S = contribution of a student

01

MODY 12 - a case report

Author/Address of institution
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Background/Introduction
MODY 12 is a rare disease. A casereport of a woman with transitory neonatal diabetes and diagnosis of diabetes with age 15 and subsequent insulin therapy. Since 2017 - when genetic testing shows result of ABCC8-mutation - modification of therapy into sulfonylurea in combination with sglt-2 inhibtor (and pausing Insulin) with good bloodsugar control.

Methods
A case report

Results
-

Conclusion
Therapyoptions for MODY 12 (sulfonylurea) also in view of new antidiabetic agents (SGLT-2).

02

Macronutrient distribution in type 1 diabetes - how does it affect post-prandial control?

Author/Address of institution
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Background/Introduction
Type 1 diabetes management has evolved from rigid meal plans, to more flexible eating patterns with carbohydrate counting. Little is known on the dietary habits of individuals with type 1 diabetes and the effect of macronutrients on postprandial glucose control. Image-based dietary recording is a novel user-friendly method to assess dietary intake under free-living conditions. We examined the association between dietary choices and measures of post-prandial glucose control in individuals with type 1 diabetes on sensor-augmented pump (SAP) therapy.

Methods
Twenty individuals with type 1 diabetes on SAP therapy (m:f =13:7; age 35[14] years, HbA1c 7.5[0.5] %, BMI 25.5[3.8] kg/m2, total daily insulin dose 0.62[0.15] U/kg/day) recorded their daily food intake, which were unrestricted under free-living conditions, over a 1 week period by taking photos with a smartphone. Dietary intake was assessed using the Prodi nutritional sofware. The 180min post-prandial period was defined from the start of the photo time stamp. Meal bolusing was performed immeidately after taking the photo. Measures of glucose control were evaluated with continuous glucose monitoring (CGM) data and sensor glucose target range was defined as 3.9-10.0mmol/l. Generalised estimating equations modelling was applied to evaluate the impact of macronutrients on glucose control.

Results
The macronutrient distribution of all meal categories (breakfast, lunch, dinner and snacks) was as follows: 53% carbohydrates (CHO), 15% protein and 32% fat. The average CHO content per meal was 50g. Mean±SD sensor glucose over the 180min post-prandial period was 8.7±2.9mmol/l without any significant differences between different meal types. The mean±SD proportion of the post-prandial period (180min) with sensor glucose in target range (3.9-10.0mmol/l) was 62±34% averaged over all meal categories. Mean±SD % time spent hypoglycaemic (< 3.9mmol/l) was 5±12% and 30±35% of time was spent above target (>10.0mmol/l). When adjusted for bolus insulin, fibre intake and consumption of unsaturated fat were independent predictors of higher %time in target, lower %time above target and lower mean glucose in the post-prandial period (fiber: B=1.7,p=0.013, B=-1.6, p=0.017, B=-0.17, p=0.004; unsaturated fat: B=0.5, p=0.09, B=-0.6, p=0.029; B=-0.05, p=0.030). CHO intake inversely correlated with mean glucose (B=-0.02, p<0.001), and was associated with %time in target (B=0.13, p=0.031).

Conclusion
In individuals with type 1 diabetes on SAP therapy, photo-based dietary assessment showed a consistent macronutrient distribution with 50% of calories coming from CHO. Intake of fibre and unsaturated fat showed favourable effects on post-prandial glucose control. CHO intake was also associated with improved control speaking against general promotion of a low carbohydrate diet in these patients.

03

Fully Closed-Loop Control in Acute Hospital: a Randomised Controlled Two-Centre Study

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Background/Introduction
Achieving satisfactory glucose control in hospital settings is challenging and imposes significant workload burden to hospital staff. As a consequence, inpatient hyperglycaemia management often remains suboptimal, with adverse consequences on length of stay, morbidity and mortality. Fully automated closed-loop insulin delivery (Artificial Pancreas) couples subcutaneous continuous glucose monitoring and insulin pump delivery in a glucose-responsive fashion and may potentially improve inpatient diabetes care.

Methods
Automated fully closed-loop (CL) insulin delivery including automated meal coverage was evaluated in a mixed medical and surgical non-critical care inpatient population in two University hospitals (Cambridge,UK and Bern,Switzerland). 47 non-type 1 diabetes adults requiring s/c insulin therapy in hospital were randomised to either CL-directed s/c delivery of rapid-acting insulin (n=22) or conventional s/c insulin therapy adjusted as per local guidelines with masked continuous glucose monitoring (n=25), for up to 15 days. Participants were matched for age (66[11] vs 73[11] years, CL vs. control), HbA1c (8.4[2.1] vs. 8.5[2.0] %) and BMI (32.7[9.2] vs. 31.8[9.0] kg/m2). Nutritional intake was not restricted during the study. Participants' usual insulin and sulphonylurea therapy were withheld during CL.

Results
In an intention to treat analysis, the proportion of time when sensor glucose was in target range (5.6-10.0mmol/l) was significantly higher during CL compared to control (59.0[19.9] vs. 35.3[15.5]%, difference 23.7% [95%CI 13.3, 34.1%], p<0.001). CL decreased time spent above target (>10.0mmol/l) by 21.1 percentage points (95%CI -35.0; -7.1%, p=0.004). Mean sensor glucose was 9.3(2.3) and 10.6(3.1)mmol/l during CL and control, respectively (p=0.11). Time spent hypoglycaemic (<3.5mmol/l) was low and comparable between groups (median,IQR: 0.16[0.0, 1.6] vs. 0.0[0.0, 3.9], p=0.79). Total daily insulin dose did not significantly differ between groups (70.7[54.6] vs. 60.8[47.4]U/24h, p=0.51).No episodes of severe hypoglycaemia or hyperglycaemia with ketonaemia occurred in either group.

Conclusion
Fully closed-loop insulin-delivery in hospital is safe, and may improve glucose control in a diverse patient population requiring s/c insulin whilst in hospital. Closed-loop insulin-delivery may be a promising modality to optimise inpatient diabetes care in the future.

04

Diagnosis of Di George Syndrome in a 52-year old patient presenting with hypoparathyroidism

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Background/Introduction
Di George syndrome is a genetic condition mostly caused by a heterozygous chromosomal deletion at 22q11.2, which leads to a defective development of the pharyngeal pouch system. The most common clinical manifestations are cardiac anomalies, hypoplastic thymus (possibly leading to an immunologic defect) and hypocalcemia resulting from parathyroid hypoplasia.

Case Report
A 52 year old woman was addressed to our clinic to investigate hypocalcemia. Her personal history included cardiac anomalies (ventricular septal defect and Arcus aortae dexter), hebephrenic schizophrenia as well as surgery for cleft palate in childhood. Also, in her medical records, a speech delay was described. Her family history was notable for a heart anomaly diagnosed in her father when he was above 70 years old. Our patient did not have any children, but two of her nephews (one of her sister's and one of her brother's children) had been diagnosed with speech delay respectively Asperger Syndrome.

Clinically, our patient had a short stature (158 cm), a small head with low nasal bridge as well as a flat midface and low-set ears. Albumin-corrected calcium was 1.89 mmol/L, Phosphate 1.62 mmol/L and iPTH inadequately low at 24 pg/mL, confirming hypoparathyroidism. White blood cell count and T-cell subpopulations as well as thyroid hormone levels were normal.

On the basis of the clinical and biochemical findings we strongly suspect Di George Syndrome in our patient. A genetic analysis is ongoing.

Conclusion
Chromosome 22q11.2 deletions are relatively common in the general population. It is probably underdiagnosed, because the phenotypic findings might be very mild in most patients. It is hence important to consider this diagnosis as a possible aetiology for hypoparathyroidism, even in adult patients.

05

Characteristics and outcome of incidental versus non-incidental thyroid nodules

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Background/Introduction
A increasing proportion of thyroid nodules are incidentalomas detected during imaging procedures not primarily targeted at the thyroid. The large number of thyroid incidentalomas has been shown to account for the sharp rise in the prevalence of papillary thyroid carcinomas. This analysis was performed in order to more clearly define the characteristics and outcome of incidentally versus clinically detected thyroid nodules.

Methods
Consecutive patients referred for the workup of thyroid nodules to our multidisciplinary clinic were eligible for the study. The work-up included clinical history and examination, thyroid ultrasound and fine-needle aspiration if considered adequate. A standardized risk stratification based on clinical and ultrasound (TIRADS-system) criteria was performed to identify nodules that qualified for a further work-up by FNA. Only nodules that underwent FNA were included in the analysis. Cytological specimen were scored according to the Bethesda classification. Nodules with a Bethesda classification of 6 and those malignant by histological workup were considered malignant. Data were analyzed by descriptive statistics and data are given as mean and 95% CI. t-tests and chi-square tests were used as appropriate and a $p < 0.05$ is considered significant.

Results
233 patients (78% females; mean age 54 years,52-56) with 272 nodules were included in the analysis. 37% (32-43) of the nodules were incidentalomas. 12% were detected by vascular US, 6% by thyroid US, 10% by parathyroid US, 37% by CT-scans, 13% by MRI and 18% by FDG-PET-CT scans. Patients referred for the workup of incidentalomas were significantly older (61years, 58-33; vs. 51 years, 49-53; p<0.00001). The mean nodule size (23 mm, 22-26 vs. 26 mm, 24-29; p=0.2), and ultrasound characteristics (TIRADS 2 5.8 vs. 9.9 %, TIRADS 3 26.2 vs. 28.1%, TIRADS 4A 43.7 vs. 33.3%, TIRADS 4B 23.3 vs. 25.1% and TIRADS 5 1.0 vs. 3.5%) were not different between incidental and non-incidental nodules. Furthermore, the proportion of malignant nodules did not differ between incidentally and clinically detected nodules (5.8%, 1.3-10.3 vs. 7.6%, 3.6-11.6; p=0.6).

Conclusion
Incidental and non-incidental thyroid nodules share identical ultrasound characteristics and carry the same risk of malignancy. Therefore, an identical workup is recommended for both symptomatic or clinically detected and incidental thyroid nodules.

06

Impact of Thyroid Hormone Therapy on Atherosclerosis in the Elderly with Subclinical Hypothyroidism: a Randomized Double-Blind Placebo-Controlled Trial

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Background/Introduction:
Subclinical hypothyroidism has been associated with atherosclerosis in observational studies. Carotid intima media thickness (CIMT) and maximum plaque thickness are established markers for atherosclerosis. We hypothesized that treatment of subclinical hypothyroidism with Levothyroxine improves carotid atherosclerosis.

Methods:
This was a sub-study of the TRUST trial, a European randomized, double-blind, placebo-controlled, parallel-group trial of community-dwelling participants over 65 years of age with untreated persistent subclinical hypothyroidism (thyrotropin level, TSH, 4.60-19.99 mIU/L; free thyroxine level within the reference range). Participants received either Levothyroxine starting at 50 µg (25 µg if weight < 50 kg or coronary heart disease) dose-titrated to achieve TSH normalization, or placebo with a mock dose titration. The main outcomes were mean CIMT measured at trial end by ultrasound of the common carotid arteries over ≥ 10mm of plaque-free wall, and maximum plaque thickness in the common, internal and external carotid arteries.

Results:
183 participants (mean age 74.1 years, 47% women, 95 randomized to Levothyroxine) underwent carotid ultrasound after a mean follow-up of 1.7 years (interquartile range 1.0-2.5 years). Mean TSH (±SD) was 6.36±1.96 mIU/L at baseline and decreased to 5.28±2.22 mIU/L with placebo, as compared to 3.56±2.14 mIU/L with Levothyroxine (p<0.001). Mean CIMT was 0.85 mm (95% confidence interval, CI, 0.82-0.89) in the Levothyroxine group and 0.82 mm (95%CI 0.80-0.85) in the placebo group (between-group difference 0.03 mm, 95%CI -0.01-0.07, p = 0.19). Plaque presence was similar in both arms (n=133, 70.5% in the Levothyroxine group and 75% in the placebo group, p = 0.50), and maximum carotid plaque thickness was 2.17 mm (95%CI 2.01-2.34) in the Levothyroxine group and 2.22 mm (95%CI 2.05-2.38) in the placebo group (between-group difference -0.04, 95%CI -0.27-0.19, p = 0.71). There were no significant interactions between Levothyroxine and mean CIMT according to sex, baseline TSH (categories 4.5-6.9, 7.0-9.9, and ≥10mmol/L) or established cardiovascular disease (all p for interaction ≥ 0.15). Sensitivity analyses including a second centralized reading of measurements and per-protocol analysis (excluding participants not on study drug/placebo at the time of outcome assessment) yielded similar results.

