beta were increased in pregnant mice compared to nonpregnant mice. Blocking IL-1beta with an anti-IL-1beta antibody in pregnant mice resulted in improved glucose tolerance without changing insulin secretion. There was no difference in insulin tolerance, pyruvate tolerance or AKT phosphorylation between pregnant mice treated with anti-IL-1beta antibody and pregnant mice treated with vehicle. Further, our data suggests that fetuses of mothers treated with an anti-IL-1beta antibody are heavier and that their glucose uptake 30min after a glucose bolus is higher than those of mothers treated with vehicle.

Conclusion
The improvement of glucose tolerance in pregnant mice treated with anti-IL1beta indicates a decrease of pregnancy associated insulin resistance, although this could not be confirmed in our mouse model by insulin tolerance tests, pyruvate tolerance tests or assessment of AKT phosphorylation. Thus, the improved glucose tolerance following anti-IL-1beta therapy possibly reflects an increase of glucose flux into the fetuses with subsequent increase in body weight.

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The genomic response of the mouse thyroid to iodine overload, and the role of the Nrf2 antioxidant system.

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Background/Introduction
Despite mice being workhorses of mammalian genetics, the tiny size of their thyroid has precluded generalized use in studies of iodine effects on the thyroid, which have been traditionally performed in rats. There is also paucity of in vivo gene expression analyses of the thyroid's response to iodine using next-generation sequencing technologies. Employing a custom extraction protocol optimized for miniscule samples, we characterized the genomic response of the mouse thyroid gland to an iodine challenge in wild-type (WT) mice. In parallel, by testing mice lacking the transcription factor Nrf2, we investigated the role of this major antioxidant response system in thyroidal gene expression and in response to iodine.

Methods
Male 3 months-old male C57Bl6J WT or Nrf2 knockout (KO) mice were exposed to 0.05% sodium iodide in their water for 7 days. Thyroid gland was excised and used for RNA preparation. RNA-seq was performed by Exiqon. The fold-change cutoff was set to 1.5. Pathway analysis of the differentially expressed genes (DEG) was performed using the Ingenuity Pathway Analysis (IPA) software.

Results
Nearly 1700 genes were differentially expressed in response to iodine; most were up-regulated. Highly enriched pathways include those related to fibrosis; integrin signaling; leukocyte extravasation; inflammation (IL-1, IL-6, IL-8) and the acute phase response; production of reactive oxygen species and nitric oxide; and the Nrf2-mediated antioxidant stress response.

Nearly 500 genes were differentially expressed between WT and Nrf2-KO mice. Highly enriched pathways were related to glutathione-mediated detoxification, xenobiotic metabolism, and the Nrf2 antioxidant response; all were down-regulated in the KO. Nfr2 also impacted the expression of thyroid-specific genes including the sodium-iodide symporter and thyroglobuline.

Conclusion
These data provide a rich foundation for understanding the adaptation mechanisms to iodine challenge such as the escape from the Wolff-Chaikoff effect, as well as the role of oxidative stress in thyroid physiology.