Conclusion:
Normalization of TSH with Levothyroxine had no relevant impact on CIMT and plaque burden in older persons with subclinical hypothyroidism after a mean follow-up of 1.7 years.

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07

Safety and efficacy of ketone body treatment in an adult patient with multiple acyl-CoA dehydrogenase deficiency

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Background/Introduction:
Multiple acyl-CoA dehydrogenation deficiency (MADD) is a rare disorder of fatty acid and amino acid oxidation, leading to a number of metabolic abnormalities including deficient ketone production. Clinical manifestations include episodic metabolic decompensation, leukodystrophy, neurodevelopmental delay, cardiomyopathy, liver disease, lipid storage myopathy, and respiratory failure. A fat- and protein-restricted diet in combination with carnitine and riboflavin supplementation is the mainstay of treatment. In some patients, severe deterioration and death may occur despite this standard treatment. In several children a novel treatment with ketone body has been described as highly effective, while no reports regarding adult patients are available. Ketone body substitution is thought to serve as substrates of cerebral metabolism and possibly as energy supply.

Methods:
We report on a 27-year-old female patient who first presented at the age of 2 years with a neurodevelopmental delay with leukodystrophy and a severe lipid storage myopathy. Despite an initial clinical improvement on standard therapy multiple metabolic decompensations occurred in the following years. At the age of 21 years, the patient experienced a seizure and an ischemic stroke in the cerebellum, confirmed by magnetic resonance imaging. Due to further deterioration and recurrent seizures a ketone body therapy has been initiated in 2015, using a racemic mixture of sodium D,L-3-hydroxybutyrate (NaHB) at a long-term dose of 600mg/kg/d.

Results:
We found a remarkable clinical improvement especially regarding attention, speech develompent, gait as well as fine motor skills. Metabolic decompensations have not occurred anymore and the frequency of seizures dropped to only one episode in the last 2.5 years. The biochemical profile prior to treatment showed low plasma ketone bodies with a sustained improvement on therapy. Magnetic resonance imaging shows stable white matter lesions as well as subcortical atrophy without any progression. Similarly, MR spectroscopy based on spectra of choline, N-acetyl-aspartate, creatin and lipids remained normal, while a slight improvement in intracerebral lactate was documented. Overall, the therapy was well tolerated without any side effects.

Conclusion:
We present the first adult MADD patient treated with D,L-3-hydroxybutyrate in addition to standard therapy leading to improvement in neurological manifestations and reduction of metabolic decompensations. It appears to be safe and well tolerated over the time of 2.5 years. Long term follow-up and larger studies are needed to confirm the efficacy and safety of this additional treatment in adult patients.

08

To big to work!
Lymphoma presenting with Primary Adrenal Insufficiency

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Background/Introduction
Background: Primary adrenal lymphoma (PAL) is a rare cause of primary adrenal insufficiency (PAI). Most often patients present with unspecific symptoms. Bilateral adrenal enlargement with signs and symptoms of PAI are clues, percutaneous biopsy after having excluded pheochromocytoma in a situation of high suspicion is diagnostic.
Most of PAL are highly malignant B-cell lymphomas with a bad prognosis.

Case
A 71-year-old patient was sent for endocrine workup because of a 2-month history of intermittent dyspnea, thoracic discomfort, weight loss and abdominal pain. An ambulant CT scan to exclude pulmonary embolism showed bilateral adrenal enlargement (right 77x31x55mm, left 63x38x41mm, native 25-29HE), which were new compared to a CT scan done one year earlier. On clinical examination, the patient was orthostatic and in an im- paired general condition. He had hyperpigmented hand lines. Laboratory evaluation showed a slight hyponatremia (131mmol/), potassium in the upper normal range (4.2mmol/l), pathologic ACTH-stimulation test (peak cortisol level: 153nmol/l) and elevated ACTH levels (231ng/l, normal range <46ng/l). Antibodies for 21-hydroxylase were negative, as well as free metanephrines in plasma, aldosterone-renin ratio was decreased (aldosterone 122pmol/l, renin 39mU/l). 17-hydroxyprogesterone was low (3.3nmol/l, normal range 1.9-6.5nmol/l). Quantiferon test was negative, and the CT scan did not raise suspicion for tuberculosis. We diagnosed PAI and started substitution with hydrocortisone (initial dose 50mg/d) and fludrocortisone (0.1mg/d). Histology of a CT-guided needle biopsy revealed infiltration of a highly malignant B-cell lymphoma. The patient was sent for oncological evaluation and start of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).

Results
PAL is a rare manifestation of primary extranodal lymphomas (1/3 of all lymph node neoplasms, PAL< 1% of all extranodal lymphomas). Only about 100 cases are published in the literature worldwide. Conversely, secondary spreading of a lymphoma to the adrenals is quite common (in autopsy studies up to 25%). Other reasons for bilateral adrenal enlargement are adrenal hyperplasia (any cause), metastasis of lung, breast and stomach (>50% of metastasis), bilateral pheochromocytoma, adrenal hemorrhage, adrenal involvement with granulomatous diseases, histicytosis and primary pigmented nodular adrenal dysplasia (PPNAD). Symptoms of PAL are unspecific (asthenia, weight loss, vague abdominal pain, fever). Diagnosis is made by percutaneous biopsy. In nearly 70% of cases PAL are bilateral, causing primary adrenal insufficiency. Average age of affected patients is around 70 years. Most of PAL are diffuse large B-cell lymphomas with BCL6 gene rearrangement and poor prognosis, as in our case. Therapy consists of R-CHOP.

Conclusion
Patients with bilateral adrenal enlargement and PAI need immediate replacement of glucocorticoid (including instructions about dosing in stressful situations) and mineralocorticoid hormones. While PAL is rare, it has a poor prognosis, thus rapid induction of treatment is necessary.

09 S

Effects of glucagon-like peptide-1 (GLP-1) analogues on hypothalamicpituitary-adrenal (HPA) axis activity in healthy volunteers

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Background:
GLP-1 analogues are well known to stimulate glucose-induced insulin secretion and reduce energy intake. Recent findings from animal and human studies indicate that GLP-1 may play a role in stress response by modulating HPA axis activity - as seen in chronic stress situations. The aim of this study was to investigate possible effects of GLP-1 analogues on HPA axis activity during a three-week treatment period with dulaglutide (Trulicity®) compared to placebo in healthy volunteers.

Methods:
In this double-blind, cross-over study dulaglutide (Trulicity®) 1.5 mg and placebo (0,9% sodium chloride) were given subcutaneously once weekly for three weeks in random order. During both treatment periods the following outcome parameters related to HPA axis activity were assessed: cortisol after 1 mg dexamethasone suppression, circadian rhythm of serum and salivary cortisol, urinary free cortisol (24 hours) and cortisol levels before and after stimulation with 1ug Synacthen® i.v.

Results:
20 healthy participants (mean age 27 years, 55% female) were included in the analysis. Further results of this study are currently being evaluated and will be presented at the SGED meeting in November 2017.

Conclusion:
In view of the widespread use of GLP-1 analogues as treatment for type 2 diabetes and obesity, possible effects of GLP-1 analogues on HPA axis activity may have relevant clinical implications.

10

Effects of IL-1β antagonism on the Hypothalamic-Pituitary-Gonadal (HPG) Axis in Men with Obesity and Metabolic Syndrome – A Randomized, Double-Blind, Placebo-Controlled Trial

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Background/Introduction:
Obese men with metabolic syndrome have a high prevalence of hypogonadism. Chronic low-grade inflammation has been proposed as a major cause for low testosterone levels in these individuals. The aim of the present study was to determine whether anti-inflammatory treatment may restore endogenous testosterone production in obese men with associated hypogonadism.

Methods:
In this double-blind, randomized, placebo-controlled trial involving men with metabolic syndrome, we randomly assigned 33 patients to receive 100 mg of anakinra (a recombinant human interleukin-1–receptor antagonist) subcutaneously twice daily for 4 weeks and 34 patients to receive placebo. The primary endpoint was the change from baseline in total testosterone levels after 4 weeks. Predefined secondary end points included changes in body composition, insulin resistance, inflammatory markers, muscle strength, hypogonadal symptoms and non-invasive hemodynamic parameters.

Results:
The median age was 55 years and baseline median total testosterone levels were 8.5 nM (95%CI 7.3 - 10.4; no difference between groups). At 4 weeks, in the anakinra group, the median total testosterone level increased by 1.1 nM while it slightly decreased by 0.1 nM in the placebo group, with a between-group difference of 1.2 nM or 14.5 % (P=0.03). This effect was most pronounced with lower testosterone levels (<10 nM) and higher inflammatory state (c-reactive protein >1.5 mg/L) with change in total testosterone of 1.7 nM with anakinra vs. decrease of 0.15 nM with placebo (P= 0.004). Treatment with anakinra led to a significant increase in non-dominant hand grip (regression coefficient 3.5 kg; 95%CI 0.23 - 6.8; P=0.04). IL-1 antagonism was also associated with a significant reduction of the stroke systemic vascular resistance index (P<0.015) and a reduced mean arterial blood pressure by 2.8 mmHg (95%CI (-5.8) - 0.1, p=0.06). Interleukin-1 antagonism had no significant benefit with respect to fatigue symptoms, but hypogonadal men who received anakinra reported an improved orgasmic function compared to placebo (p=0.053).

Conclusion:
IL-1 antagonism in obese men with low testosterone levels and features of the metabolic syndrome led to an increase in total testosterone, improved muscle strength and reduced systemic vascular resistance. IL-1 antagonism may therefore be a novel treatment option to improve low testosterone levels in obesity.

11

Psychosocial impact of living with diabetes: initial findings from the DAWN2 study in Switzerland

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Background/Introduction:
Diabetes mellitus (DM) constitutes a psychosocial burden for patients and their family members (FM) alike. Besides optimal pharmacological therapy, proper nutrition and physical exercise, successful treatment of DM demands psychosocial support and monitoring. Emotional well-being, support for active self-management, as well as availability and use educational resources are crucial aspects to take into consideration in diabetes management. The Swiss DAWN2 study aims to assess potential drivers and barriers to successful management of diabetes among patients, their family members, and health care providers. The present report presents descriptive data of a survey performed on psychosocial correlates in diabetic patients in Switzerland.

Methods:
Measures included sociodemographic data, diabetes profile, diabetes control, diabetes management, attitudes and beliefs, diabetes impact and burden, healthcare support, education and information, family and social support, health and quality of life. Patients with diabetes were notified about the study through the Swiss Diabetes Society, from which they received an online- or paper-based invitation to participation. WHO quality of life questionnaire was used to measure quality of life (QoL), EQ-5D self-reported questionnaire was used to record self-rated health status, psychological well-being was measured with the Well Being Index (WHO-5), and diabetes distress was estimated using the Problem Ares in Diabetes scale (PAID-5).

Results:
A total of 157 diabetic patients completed the survey, of whom 90 patients had type 2 diabetes (T2DM) and 64 patients had type 1 diabetes (T1DM). Mean age was 52±28 years, and 50% were female. Concerning current treatment regimens, 130 patients received insulin (66 T1DM, 64 T2DM), 38 received oral antidiabetic drugs (1 T1DM, 37 T2DM), and 110 patients were treated with lifestyle intervention (41 T1DM, 69 T2DM). A total of 82.4 % T1DM and 78% of T2DM patients considered their quality of life (QoL) as good or very good. The mean self-rated health status was 82.8 (25-100) among T1DM patients and 77.9 (25-99) in T2DM patients. Mobility (97.4%/91.3%), self-care (100%/99.1%), usual activities (97.4%/93.9%), pain/discomfort (90.8%/80.7%), anxiety/depression (85.3%/91.3%), and psychological well-being (91.8%/91.3%) were well-controlled in T1DM/T2DM patients. The majority of diabetic patients reported low diabetes-related distress (T1DM 91.7%, T2DM 99.1%).

Conclusion:
The data presented are preliminary and have to be interpreted with caution. However, quality of life, self-dependence, and autonomy was high, while diabetes-related distress, physical or psychosocial discomfort was considered low among diabetic patients participating in the Swiss DAWN2 study. This may be ascribed to the availability of modern treatment options and diversified medical support. Recruitment is ongoing, which will enhance both validity and significance of the present survey.

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Associations between maternal stress during pregnancy and fasting glucose with obstetric and neonatal outcomes

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Background/Introduction
Maternal stress during pregnancy is linked with less favorable obstetric and neonatal outcomes but more evidence is needed. This study investigated associations between maternal stress exposure (major life events, pregnancy-related major life events), psychological stress measures (perceived stress, depression, anxiety, and stress responses), fasting glucose levels during pregnancy and obstetric and neonatal outcomes. We hypothesized that higher maternal stress exposure and maternal stress responses were related to more adverse obstetric and neonatal outcomes and that any observed associations would be moderated by fasting glucose levels.

Methods
This prospective study included 203 pregnant women attending a routine appointment at a maternity department of a Swiss University Hospital between 24 to 30 weeks gestation. Pregnancy-related and -unrelated major life events, maternal stress perception (Perceived Stress Scale), and maternal psychological stress measures (Depression, Anxiety, Stress Scale-21) were assessed by validated self-report questionnaires. Birth outcomes included instrumental delivery (forceps, vacuum extractor or cesarean section) and neonatal outcomes included APGAR score at 5 minutes, large for gestationnal age, small for gestationnal age, birth weight, venous cord blood pH, NICU hospitalisation, hypoglycemia and breastfeeding at hospital discharge. Fasting glucose was measured using fasting morning blood samples.

Results
Regarding obstetric outcomes, significant positive associations between pregnancy-related majorlife events (p=.016) and instrumental delivery were found. Regarding neonatal outcomes, exposure to major life events in the last 12 months was negatively associated with cord blood venous pH values (p=.036) and positively associated with NICU hospitalisation (p=.05), and neonatal hypoglycaemia (p=.04). Maternal stress perception was associated with NICU hospitalisation (p=.019). Many of these associations were moderated by fasting glucose levels and remained significant when important confounders were controlled for.

Conclusion
Maternal stress exposure and perception are linked with less favorable obstetric and neonatal outcomes and fasting glucose moderates the relationship between stress and these outcomes..

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Case report: Dexmedetomidine-induced polyuria

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Introduction:
Dexmedetomidine is a highly selective alpha$_2$-adrenergic receptor agonist with anxiolytic, analgesic, sedative and sympatholytic properties with widespread use in critical care medicine for sedation, as an adjunct in anesthesia and useful agent in the treatment of alcohol withdrawal syndrome.
We report a case of dexmedetomidine-induced polyuria in an agitated ICU-patient with pneumococcal meningitis.

Case:
A 61-year old Swiss man was admitted with acute onset of delirium. He presented with altered mental status and fluctuating level of consciousness. Physical examination revealed neck stiffness, but he was afebrile. Head CT showed no intracranial pathology. Leukocyte count was 20.5 G/l and CRP was 190 mg/l. Bacterial meningitis was suspected and therefore, ceftriaxon and high-dose dexamethasone were initiated.
The patient was admitted to the ICU. Sedation with benzodiazepine and propofol as well as moderate fluid replacement (60 ml/h) were started. Lumbar puncture was performed, and cerebrospinal fluid (CSF) showed characteristic findings for bacterial meningitis. PCR of the CSF confirmed pneumococcal meningitis. Despite sedative treatment, his state of agitation was initially difficult to control. We therefore initiated a continuous infusion of dexmedetomidine (44.8 ug/h). This strategy resulted in a state of cooperative sedation.
Urine output increased within 2 h of the start of dexmedetomidine to 400ml/h and reached 850ml/h by 3 h. Meanwhile, there was a mild decrease of the mean arterial pressure. Fluid replacement with crystalloids was initiated. Serum sodium rose from 129 mmol/l to 137 mmol/l after 5 h of dexmedetomidine treatment, and serum osmolality increased from 274 to 293 mOsmol/kg. Urinary sodium was 29 mmol/l compared to 80 mmol/l initially, and urine osmolality decreased from 767 to 383 mOsmol/kg. Copeptin level during polyuria was later found to be at 5.3 pmol/l. We added 5% glucose infusion at a rate of 125 ml/h. At this point, dexmedetomidine infusion rate was reduced, but urine output remained high (500-700 ml/h). We found no evidence of other causal or contributing factors to polyuria than dexmedetomidine and therefore discontinued it after 7½ hours. Urine output decreased within 2 h from 950 to 230 ml/h. Serum sodium did not exceed 140 mmol/l, and fluid replacement therapy could be reduced. Serum and urine osmolality normalized over the next 36 hours. The patient's state improved continuously. 20 hours after admission, there was complete recovery with no presence of agitation and confusion. No neurological deficits remained.

Discussion:
Dexmedetomidine has become a popular sedative in critical care medicine since its authorization in Switzerland in 2012. The most frequently observed adverse effects are hypotension and bradycardia. We documented the case of a patient with a rarely described side effect of dexmedetomidine, namely dexmedetomidine-induced polyuria. Clinicians should be aware of this very rare condition.

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Changes in length of hospital stay and clinical outcomes for patients with diabetes after the Introduction of the DRG reimbursement: A longitudinal analysis in Switzerland using administrative data

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Background/Introduction
To study the effects of the Diagnosis Related Groups (DRG)-reimbursement system introduced in 2012 on in-hospital length of stay (LOS) and clinical outcomes in hospitalized patients with diabetes using administrative data in Switzerland.

Methods
We analyzed LOS, readmission, and in-hospital mortality in adult medical inpatients using nation-wide administrative data from the Swiss Federal Office for Statistics during the years 2011 to 2015. We used linear regression models and compared LOS before and after introduction of the DRG- reimbursement by calculation of a LOS change over time. Patients were stratified by main diagnosis of diabetes and diabetes as a comorbidity based on ICD-10 codes.

Results
We included 19,536 patients with a main diagnosis of diabetes, 261,378 patients with diabetes as comorbidity, and 1,473,800 control patients with no diabetes. Overall, mean (±SD) LOS was longer in patients with diabetes as comorbidity (8.9±9.5 days) and in patients with a main diagnosis of diabetes (8.3±8.3 days), compared to patients without diabetes (7.2±2.9 days, p<0.001). Whereas the mean LOS decreased from 7.7±14.1 to 7.2±17.3 days within five years, corresponding to a quarterly reduction of -0.03 days (95% CI -0.034 to -0.026) in the control population with no diabetes, the quarterly reduction was moderate in patients with main diagnosis of diabetes (-0.036 day [95% CI -0.057 to -0.015]), but largest and in patients with diabetes as comorbidity (-0.05 day [95% CI -0.056 to -0.044]). Results for patients treated in tertiary care and non-tertiary care hospitals were similar. Patient outcomes such as readmission and in-hospital mortality did not increase during this time.

Conclusion
After the introduction of the DRG-reimbursement in Switzerland in 2012, we observed a steady and safe reduction in LOS, most prominently in patients with diabetes as a comorbidity. Novel patient-centered transition strategies are needed particularly for patients with a main diagnosis of diabetes to further optimize in-hospital treatment without compromising patient safety.

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Consumption of Sugar-Sweetened Beverages impairs the LDL Subclass profile – Data from a double-blind randomized controlled trial

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Background/Introduction:
The consumption of Sugar-Sweetened Beverages (SSB) is associated with adverse effects on various metabolic parameters, suggesting a causal relationship between SSB consumption and components of the metabolic syndrome as overweight, insulin resistance or altered lipid metabolism. However, only few controlled intervention studies have investigated changes in lipid metabolism so far.
A Low-density-lipoprotein profile with a predominance of small, dense LDL particles is associated with an increased cardiovascular risk and is typically seen in patients with features of the metabolic syndrome.
Earlier data from a short (3 weeks) crossover trial from our institution suggests adverse effects of SSB (and in particular fructose sweetened beverages) on LDL particle subclasses.

Methods:
Lipid profiles were analyzed in a sub-study of a double-blind, randomized controlled trial in healthy young men who were randomized to an 8-week intervention with beverages sweetened with either glucose, fructose or sucrose (80g per day) or to a control group.
Blood was drawn in the fasted state after the intervention and analysis of LDL size and subclasses was performed using nondenaturing polyacrylamide gradient gel electrophoresis of plasma.

Results:
94 subjects (23 to 24 per group) were included in the study (all male, age 22.7 years, weight 72.0kg, BMI 22.0kg/m2).
The consumption of sugar-sweetened beverages for 8 weeks induced a significant increase in the proportion of small, dense LDL particles (class III) from 26.4% to 27.5% ($p < 0.05$). In parallel, the proportion of large LDL particles (class I) decreased from 19.1% to 17.7% ($p < 0.05$). In the control group, no changes in LDL particle size distribution was observed.
When assessing the three groups of subjects exposed to SSB with different sugars separately, we observed a statistically significant decrease in large LDL particles in the group exposed to sucrose sweetened SSB only ($p < 0.05$). On the other hand, a tendency towards an increase in small LDL particles was observed in the group exposed to fructose containing SSB ($p=0.06$). No significant adverse effects were observed in the group exposed to glucose containing SSB.

Conclusion:
The consumption of Sugar-Sweetened Beverages in moderate amounts (comparable to the consumption of SSB in everyday life) results in adverse LDL subclass profile changes, promoting an increase in small, dense LDL particles and a decrease in large, buoyant LDL particles. In particular, the consumption of fructose containing beverages (free fructose or sucrose), but not of beverages containing glucose alone, induced such changes.

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Hypertension, edema and hypokalaemia in an old man with prostatic cancer

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Background/Introduction
A 71-year-old man with a 3 years history of a metastatic (bone, lymph nodes) prostatic adenocarcinoma (Gleason Score 9) previously treated with androgen suppression (leuprorelin and bicalutamid), chemotherapy (docetaxel 6 cycles), local radiotherapy to the sacrum and more recently with Radium 223 and Enzalutamide due to disease progression was admitted to our hospital because of recent onset of hypertension, edema, hypokalemia (2.7 mmol/l) and hyperglycemia. The initial clinical exam was remarkable for hypertension (bp 211/98 mmHg), pitting lower leg edema and basal lung rales. Subsequent echocardiography showed normal cardiac function and deep vein thrombosis was ruled out by ultrasound. Ectopic paraneoplastic ACTH secretion was suspected and biochemically confirmed by markedly increased serum and urinary cortisol (basal 1155 nmol/l, 1050 nmol/l following 1 mg overnight dexamethasone; urinary free cortisol excretion 1013 ug/d, normal < 136) and ACTH (140 pg/ml) concentrations. Restaging by a thoracoabdominal CT-scan showed progressive disease with new onset of lung and liver metastases. Liver biopsy revealed a small-cell neuroendocrine cancer with a proliferative index (Ki-67) of 70% and scattered immunoreactivity for ACTH. Thus, the final diagnosis of a small-cell neuroendocrine prostate carcinoma with paraneoplastic ACTH-secretion was established. Chemotherapy with carboplatin and etoposide was begun and ketoconazole was started because of the clinically and biochemically severe cortisol excess resulting in a rapid decline in serum cortisol and clinical improvement. Metyrapone was added and further improved cortisol excess with no increase in serum androgen concentrations.

Methods
Small cell carcinoma of the prostate represents only 1% to 2% of all prostatic cancers, and prostatic tumors account for less than 2% of all cases of ectopic ACTH secretion. Neuroendocrine differentiation in prostate cancer usually coexists with an adenocarcinoma and has been reported to occur in patients previously treated with androgen ablation. Severe hypercortisolemia with high levels of corticotropin develops quickly and metabolic abnormalities tend to be the predominant clinical manifestation. Excess of cortisol or its metabolites may induce volume retention by overwhelming renal 11-beta-hydroxysteroid dehydrogenase typ 2 and activating the mineralocorticoid receptor. Ketoconazole and arbiraterone acetate are the preferred initial agents to control adrenal cortisol excess since the use of metyrapone leads to an increase in adrenal androgen secretion and should be avoided in prostate cancer

Conclusion
SCC of the prostate is a rare entity, presentation with features of Cushing syndrome due to ectopic ACTH secretion is even rarer. The typical features of this type of hypercortisolaemia are hypertension, leg edema, hyperglycaemia, metabolic alkalosis and hypokalaemia. Cushingoid phenotype is less likely to be present due to rapid onset of the disease. It may be suspected when clinically and laboratory features appear in patients.

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The effect of exercise on skeletal muscle acetylcarnitine in adult growth hormone deficiency (GHD)

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Background/Introduction
Acetylcarnitine (AcCrn) in skeletal muscle is increasingly formed when the generation of acetyl-Coenzyme A (AcCoA) from glycolysis or beta-oxidation exceeds the oxidative capacity of the tricarboxylic acid (TCA) cycle, e.g. during strenuous exercise. This process avoids the accumulation of excess AcCoA which is essential to maintain aerobic carbohydrate oxidation by sustaining TCA cycle flux. Growth hormone (GH) is known to have a lipolytic effect. We therefore hypothesize that in GH deficiency (GHD) lipolysis and accumulation of AcCoA are reduced during exercise, and that consequently this would result in reduced formation of AcCrn – possibly contributing to the impaired exercise capacity observed in these patients. The aim of our study was to determine the effect of exercise on skeletal muscle AcCrn, which is in equilibrium with AcCoA, in GHD patients compared to healthy controls.

Methods
We compared skeletal muscle AcCrn concentrations in male adult patients with severe GHD to those in male sedentary control subjects (CS) matched for age, BMI and waist circumference. Skeletal muscle AcCrn concentrations were non-invasively measured in the M. vastus intermedius by proton magnetic resonance spectroscopy (1H-MRS) on a 3T scanner. Measurements were performed before and after 2 hours of moderately intense aerobic exercise (50% of VO2max), a third measurement was performed 24 hours post-exercise.
All participants had subcutaneous and visceral fat mass determined with whole body MRI.
Diet and physical activity were standardized during the study.

Results
Seven male GHD patients and 7 male control subjects (CS) were well matched (age, BMI, waist circumference) and had similar visceral and subcutaneous fat mass.
During exercise AcCrn levels increased in both groups. The mean increase in acetylcarnitine levels was lower in the GHD patients (+0.97 ±1.10 mmol/L) compared to control subjects (+1.63 ±1.50 mmol/L), although this did not reach statistical significance.
24 hours post-exercise acetylcarnitine levels decreased towards baseline levels. Compared to baseline the change was similar in both groups: +0.29 ±0.57 in GHD patients and +0.50 ±0.84 in controls.
In the subjects examined changes in AcCrn levels did not significantly correlate with age, BMI, VO2max, HOMA, total fat mass, visceral fat mass or subcutaneous fat mass.

Conclusion
1) 1H-MRS allows to reliably determine AcCrn in skelettal muscle after exercise

2) A 2h aerobic exercise at 50% of VO2max results in a transitory increase in skeletal muscle AcCm, and thus AcCoA

3) GHD does not significantly impact on changes in skeletal muscle AcCrn/AcCoA probably due to the redundant lipolytic action of other hormones (catecholamines, cortisol)

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Short-term effects of dapagliflozin on hormonal glucose regulation in male type 1 diabetics - a placebo-controlled, double-blind, cross-over pilot study

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Background/Introduction
Inhibitors of the sodium-glucose transporter-2 (SGLT-2) are the latest therapeutic agents introduced to support glycemic control in type 2 diabetes mellitus. SGLT-2 inhibitors significantly decrease renal glucose and sodium absorption. SGLT-2 inhibition may be similarly used in conjunction to insulin in type 1 diabetes mellitus (T1DM) due to its potential ability to attenuate postprandial glucose excursions. Available proof-of-concept studies in T1DM revealed promising results concerning glycemic control and clinical safety. However, it is yet unknown whether SGLT-2 inhibition also modifies the release of counter-regulatory hormones or ketogenesis in the postprandial state in T1DM. The present study aimed to evaluate the effects of SGLT-2 inhibition on glucagon release and ketogenesis after a standardized oral glucose-load in male T1DM patients.

Methods
A total of 7 male T1DM patients was recruited in an randomized, placebo-controlled, cross-over pilot study. Interventions included sequential treatment with either dapagliflozin 10mg daily or placebo as adjunct to insulin for 3 days, intermitted by a wash out period of 14 days. Basal insulin was discontinued on day 3 of each intervention period, prior to a 120 minutes oral glucose tolerance test (OGTT) using 50 grams of glucose. Required insulin doses were calculated and administered intravenously over 60 minutes. Plasma glucose concentrations were drawn from arterialized venous blood every 5 minutes using a bedside point of care laboratory system. Plasma samples were collected before and every 15 minutes during OGTT to measure insulin, total ketone bodies (TKB), and glucagon.

Results
Dapaglilfozin did not attenuate postprandial glucose excursion (Area under the curve (AUC) for plasma glucose 102260 mg/dl/min for dapagliflozin and 93748 mg/dl/min for placebo; p=0.596). Postprandial blood glucose concentrations exceeded the target range (3.9 - 10.0 mmol/l) in every patient. TKB were significantly higher (AUC 49983 mmol/l/min for dapagliflozin vs. 21999 mmol/l/min for placebo; p=0.008) while glucagon concentrations were significantly lower (AUC 61.89 pg/ml/min for dapagliflozin vs. 76.69 pg/ml/min for placebo; p=0.008) under treatment with dapagliflozin. TKB were neither associated with plasma glucose (p=0.987) nor insulin concentrations (p=0.858) in dapagliflozin treated subjects.

Conclusion
Even though short-term treatment with dapaglilfozin did not affect postprandial glucose excursions, the hormonal response to relative insulin deficiency was significantly altered compared to placebo. Dapagliflozin amplified ketogenesis and attenuated glucagon secretion irrespective of actual glucose concentrations. In conclusion, dapagliflozin may modify substrate metabolism in the hyperglycemic, postprandial state, hereby favouring ketogenesis over hepatic glycogenolysis.

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DIAfit - encouraging type 2 diabetic patients for a healthy lifestyle

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Background/Introduction
Type 2 diabetes mellitus is a common disorder associated with obesity and sedentary lifestyle. Even though pharmacological treatment options made significant progress, a healthy lifestyle forms the essential basis for successful treatment. Lifestyle interventions include nutritional advise, regular physical acitivity and psychosocial motivation in order to optimize the metabolic risk profile. DIAfit is a Swiss intervention program encouraging physical activity, healthy nutrition and general health care in patients with T2DM. The present study investigated the effects of a 9 months structured lifestyle training schedule adressing physical performance, glycemic control and cardiovascular risk in T2DM patients.

Methods
A total of 235 patients conducted the program in 18 DIAfit centres throughout Switzerland between 2015 and 2016. Eligible patients participated in 2-3 units of supervised physical exercise, nutritional support, and healthcare instructions per week for 9 months. Physical exercise comprised 150 minutes of moderate aerobic and anaerobic exercise per week. Bicycle ergometer performance (defined as Watts per second), 6 minutes walking distance, glycated hemoglobin (HbA1c), and low-density lipoprotein cholesterol (LDL-C) concentration were determined prior to and after completion of training schedule. Training schedules were supervised by healthcare professionals. Shapiro-Wilk test was used to determine data distribution, dependent Student's T-Test or independent T-test was used to compare related means or unrelated means, respectively. Pearson's approach was used for bivariate correlation.

Results
Mean age was 60.21± 10.17 years, 95 participants were female, 140 were male. Ergometer peak power increased from 114.67 ± 41.72 to 125.85 ± 41.84 watts (p<0.001), mean 6 minutes walking distance increased from 497.24 ± 67.97 to 540.25 ± 88.74 meters (p<0.001), HbA1c decreased from 7.51 ± 1.33 to 7.17 ± 1.14 percent (p<0.001), and LDL-C decreased from 2.96 ± 1.28 to 2.81 ± 1.24 mmol/L (p=0.001). Female participants increased their ergometer peak performance from 99.60 ± 33.82 to 107.02 ± 32.56 watts (p<0.001), 6 minutes walking distance increased from 480.20 ± 66.92 to 518.81 ± 69.16 meters (p<0.001), HbA1c decreased from 7.21 ± 1.29 to 6.88 ± 1.11 percent (p<0.001). LDL-C remained statistically unchanged (mean difference of 0.11 ± 0.62 mmol/L; p= 0.139). Male participants increased their ergometer peak performance from 124.82 ± 43.54 to 137.73 ± 42.81 watts (p<0.001), 6 minutes walking distance increased from 506.30 ± 67.47 to 552.37 ± 96.70 meters (p<0.001), HbA1c decreased from 7.70 ± 1.31 to 7.37 ± 1.13 percent (p<0.001), and LDL-C decreased from 2.91 ± 1.32 to 2.70 ± 1.23 mmol/L (p=0.003). Ergometer peak performance inversely correlated to age (r=-.159; p=0.04) and female gender (r=-.171; p=0.028) Baseline ergometer peak performance was higher in men (p=0.016).

Conclusion
DIAfit is an effective and readily available intervention program in order to emphasize physical activity and a healthy lifestyle in T2DM patients in Switzerland. Effects - with the exception of ergometer peak power - were independent of sex and more distinct in younger T2DM patients.

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Analyses of emergency department visits attented by diabetic patients in the canton of Berne

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Background/Introduction
Diabetes mellitus approximately affects 500'000 patients in Switzerland. Suboptimal disease management may provoke acute metabolic decompensation as well as microvascular and macrovascular complications in the long term. Diabetes-related complications and therapeutic malcompliance significantly increase the necessity for emergency department visits and hospitalization in diabetic patients. However, the incidence rates of emergency department visits in diabetic patients in Switzerland are unknown albeit useful in terms of risk estimation, quality management and determination of timewise trends. The present study analysed emergency department visits, which were attented by diabetic patients from 2012 to 2017 in the canton of Berne.

Methods
A total of 1131 emergency department visits of diabetic patients were extracted from the database of the emergency center at the University hospital of Berne. Elgibile cases were selected by text mining the database for "hypoglycemia", "hyperglycemia", "keto-acidosis" and "insulin pump". Reasonable cases were then filtered manually according to initial blood glucose measurement at the emergency department, anamensis and principal diagnosis. Analysed data comprised clinical background, demographic data, treatment regimens, glycemic control, time of attendance, and primary cause of the emergency department visit.

Results
A total of 390 cases of hypoglycemia was selected. Of these, hypoglycemia was the primary cause of emergency attendance in 161 patients (89 males, 72 females), of which 18 patients had Hypoglycemia II°and 40 patients had hypoglycemia III°. In total, 33 patients had type 1 diabetes mellitus, 317 patients had type 2 diabetes mellitus, and 40 patients had hypoglycemia due to reasons other than diabetes. A total of 57 diabetic patients received no medication, 25 received oral antidiabetic drugs, 74 patients had multiple daily injections of insulin, and 5 patients used an insulin pump. Hypoglycemia was caused by malcompliance in 23 cases, alcohol and/or drug abuse in 23 cases, 6 cases were triggered deliberately in suicidal attempts, and physical exercise preceeded in 4 cases. A total of 58 hypoglycemic events occurred while patients participated in traffic. Younger age correlated to alcohol and/or drug abuse correlated (r.2.7; p<0.001), hypoglycemia during traffic (r.35; p=0.002), and therapeutic malcompliance (r.20; p<0.020). Male patients had a significantly higher proportion of hypoglycemia III° than female patients (p=0.022).

Conclusion
This the first analysis of emergency department visits attended by diabetic patients in the canton of Berne. The risk for an emergency visit was highest in young, male type 1 diabetic patients. The present results may help to determine attributes and risk factors of diabetic patients that increase the necessity for emergency department visits.

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Familial hypocalciuric Hypercalcemia or Primary Hyperparathyroidism?

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Background/Introduction
Mutations of the sigma subunit of the clathrin-mediated endocytic adaptor protein-2, AP2σ, have been identified in patients with familial hypocalciuric hypercalcaemia type-3 (FHH3). FHH3-associated AP2σ-mutations cause delays in internalisation of CaSR, thereby indicating a likely important role for CaSR endocytosis in regulating CaSR cell surface expression and signaling.

Case Report
A 54 year man presents to our clinic due to hypercalcemia. His sister had been a patient at our clinic due to the same problem, but we had lost follow-up due to her psychic problems. He has a brother with unsuccesful parathyroidectomy years ago. A second brother and a second sister are living abroad with unknown calcium status.

At the first visit calcium was 2.95 mmol/L, iPTH 72 pg/mL and the fractionated urinary calciumexcretion 0.7 %. Due to the fractionated urinary calcium excretion below 1 % and the family history familial hypercalciuric hypercalcemia was suspected. Molecular genetic analysis revealed a pathogenetic pathogenetic heterozygot AP2S1-variant (c.44G> t p (Arg15Leu), while negative for mutations in CASR, CDC73, MEN1 and RET. Osteodensitometry showed no osteoporosis and no further therapy was initiated.

However, during regular follow-up visits the hypercalcemia increased up to 3.21 mmol/L and the patient suffered from two episodes of nephrolithiasis, while fractionated urinary calcium excretion increased up to 1.6 %. Ultrasound and Sestamibi-Scintigraphy suggested a possible parathyroid adenoma an the right side, but F-Cholin-PET/CT did not show respective signs. Therefore, treatment with cinacalcet was introduced, dropping calcium to around 2.75 mmol/L without any further episodes of nephrolithiasis.

Conclusion
FHH is a heterogenous condition. FHH3 represents a more severe variant of a mutation in the AP2S-1 Gen, possibly leading to a more pronounced hypercalcaemia and secondary complications similar to primary hyperparathyroidism.

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Rapid remission of severe Graves' disease without thionamides under glucocorticoid treatment for concomitant autoimmune hepatitis.

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Background/Introduction
Even though thionamides are a first-line treatment for Graves' disease, their potential hepatotoxicity renders their use challenging in cases of concomitant liver disease. For such cases, and if radioactive iodine and surgery cannot be used, alternative medical treatments are not well established.

Methods
Case report of a 28-year-old Causacian female with unremarkable medical history that consulted initially for progressive jaundice. Medical investigations led to diagnosis of thyreotoxicosis due to Graves disease with concomitant autoimmune hepatitis

Results
Laboratory tests showed an alanine aminotransferase of 1437 U/l and a total bilirubin of 286 µmol/l. Investigations revealed type I autoimmune hepatitis, with positive anti-nuclear and anti-smooth muscle autoantibodies and a typical histology. Medical history revealed recent restlessness, rapid heartbeat and increased stool frequency. The clinical exam showed signs of hyperthyroidism (sinus tachycardia, fine tremor, hyperactive Achilles tendon reflexes). Free T4 and free T3 were increased at 60 pmol/l (normal range, 12-22 pmol/l) and 14.6 pmol/l (normal range, 3.1-6.8 pmol/l), respectively. Thyrotropin receptor antibodies (TRAb) were strongly positive (11.1 UI/l; normal range, <1.75 UI/l). Ultrasonography revealed a normally sized but heterogeneous thyroid with increased vascularity. Given the hepatic impairment, thionamides were withheld and only propanolol and a low dose of cholestyramine (4 gr per day) were prescribed. Prednisone was started at a dose of 50 mg per day, with rapid improvement of the patient's clinical condition and liver tests, allowing for the introduction of azathioprine and the progressive tapering of corticosteroids. After 3 months of azathioprine and without any thionamide use, free T4 and T3 were normal and TRAb decreased to 1.96 UI/l.

Conclusion
Glucocorticoids and other immunosuppressive agents are an alternative medical option for Graves' hyperthyroidism when contraindication to thionamides is present. In addition to the well-established suppression of T4 conversion to T3, reduction of TRAb-mediated thyrocyte stimulation seems to be the main mechanism of action.

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

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Background/Introduction
Aim was to improve the care for diabetes type 2 patients (T2DM) 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 the patient population.

Methods
Patients were selected via the search criteria "any patient with at least one single HbA1c value more than 6.4% in our group practice in the Achilles©/Axonlab software. 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 analyzed 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 analyzed with an Excel spreadsheet developed by QualiCCare and a score was calculated for the total cohort and for the sub-cohorts of each physician.

Results
65 patients were included at baseline 2013. For the two intervention years 2014 and 2015 78 respective 88 patients were included. 62% of our patients were male 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 was 30 (range 30-43 for the sub-cohorts) 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 average BMI was decreased by 0.8kg/m2.

Conclusion
It was possible to improve 7 out of 8 diabetes care scoring criteria with only small intervention. 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 software application which calculatea the scores automatically.

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Localization of recurrence of primary hyperparathyroidism in MEN 1 – a case report

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Background/Introduction
The optimal approach of surgical therapy of primary hyperparathyroidismus in multiple endocrine neoplasia Typ 1 (MEN 1) is controversial. There are different surgical options, mainly subtotal parathyroidectomy (removal of three and a half glands) or total parathyroidectomy with autotransplantation. With both strategies localization of recurrent adenomas/hyperplasias can be a challenge.

Case Report
The 45-year-old patient was diagnosed with primary hyperparathyroidism associated with MEN 1 (mutation exon 5 and polymorphism exon 9 of the menin gene) at the age of 32 years. The same year he was diagnosed with a neuorendocrine tumor of the pancreas (treated with total pancreatectomy) and a hormonal inactive pituitary microadenoma (stable since). Due to severe hypercalcemia (albumin-corrected max. 3.4 mmol/L) and recurrent symptomatic renal stones total parathyroidectomy with autotransplantation of one and a half parathyroid glands into the left tibialis anterior muscle was performed. In the following 6 years, calcium values remained normalized and the patient was free of further renal stones. Seven years ago recurrence of hypercalcemia was found, initially mild and in the course moderate (albumin-corrected max. 2.88 mmol/L). In addition, symptomatic renal stones started to recur 4 years ago. Ultrasound was suspicious for a parathyroid adenoma behind the right lower thyroid lobe, 99mTc-Sestamibi SPECT-CT on the other hand showed increased activity at the left tibialis anterior muscle, although without correlation in the native CT-Scan. 18F-Cholin-PET/CT suggested parathyroid glands at both mentioned sites. Therefore, we performed a simultaneous venous sampling at the left inguinal vein and the right brachiocephalic vein. As there was a marked difference of iPTH (498 vs 89 pg/mL) suggesting that mainly the autotransplanted glands in the leg are responsible for the recurrence, we abstained form additional selective venous sampling of the thyroid veins and the patient was sent to the surgeon to remove the autotransplanted parathyroid glands in the left tibialis anterior muscle.

Conclusion
In addition to ultrasound, 99mTc-sestamibi SPECT-CT and 18F-Cholin-PET/CT, selective venous sampling can be a valuable localization tool in recurrent primary hyperparathyroidism, especially in the case of autotransplanted parathyroid glands.

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Hypercalcemic Crisis in Third Trimenon: Evaluating the Optimal Treatment Strategy

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Background
Hypercalcemia due to primary hyperparathyroidism during pregnancy is a rare condition which is associated with a considerably increased morbidity and mortality for both the mother and the unborn child. Whereas parathyroidectomy is favored during the second trimester, no clear recommendations exist for its management during the third trimenon.

Case presentation:
A 26 year old woman in the 29th week of her first pregnancy was admitted to our clinic with hypertension, intra-uterine growth retardation and polyhydramnios. Severe hypercalcemia due to primary hyperparathyroidism was diagnosed (total calcium 3.34 mmol/l; intact PTH 216 pg/ml) but no enlarged parathyroid gland could be localized by ultrasound. Treatment with calcitonin and cinacalcet did not result in normalization of calcium levels. Therefore the indication for explorative surgery was given. Intraoperatively, a single parathyroid adenoma was located and resected, ultimately resulting in a normalization of serum calcium levels. The surgical procedure was tolerated well by the mother and fetus, and the hypercalcemia-induced hypertension and polyhydramnios ameliorated before C-section was performed.

Conclusion:
Early diagnosis and treatment of primary hyperparathyroidism is crucial for mother and fetus. However, if diagnosed in the third trimenon, an interdisciplinary approach is important. If medical treatment does not result in sufficient control of hypercalcemia, surgical parathyroid exploration should be considered even in cases of unsuccessful localization of adenomatous parathyroid glands.

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Use of Copeptin in the Differential Diagnosis of Diabetes Insipidus – a Prospective International Multicentre Study

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Background:
The classical water deprivation test is considered the gold standard test to evaluate polyuria-polydipsia syndrome. However, it is cumbersome to conduct and often misleading. Serum copeptin levels are a potential new tool in the diagnostic workup.
Herein we compared the diagnostic accuracy of copeptin after osmotic stimulation with hypertonic saline infusion and water deprivation test to the water deprivation test alone.

Material and Methods:
Prospective multicentre study from 5 Swiss, 5 German and 1 Brazilian tertiary referral centres of adults with polyuria-polydipsia syndrome. Copeptin values after a 3% saline infusion test (targeting a serum sodium level of 150mmol/l) as well as before and after standardized water deprivation test were measured. Final diagnosis was based on the water deprivation test results, patient history and clinical information as well as treatment response and was blinded to copeptin levels.

Results:
156 consecutive patients with polyuria-polydipsia syndrome were included in the study of which 144 (92%) completed both tests (water deprivation test and hypertonic saline infusion) and received a final diagnosis. Primary polydipsia was diagnosed in 72 (50%), central diabetes insipidus in 68 (47.2%) and nephrogenic diabetes insipidus in 4 (2.8%) patients. Analysis of the diagnostic accuracy of the two tests and copeptin values are being evaluated and will be presented at the meeting.

Conclusion:
Depending on the results, stimulated copeptin levels might improve diagnostic accuracy in the evaluation of patients with polyuria-polydipsia syndrome.

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A case of Graves' disease after radioiodine therapy for toxic thyroid adenoma

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Background/Introduction
Within weeks or months after radioiodine therapy of autonomous thyroid nodules, euthyroidism is observed in the majority of patients, whereas some patients develop hypothyroidism. Transient thyrotoxicosis may be observed early after the treatment, secondary to the radioiodine-induced inflammation with release of thyroid hormones. New-onset Graves' disease after radioiodine therapy of toxic goiter is a rare phenomenon.

Methods
We describe the case of a 64-year-old woman known for a toxic thyroid adenoma since 1997 and treated with carbimazole. Ultrasound showed a multinodular goiter with an autonomous nodule at the upper right thyroid lobe. The nodule's autonomous nature was confirmed by scintigraphy.

Results
Due to an exacerbation of hyperthyroidism, dosimetry-based radioiodine therapy was performed (367 MBq). Three months later, the patient presented persistent hyperthyroidism with symptomatic tachycardia and tremor. Palpation showed diffuse goiter, without palpable nodules. Ultrasound confirmed a multinodular goiter with marked heterogeneity typical of autoimmunity, and with increased vascularization, except in the area of the previously treated nodule. Antibodies against the TSH receptor, which were previously negative, were now positive. Scintigraphy showed diffusely increased uptake, except in area of the previously treated nodule. The constellation of a typical ultrasound pattern, positive anti-TSHR antibodies and diffuse autonomy on scintigraphy confirmed the diagnosis of new-onset Graves' disease which occured 3 months after radioiodine therapy. Carbimazole was restarted with subsequent clinical and biochemical improvement

Conclusion
The clinician should be aware that, on rare occasions, persistent hyperthyroidism after radioiodine treatment for toxic thyroid nodules may be due to new-onset Grave's disease rather than incomplete ablation of the autonomous nodules.

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Chronic care management program for diabetes mellitus typ 2 in primary care: Quality of disease management

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Background/Introduction
There is an increasing number of diabetic patients requiring continous medical care. On the other hand, there is a shortage of primary care physicians. In addition, adherence of primary care physicians to medical standards in patients with type 2 diabetes (T2D) care in Switzerland is low. Partial or nonadherence to guidelines has a negative impact on all-cause mortality and is associated with an increased risk of future hospitalization.
An approach to solve this issue is a guideline-based interprofessional chronic care management (CCM) program. Teams of medical doctors and coaches (specially trained medical assistants) work together in a structured manner to implement medical standards in daily practice.

Methods
We performed a retrospective analysis (2014-2016) of the patient cohort of twelve Swiss primary health care group practices offering interprofessional CCM programs to patients with advanced T2D alone or in combination with arterial hypertension. Performance measures were based on the score for disease-management for diabetes mellitus ("good clinical practice") of the Swiss Society of Endocrinology and Diabetology (SGED/SSED). This score includes eight items (regular visits, life style counselling with regard to nutrition, physical activity and smoking cessation, regular assessment of HbA1c (at least 3/year) and LDL-cholesterol (LDL-C; at least 1/year), control of blood pressure (BP) and evaluation of possible complications (1/year; microalbuminuria, ophthalmological control and control of feet). A mean score of 75 (out of 100) of all patients with T2D per primary health care structure is considered as good clinical practice.

Results
A total of 235 patients with T2D were enrolled (age 66.3±10.8 years, 41% female, 59% male). At the inclusion in the CCM program BMI was 31.7±5.2 kg/m2, LDL-C 2.7± 1.1 mmol/L, BP 142/82±19/12 mmHg, HbA1c 7.2± 1.3%. Only 1/4 of patients was physically active. At the end of the investigated period body weight decreased by 2.3 kg and 1/3 patient was physically active. LDL-C decreased by 0.1± 0.8 mmol/L, BP 6/4± 21/10 mmHg, HbA1c by 0.5± 1.3%. The treatment according to the CCM program fulfilled the criteria for good disease management according to the SGED/SSED score with the achievement of 85/100 points. All patients received the necessary physician consultations and lifestyle counselling by the coaches (concerning weight, physical activity, smoking cessation). The required percentage of patients achieved the therapeutic goals for glycaemic control and LDL-Cholesterol level, while the blood pressure goal was missed. The nephropathy status, the comprehensive foot evaluation and regular ophthalmologic visits were requested by the guidelines. No hospitalisations were reported.

Conclusion
• A structured program including an interprofessional team (CCM) is feasible in patients with T2D.

• The guideline based score for management of patients with T2D is useful in clinical practice.

• Treating patients with T2D according to an interprofessional CCM program is promising to face the lack of primary care physicians and to facilitate adherence to guidelines.

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Seasonality of profound hyponatremia in the medical emergency department

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Background:
Hyponatremia is the most common electrolyte disturbance in hospitalised patients. Several risk factors precipitating hyponatremia are known, e.g. comorbidities such as heart failure, liver cirrhosis or the use of diuretics. Little is known about seasonal variation and the frequency of hyponatremia. The aim of this study was to analyse the occurrence of profound hyponatremia throughout the year.

Methods
In this prospective observational study we included all consecutive patients with profound hyponatremia (<125mmol/L) admitted to the medical emergency department of two tertiary care centres between June 2011 and October 2013. Seasonal variations and the aetiology of hyponatremia in all patients was compared between summer (June, July, August) and winter months (December, January and February).

Results:
277 patients (median age 72 years, IQR 61-80, 65% were female) were included in the analysis. 91 patients were hospitalised during summer months, and 60 patients during winter months (p=0.09). Hyponatremia occurred most frequently in July with 33 cases, and least frequently in December with 18 cases respectively. During the summer months, SIADH, diuretic-induced hyponatremia and primary polydipsia occurred more frequently, other aetiologies of hyponatremia were distributed evenly between the summer and winter months. Overall quantities of fluid intake increased during the summer months compared to the winter months (mean volume of fluid intake in summer vs winter: 2000ml vs 1500ml). Patients with primary polydipsia drank on average 2750ml, patients with SIADH and diuretic-induced hyponatremia 1500ml respectively.

Conclusion:
Profound hyponatremia occurs most commonly in the summer months. A possible explanation may be an excess in free water during summer months due to increased fluid intake in patients with primary polydipsia and SIADH, and solute loss in diuretic-induced dehydration common in old age.

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Characteristics, Comorbidities, and Outcomes in Acromegalic Patients Treated at a Swiss Tertiary Referral Center

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Background/Introduction
Up to 10% of adults (depending on the detection method) have an pituitary adenoma. If it's a homone sectretory tumor with increased growth hormone secretion, secondary stimulating production of Insulin-like growth factor 1 (IGF-1) in the liver, this can lead to systemic complications and somatic disfigurement collected in the diagnosis acromegaly. The aim of this study was to gain an insight into the characteristics, treatment modalities and comorbidities in patients with acromegaly referred to the Kantonsspital Aarau.

Methods
Data of patients who were either operated at the Department of Neurosurgery or referred to the Department of Endocrinology in the Kantonsspital Aarau between 2006 and 2016 were entered in a multicentric registry, initiated by the Kantonsspital Aarau (SwissPit) and thereby analyzed. 21 patients with acromegaly were retrospectively screened to be included in the study. The diagnosis of acromegaly was indicated by laboratory results and further validated by neuroradiological findings. Remission was defined as normalization of IGF-1 and normal random human growth hormone (hGH) levels.

Results
The most prevalent symptoms present at diagnosis were acral enlargement (n=17, 81%), headaches (n=6, 29%), macroglossia (n=6, 29%) and visual field defects (n=4, 19%), while the most prevalent comorbidities were arterial hypertension (n=14, 67%), carpal tunnel syndrome (n=8, 38%), obesity (n=7, 33%) and diabetes mellitus type 2 (n=5, 24%). The mean age was 48.9 years (14.9 SD), the median initial IGF-1 level was 440 µg/L (IQR: 101-639) and the median initial hGH-level was 25.7 µg/L (IQR: 6.34-34.85). Out of the 19 (90%) patients that received initial surgical treatment, 5 (26%) remained uncontrolled, 6 (32%) went into remission with ongoing medical treatment, and 8 (42%) went into complete remission without ongoing medical treatment. Invasion of the cavernous sinus (Knosp grade 3 and 4) was a significant predictor for non-curative surgery (p=0.01).

Conclusion
Successful management of acromegaly goes beyond treatment of the disease itself and includes careful screening for commonly associated comorbidities. Remission after surgery is strongly dependent of invasive tumor growth and in case of disease persistence a multimodal approach using drug and radiotherapy is mandatory.

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Denosumab disguises the true cause of severe and sustained hypophosphatemia in a patient with advanced prostate cancer

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Background/Introduction
Concurrent hypophosphatemia and hypocalcemia are well known adverse events in treatment with denosumab, which is widely used in metastatic bone disease. Fibroblast growth factor 23 (FGF23) mediated tumor induced osteomalacia (TIO) is a rare paraneoplastic syndrome, leading to severe hypophosphatemia. Here, we present a patient with advanced prostate cancer, who developed hypocalcemia and severe, sustained hypophosphatemia after initiation of denosumab therapy, primarily masking the cause of phosphate wasting, which in particular was due to FGF23 induced TIO.

Case Report
A 79-year old man with bone and lymph node metastases from castration-resistant prostate cancer (mCRPC) presented with severe hypophosphatemia (0.2mmol/L, normal range 0.8-1.5mmol/L) and hypocalcemia (1.5mmol/L, normal range 2.2-2.6mmol/L). Treatment with abiraterone/prednisone and denosumab had been initiated three weeks earlier. Laboratory studies revealed normal renal function, elevated parathyroid hormone (PTH) and normal levels of 25-OH and 1,25-(OH)2 vitamin D3 under oral calcium and vitamin D3 supplementation. Inadequately high renal phosphate excretion without additional urinary electrolyte wasting was detected (phosphate excretion fraction: 24%). Treatment with high parenteral doses of calcium, phosphate, oral 25-OH and 1,25-(OH)2 vitamin D3 normalized serum calcium- and PTH levels within one month. However, severe hypophosphatemia due to urinary phosphate loss persisted despite high doses of phosphate supplementation (6.9g/d). Additional work-up revealed a distinct elevated serum level of FGF23 (4 times above upper limit of normal). Phosphate and calcitriol supplementation was continued until the patient died from progressive prostate cancer 13 months later.

Conclusion
Denosumab induced hypophosphatemia and –calcemia or abiraterone induced fanconi-like syndrome was initially suspected in this patient with mCRPC. FGF23 induced hypophosphatemia is an uncommon but potentially life-threatening paraneoplastic syndrome most commonly found in mesenchymal tumors. TIO in mCRPC is rare but may be underdiagnosed and should be considered in severe and sustained hypophosphatemia. Although clinical studies are lacking, several lines of evidence suggest that TIO may be associated with aggressive mCRPC behavior. FGF23 excess and severe hypophosphatemia per se may both contribute to a poor prognosis in affected patients. FGF23 receptor inhibitor treatment is under preclinical/clinical development and may be an approach to control TIO and the underlying malignant disease in the future.

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Nasal Glucagon for the Treatment of Moderate-to-Severe Hypoglycemic Episodes in Real-world Settings in Adults with Type 1 Diabetes

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Background/Introduction:
This study evaluated nasal glucagon (NG) for effectiveness and ease-of-use in moderate or severe hypoglycemic episodes (HEs) in real-world settings in adult patients (pts) with type 1 diabetes (T1D).

Methods:
Pts and caregivers (CGs) were taught to administer NG 3 mg for symptomatic HE and to assess for return to normal status over time. In addition, HE symptoms, blood glucose (BG), adverse events (AEs), and ease-of-use were evaluated through questionnaire.

Results:
In the efficacy population (EP), 69 pts (100%) experienced a total of 157 HEs (mean [SD], 2.3 [1.77] events/pt). In 96.2% of HEs, pts met the primary objective, return to normal status within 30 minutes of NG dosing. There were 6 HEs in which the recovery did not occur within 30 minutes. In 5 of these 6 events, pts recovered within 30 to 45 minutes and in 4 events, BG was ≥70 mg/dL at 30 minutes. Mean BG at HE onset was 47.9 (range 21.6 to 73.9) mg/dL and rose to 84.4 (range 39.6 to 153.2) mg/dL by 30 minutes. BG continued to rise over time and no emergency service calls were made. Twelve severe HEs in 7 pts were observed in the EP. All severe HEs resolved and pts awoke or returned to normal status within 15 minutes. NG administration time was <30 seconds for most HEs (70.4%) and was <2 minutes in nearly all (97.7%) HEs. The safety population included 74 pts who had a total of 179 HEs. At least 1 AE was experienced by 87.8% of pts, with the most common being nasal irritation (82.4%) and headache (54.1%). Most AEs during HEs lasted ≤1 hour (59.5%) and were of low or moderate severity. There were no serious drug-related AEs and CGs were satisfied or very satisfied with NG after most HEs (82.7%).

Conclusions:
NG showed real world effectiveness when administered to treat moderate or severe HE in pts with T1D. Nearly all pts recovered within 30 minutes and there were no emergency calls. The majority of CGs were highly satisfied with NG. Data suggest that NG is a viable alternative to currently available injectable recombinant glucagons.

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Title: Comparison of Six 4th Generation TSH-Receptor Antibodies for their ability to predict Relapse of Graves' disease Results from an observational study

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Background:
Despite the use of antithyroid drugs in patients with Graves' disease, risk of relapse remains high. Early prediction of relapse may improve initial patient management. Herein, we assessed six different TSH-receptor antibody [TRAb] tests for their ability to predict relapse of Graves' disease and compared them to the clinical GREAT [Graves' Recurrent Events After Therapy] score.

Objective:
To analyze four new TRAb tests, and two new cAMP bioassays in their utility in predicting relapse in GD at beginning of ATD treatment.

Design, Setting and Participants:
We retrospectively analyzed data of patients with their first episode of Graves' hyperthyroidism from a Swiss hospital based endocrine referral center and an endocrine private practice. We used multivariate Cox regression to study associations of TRAb levels with relapse risk and calculated area under the receiver operating characteristics curve [AUC] to assess discrimination.

Main Outcome Measures:
Relapse of hyperthyroidism.

Results:
Overall, 19 of 96 (19.8%) subjects experienced a relapse after a mean follow-up time of 25.6 ± 26.1 months after ATD withdrawal. In Cox regression, significant associations comparing the highest quartile versus the lower three quartiles showed the highest hazard ratio [HR] for TSH-R BRAHMS (2.98, 95% CI 1.13 - 7.84), TSI Siemens (2.40, 95% CI 0.91 - 6.35), TSH-R Phadia (2.05, 95% CI 0.82 - 5.10), Fast TRAb (1.80, 95% CI 0.73 - 4.43), followed by INHIBITION (0.88, 95% CI 0.25 - 3.12) and STIMULATION (1.18, 95% CI 0.46 - 2.99). Discrimination analyses showed AUCs of 0.68 for TSH-R BRAHMS KRYPTOR, 0.65 for TSI Siemens IMMULITE, 0.64 for TSH-R Phadia, 0.64 for Fast TRAb DSX, 0.49 for TSAb/TBAb INHIBITION, and 0.59 for TSAb/TBAb STIMULATION. Compared with the 0.67 of the GREAT score itself.

Conclusions:
TRAb levels are associated with relapse risk in Graves' disease with differences among the different commercially available tests and best results for the more specific stimulatory TRAb assays.

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"An iron hard tumefaction of the thyroid" - a case report

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Background/Introduction:
Riedel's thyroiditis is a rare disease with an incidence of 1/100.000. Women are four times more likely than men to be affected. The aetiology of Riedel's thyroiditis is unknown. Autoimmun mechanisms are discussed, and an association with systemic fibrosis (e.g. retroperitoneal fibrosis) and IgG4 related systemic diseases is descriped.

Methods:
Case report

Results:
We report a case of an otherwise healthy 59-year-old woman who presented with a bilateral " iron hard tumefaction of the thyroid" as Riedel described it 1896. The patient complained a growing goiter with anterior neck pressure, dysphagia and hoarseness. Clinical examination showed a firm, bilateral, painless goiter. Thyroid ultrasound showed a massive enlarged thyroid gland with tracheal compression. Repeated fine needle aspiration was non-diagnostic. Therefore open biopsy was performed. Histology showed unspecific fibrosis, no definitive diagnosis could be made, not even after repeating an extended biopsy. Extended clinical and laboratory examination showed no sign of systemic fibrosis, autoimmune diseases or IgG4 associated diseases. There were neither any signs of malignant disease. Because of progressive compression symptoms a glucocorticoid therapy was initiated. Soon after initiation of high dose glucocoticoid therapy, the thyroid turned softer and compression symptoms disappeared. After several weeks (glucocortcoids were tapered), the thyroid volume decreased by about one third. Despite missing histological confirmation Riedel thyroiditis remained the most likely diagnosis in this patient.

Conclusion:
Diagnosis of riedel's thyroiditis is challenging, and the clinical presentation and examination remains an important diagnostic cornerstone. Biopsy is mandatory to exclude a malignoma (i.e. anaplastic carcinoma). In this case no definitive histological confirmation of the diagnosis could be made, however glucocorticoid treatment proved to be very effective.

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Decrease of sDLK1/FA1/Pref-1 and sKlotho in patients with acromegaly following pituitary surgery

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Background/Introduction
Klotho was identified as a lifespan-influencing gene in mice. The transmembrane protein Klotho is predominantly expressed in the kidneys, parathyroids, and choroid plexus. An ectodomain-clipped, soluble form (sKlotho) circulates in the blood. In patients with acromegaly, serum sKlotho is increased in relation to excessive growth hormone (GH) and decreases after surgery, to a similar extent as insulin-like growth factor (IGF-1).
DLK1 (Delta-like 1 homolog) was identified simultaneously by three independent groups, and is also known as FA1 (fetal antigen 1) or Pref-1 (preadipocyte factor 1). The transmembrane protein DLK1 is expressed in the adult adrenal gland, pancreatic islets, pituitary, placenta, and preadipocytes. Soluble DLK1 (sDLK1), like sKlotho, arises by enzymatic ectodomain clipping. It inhibits adipocyte differentiation and may be involved in the antiadipogenic actions of GH. Indeed, the inhibitory effects of GH on adipocyte differentiation were mimicked and suggested to be mediated by DLK1 in vitro.

Methods
Levels of GH, IGF-1 (RIA), sKlotho and sDLK1 (both by ELISA) were measured in 35 treatment-naïve acromegalic patients (16 females/19 males), before and 1-3 months after transsphenoidal surgery.

Results
Surgery resulted in declining GH values in all patients; 25 of them achieved a GH nadir of <1 µg/l on oral glucose tolerance testing. Likewise, IGF-1 and sKlotho decreased in all patients (from median 607 [IQR 444-733] to 187 [IQR 128-271] ng/ml, and 4.0 [IQR 2.7-6.7] to 0.7 [IQR 0.5-1.2] ng/ml, respectively, p<0.0001). sDLK1 levels fell in 33 of the 35 subjects (from median 9.4 [IQR 5.6-14.0] to 7.1 [IQR 3.6-10.1] ng/ml, p<0.0001).

Conclusion
There was a massive decrease of sKlotho and a less pronounced decline of sDLK1 after removal of the GH-producing adenoma in our acromegalic patients. Enhanced enzymatic shedding of sKlotho and sDLK1 under the influence of excessive GH in selected target tissues may account for these findings. Declining GH levels after surgery with subsiding enzymatic clipping may explain the clinical observation of increasing fat mass.

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Constant growth to bilateral giant adrenal myelolipoma despite normal ACTH levels in congenital adrenal hyperplasia. A case report.

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Background/Introduction
Myelolipomas are circumscribed benign masses composed of mature fat and bone marrow elements. Myelolipomas are frequently found among patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Several case reports and small case series suggested that their growth is stimulated by chronic exposure to high levels of ACTH, most commonly associated with low adherence to glucocorticoid replacement therapy.

Methods
We describe the clinical presentation, imaging and intraoperative findings of a patient with giant bilateral myelolipomas in congenital 21-hydroxylase deficiency.

Case Report
The 21-hydroxylase deficiency of this 43-year old man had been detected at birth and he was treated with hydrocortisone, prednisone and fludrocortisone ever since. As long as the patient remembers he was treated with supraphysiologic glucocorticoid doses. Accordingly, our records of the last 10 years show ACTH levels constantly within the lower reference range. Despite normal ACTH levels, the right-sided adrenal mass continuously grew from 13 cm 6 years ago to 26 cm and became increasingly symptomatic. In addition, multiple lumps myelolipomas developed on his arms and thorax wall. Given abdominal discomfort and complete adrenal function loss, an interdisciplinary decision was made to resect both adrenal glands. Intraoperative findings were consistent with preoperative imaging, both sides (26 cm right, 15 cm left side) were histologically confirmed to be myelolipomas. The patient recovered well and left hospital after 5 days.

Conclusion
Growth of myelolipomas in congenital adrenal hyperplasia due to 21-hydroxylase deficiency is not necessarily mediated through chronically elevated ACTH levels, other reasons have to be considered.

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Ketoacidosis – when a 72h-fast ends on a sour note…

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Background/Introduction
Ketonemia is a normal physiologic reaction to a prolonged fast. In cases of increased glucose re-quirements (e.g. in pregnancy or due to lactation) this can evolve into a ketoacidosis.

Methods
A 32-year-old woman presented to our outpatient clinic with a three-year history of hypoglycemic symptoms. She described several episodes with neuroglycopenic symptoms (apathy, confusion and possible focal seizures/neurologic deficits). Symptoms occurred mainly postprandial but morn-ing/fasting symptoms were also present. Her medical history was uneventful except for a possible biliary cirrhosis, which remained without further investigation. She took no medications and denied the use of any hypoglycemic agents and the abuse of ethanol and/or drugs. Clinical examination showed a normotensive patient with no signs of Addison's disease or liver cirrhosis. Adrenal insuffi-ciency, autoimmune insulin syndrome and liver/renal insufficiency were excluded by laboratory testing.

Owing to the mainly postprandial symptoms, functional testing started with a mixed meal tolerance test which was normal. Due to the severity of symptoms, the patient then was admitted for a 72h-fasting test. The patient wished to continue breast-feeding her eight-month-old younger son. After 62 hours plasma glucose reached a minimum of 2.9 mmol/l and blood gas analysis found a con-comitant metabolic acidosis with increased anion gap (pH 7.28, base excess - 10.90 mmol/l, anion gap 21.1 mmol/l). Lactate levels, acylcarnitine profile and determination of urine organic acids were normal. However, there was a 40-fold elevation of beta-hydroxybutyrate in the serum. During the test the patient remained completely asymptomatic with no symptoms/signs of neuroglyocopenia or acidosis. Acidosis resolved quickly after stopping the fasting test.

Results & Conclusion
Glucose and ketone bodies are essential for energy metabolism in fasting periods. Normally a bal-anced homeostasis leads to fasting ketosis without acidosis. Glucose demands in lactating women are increased (up to 30%), this can lead to a quicker consumption of stored glucose, earlier release of larger amounts of ketone bodies and subsequent ketoacidosis. Therefore, a diagnostic 72h-fast in these situations should be performed only under tight control of blood pH for early detection of acidosis or postponed after termination of lactation.

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Pancreatic islet transplantation in the anterior chamber of the human eye – a pilot study

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Background/Introduction
Recent studies, which explored the anterior chamber of the eye as an islet transplantation site to correct hyperglycemia in rodent and non-human primates have demonstrated the feasibility of islet transplantation into the anterior chamber of the eye and its efficacy in restoring or improving glycemic control. In this study, we aim to demonstrate the feasibility of islet cell transplantation in the human eye, which would bring numerous advantages in islet cell transplantation such as the simplicity of procedure, reduced bleeding risk, smaller required number of islets and availability of non-invasive monitoring and asseessment of islet grafts.

Methods
About 40'000 freshly prepared and isolated allogenic human islets (95% purity in 200 microliter) were transplanted into the anterior chamber of a legally blind eye of a c-peptide negative diabetic patient with ongoing immunosuppression as a kidney transplant recipient. Follow up visits over 3 months with regular clinical examination of the eye as well as measurements of insulin, c-peptide and blood sugar levels were performed.

Results
Intraocular pressure increased to up to 50 mm Hg the first night but normalized over the next weeks. Otherwise, no inflammation or other ophthalmic complications were found in the transplanted eye. 90 days post transplantation c-peptide levels were measurable in the peripheral blood after a mixed meal tolerance test.

Conclusion
Our results show that allogenic human pancreatic islet transplantation can be performed without causing damage in the anterior chamber or deteriorating the situation of the damaged parts of the eye and that transplanted islets could survive and be functional after 3 months.

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18F-Choline-PET-CT has the potential to predict a parathyromatosis as cause of recurrent hyperparathyroidism

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Background/Introduction:
Parathyromatosis is an extremely rare cause of recurrent primary hyperparathyroidism (pHPT) consisting of multiple micro- and macroscopic foci of benign autonomous parathyroid tissue. It is caused by the rupture of an adenoma during first-time surgery leading to a spread of fragmented hyperfunctioning parathyroid tissue in the surgical field. As the autonomous foci grow with time, biochemically or clinically manifest recurrent pHPT will develop.
18F-Choline PET-CT is a new imaging modality for the localization of pathological parathyroid glands in pHPT which according to preliminary reports seems to be more sensitive that the widely used (99m)Tc-sestamibi-scintigraphy.

Methods:

Results:
We report on a 70 years old patients referred to us for reexploration in recurrent pHPT 20 years after initial surgery. According to the operating report a posteriorly descended adenoma of the superior right parathyroid had been removed without mentioning any surgical problems.
In order to localize preoperatively the actual source of the parathyroid autonomy we had 18F-Choline-PET-CT performed showing a dominant focus possibly corresponding to the right inferior parathyroid gland and some more and smaller foci surrounding it.
Intraoperatively we found a normal inferior parathyroid and multiple dispersed “micro-adenomas” from 0.5 to 10mm in size consistent with a parathyromatosis. The biggest “micro-adenomas” corresponded perfectly with the foci described in the 18F-Choline-PET-CT preoperatively.

Conclusion:
In reoperative pHPT-surgery the preoperative localisation of the pathological parathyroid gland is essential to enable a targeted surgical approach. The fact that 18F-Choline-PET-CT was even able to detect minimal amounts of autonomous parathyroid tissue in a case of a parathyromatosis confirms the most promising results of 18F-Choline-PET-CT in detecting pathological parathyroid glands in recent literature and therefore should be recommended in every case of persistent or recurrent pHPT.

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Comparable Glycemic Control, Greater Weight Loss, and Lower Hypoglycemia with Once Weekly Dulaglutide versus Insulin Glargine, Both Combined with Lispro, in Type 2 Diabetes and Moderate to Severe Chronic Kidney Disease (AWARD-7)

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Background/Introduction
The objective was to demonstrate dulaglutide (DU) noninferiority for HbA1c change after 26 weeks.

Methods
This phase 3 study compared once weekly DU to titrated daily insulin glargine, both combined with insulin lispro, in people with type 2 diabetes (T2D) and chronic kidney disease (CKD) stages 3-4. Participants were randomized (1:1:1) to DU 1.5 mg or DU 0.75 mg or titrated insulin glargine.

Results
Baseline characteristics (N=576) included: [mean±SD] age 64.6±8.6 years, HbA1c 8.6±1.0%, eGFR 38.3±12.8 mL/min/1.73m2, BMI 32.5±5.2 kg/m2, daily insulin dose 58.2±31.8 U. DU was non-inferior to insulin glargine for HbA1c change (table). Body weight decreased with DU, whereas it increased with insulin glargine. The hypoglycemia rate (≤70 mg/dL) was lower for DU 1.5 mg and 0.75 mg vs insulin glargine (5.5, 7.8 and 17.1 events/participant/year; p<0.001). Nausea, vomiting and diarrhea were more common with DU 1.5 mg (19.8%, 12.0%, 15.6%) and DU 0.75 mg (11.1%, 5.8%, 13.7%) vs insulin glargine (2.6%, 3.1%, 3.1%).

Conclusion
DU produced comparable glycemic control, greater weight loss, and lower hypoglycemia rate vs insulin glargine in people with T2D and CKD stage 3-4.

Primary Endpoint (26 wk, mITT population (safety population for weight))	DU 1.5 mg (N=183)	DU 0.75 mg (N=180)	Insulin Glargine (N=186)
HbA1c change, %(primary)	-1.2(0.1)††***	-1.1(0.1)†***	-1.1(0.1)**
Percentage of pt with HbA1c<7%/HbA1c<8% Weight change, kg	37.5 / 78.3 -2.8 (0.4)$^{**\#\#}$	31.7 / 72.6 -2.0 (0.4)$^{**\#\#}$	34.6 / 75.3 1.1 (0.3)*

Data are reported as LSM (SE) unless otherwise indicated; †, †† multiplicity adjusted 1-sided p<0.001 for noninferiority versus insulin glargine with a 0.4% margin or 0.3% margin, respectively, *2-sided p<0.05 and **2—sided p<0.001 change from baseline, $^{\#\#}$2-sided p<0.001 versus insulin glargine. Abbreviations: BMI=body mass index; CI=confidence interval; eGFR=estimated glomerular filtration rate (CKD-EPI creatinine equation); mITT=modified intent-to-treat; LSM=least squares mean; SE = standard error; pt =participant(s)

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Dulaglutide versus Glargine, Both Combined with Lispro, Mitigated eGFR Decline in People with Type 2 Diabetes and Moderate to Severe Chronic Kidney Disease (AWARD-7)

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Background/Introduction
In short-term studies, dulaglutide (DU) reduced albuminuria and did not change estimated glomerular filtration rate (eGFR) in people with type 2 diabetes (T2D) and normal kidney function.

Methods
This phase 3 study compared weekly DU 1.5 mg or 0.75 mg to daily titrated insulin glargine (IG), both combined with insulin lispro, in people with chronic kidney disease (CKD) stages 3-4 and T2D. The study met its primary objective of DU noninferiority to IG in HbA1c reduction at 26 weeks. This pre-specified secondary analysis was designed to determine effects of DU on eGFR and albuminuria.

Results
Baseline characteristics (N=576) included: [mean±SD] age 64.6±8.6 years, HbA1c 8.6±1.0%, Baseline characteristics were similar between treatment groups [mean±SD] eGFR (CKD-EPI): 38.3±12.8 mL/min/1.73m2, HbA1c: 8.6±1.0%, age: 64.6±8.6 years, duration of T2D: 18.1±8.7 years, 30% (n=174/576) had eGFR <30 mL/min/1.73m2, 45% (n=258/575) had urine albumin-to-creatinine ratio (UACR) >300 mg/g. At 26 weeks, eGFR remained stable with DU, but significantly decreased with IG (table). UACR was lowered in all treatment groups. Results were driven by participants with UACR >300 mg/g who had less decline in eGFR with both DU doses and greater reduction in UACR with DU 1.5 mg.

Conclusion
DU mitigated eGFR decline in people with T2D and moderate to severe CKD. The DU effect to lessen loss of kidney function and reduce albuminuria was most evident in people with UACR >300 mg/g.

Treatment arm	All Participants (N=576)		Participants with UACR >300 mg/g (n=258)		Participants with UACR ≤300 mg/g (n=317)	
	Δ eGFR, mL/min/1.73m^2	Δ UACR, %	Δ eGFR, mL/min/1.73 m^2	Δ UACR, %	Δ eGFR, mL/min/1.73m^2	Δ UACR, %
DU 1.5 mg (N=192)	-0.1$^{\#}$ (-1.2, 1.0)	-27.7** (-38.7, -14.8)	-1.9$^{*\#}$ (-3.5, -0.4)	-43.1$^{**\#}$ (-54.7, -28.6)	0.3 (-1.0, 1.7)	-0.4 (-19.2, 22.8)
DU 0.75 mg (N=190)	-0.4$^{\#}$ (-1.4, 0.7)	-26.7** (-37.9, -13.5)	-2.6$^{**\#}$ (-4.2, -1.1)	-25.3* (-40.2, -6.8)	0.3 (-1.0, 1.7)	-18.0 (-33.6, 1.3)
Glargine (N=194)	-1.9** (-3.0, -0.9)	-16.4* (-29.0, -1.5)	-4.8** (-6.3, -3.4)	-14.3 (-30.9, 6.3)	-0.7 (-2.0, 0.7)	-5.7 (-23.2, 15.8)

Data presented as change from baseline LSM (95% CI); safety population. *2-sided p<0.05 and **2-sided p<0.001 change from baseline; $^{\#}$2-sided p<0.05 versus insulin glargine. Abbreviations: CI=confidence interval; DU=dulaglutide; eGFR=estimated glomerular filtration rate; IG=insulin glargine; LSM=least squares mean; UACR=urine albumin/creatinine ratio

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Clinical presentation of 54 Patients with Endogenous Hyperinsulinemic Hypoglycaemia: A Neurological Chameleon

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Background/Introduction
Important causes of endogenous hyperinsulinemic hypoglycaemia (EHH) in adult patients are benign insulinoma (+/- genetic context) and nesidioblastosis. Data on leading symptoms in EHH are scarce and controversial. Similarly, data on biochemical cut-offs for the diagnosis of EHH is debated. We, therefore, analysed leading symptoms and the biochemical work-up of 54 patients with EHH. This analysis is part of a prospective trial which investigated GLP-1 receptor imaging in EHH.

Methods
Inclusion criteria were biochemically proven EHH with hypoglycemic symptoms. Demo-graphic characteristics and aetiologies of the patients with EHH were retrieved. Leading symptoms were categorized into unspecific (weight gain, headaches, gastrointestinal, fatigue-malaise-vertigo-weakness), sympathicoadrenal (sweating, tremor, palpitation, hunger, shivering and pallor) and neurological symptoms. The latter were subdivided in moderately (confusion, dizziness, disorientation, somnolence, delirium) or severely) impaired consciousness (loss of consciousness and apathy), visual, speech and sensomotor impairment, attention deficit, seizure and personality change. Biochemical assessment and duration of EHH at the end of a fasting test was recorded.

Results
Fifty-four patients with full documentation were included in the analysis (74% female and 26% male; 53.6±15.1, years, mean age, ± SD). Thirty-seven (68.5%) of the patients had a single Insulinoma, 3 (5.6%) patients multiple Insulinomas (MEN-1) and 5 (9.3%) patients had nesidioblastosis. Nine (16.7%) patients manifested laboratory findings for an EHH without a clear histological diagnosis. The interval from onset of symptoms to diagnosis of EHH was 23.2±25.2 months. Fifty (92.6%) patients had neurological symptoms, these included moderately impaired consciousness in 44.4%, severely impaired consciousness in 37%, visual, speech and sensomotor function impairment (44.4%), disturbance of attention (29.9%), seizure (16.7%) and personality change (13%). More than half of these patients (53%) presented with >2 neurological symptoms. Sympathicoadrenal symptoms were present in 33 (61.1%) patients. Weight gain was reported in 21 (38.9%) patients. Unspecific symptoms occurred in 32 (59.3%) patients. Plasma glucose values at the end of the fasting test were 2.0±0.4 mmol; insulin 11.65±42.2 mU/l (IQR 14.33) and C-Peptide 875.5+587.7 pmol/l. Fasting test lasted for 23.7±18 h.

Conclusion
• A wide variety of different neurological symptoms (“chameleon”) are characteristic for patients with EHH

• Sympathicoadrenal symptoms and weight gain are less frequent than reported in the literature

• Demographic findings (female preponderance, mean age, genetic context) are consistent with the literature.

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Despite a high prevalence of osteoporosis elderly women after differentiated thyroid carcinoma on long-term thyrotropin-suppressive therapy lacked lower bone mineral density than age-matched controls

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Background/Introduction
Patients with differentiated thyroid carcinoma (DTC) are commonly treated with thyroxine-based long-term thyrotropin (TSH)-suppressive therapy resulting in a state of chronic subclinical hyperthyroidism. Reported effects of TSH-suppressive therapy on bone are inconsistent.

Methods
Case-control study of consecutive women (>65 years) with DTC under current long-term (>3 years) TSH-suppressive therapy followed at the University Hospital of Berne, Switzerland, (cases) and age-matched healthy women from a representative age-matched population sample (controls). BMD was measured at lumbar spine, hip, radius and tibia by Dual Energy X-ray Absorptiometry (Hologic Discovery). Vertebral fracture assessment (VFA) was performed and the individual history of previous clinical fragility fractures collected. Fractures were categorized into major osteoporotic fractures (hip, spine, distal radius, and proximal humerus) and non-MOF. Significances were assessed by Mann-Whitney U-test.

Results
Of 61 cases identified, 39 could be matched with controls. Mean (± SD) age was 76±4 vs. 75±4 years, respectively. Mean duration of TSH-suppression was 7.1±3.4 years. Mean BMD T-scores at all measurement sites were not significantly different between cases and controls. The prevalence of densitometric defined osteoporosis did not differ (40 % of the cases and 43 % of the controls). Similarly, the prevalence of morphometric vertebral fractures assessed by VFA, MOF, and non-MOF were not significantly different between groups.

Conclusion
In elderly women with DTC under long-term TSH-suppressive therapy, BMD T-scores at major skeletal sites and fragility fracture prevalence were not significantly different from those in age-matched healthy controls.

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Copeptin values after arginine infusion: a new test in the differential diagnosis of diabetes insipidus?

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Background/Introduction:
To discriminate between diabetes insipidus (DI) and its differential diagnosis primary polydipsia (PP) is important as treatment differs considerably. Available diagnostic test methods are cumbersome and often misleading. Herein we hypothesized that copeptin measurements (the C-terminal segment of the arginine vasopressin precursor peptide) after arginine infusion provide a new diagnostic approach in the differential diagnosis of DI.

Methods:
Patients with known central DI or PP and healthy controls (adults and children) were included in this prospective observational study. Participants underwent an arginine infusion at a dose of 0.5g/kg bodyweight and measurements of copeptin values at 0, 30, 45, 90 and 120 minutes after arginine infusion. The primary endpoint was the diagnostic accuracy of copeptin values at each measurement after arginine infusion.

Results:
30 (58%) of 52 patients had PP, 12 (23%) complete DI and 10 (19%) partial DI.
Copeptin values after arginine infusion increased in patients with PP and to a lower extent in patients with partial DI whereas no increase was seen for patients with complete DI. The highest accuracy [95% CI] with 0.904 [0.794, 0.961] to discriminate between patients with DI or PP was observed for copeptin values at 60 minutes after arginine infusion, using a cut-off of 3.5 pM/L (sensitivity 86.4%, specificity 96.7%). In healthy adults (n=20) and children (n= 42) median [IQR] copeptin levels increased significantly during arginine infusion from 3.6 pM/L [2.4, 6.9] to 7.3 pM/ L [4.3, 9.1] and 4.4 pM/L [3.2, 6.2] to 6.1pM/L [4.7, 8.2]), respectively.

Conclusion:
Arginine infusion is a potent stimulus of the neurohypophysis. Copeptin values after arginine infusion discriminate patients with central DI versus PP with a high diagnostic accuracy.

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Glucagon-like peptide-1 (GLP-1) analogues modulate fluid intake in healthy volunteers

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Background:
GLP-1 analogues are well known to stimulate glucose-induced insulin secretion and reduce energy intake. Recent findings from animal and human studies suggest a role of GLP-1 in regulating water and salt homeostasis. The aim of this study was to elucidate whether GLP-1 analogues reduce fluid intake in healthy volunteers compared to placebo.

Methods:
In this double-blind, cross-over study dulaglutide (Trulicity®) 1.5 mg and placebo (0,9% sodium chloride) were given subcutaneously once weekly for three weeks in random order. At the end of each treatment period participants attended an evaluation visit from 8 a.m. to 4 p.m. at the study centre, where they were requested to eat two standardised salty meals (breakfast and lunch) and invited to drink mineral water ad libitum. During the observational period of 8 hours total fluid intake in ml was assessed as primary endpoint, as well as total urine output and serum sodium levels, thirst perception and nausea at 8 a.m.

Results:
20 healthy participants (mean age 27 years, 55% female) were included in the analysis. At both visits serum sodium level at 8 a.m. was 140 mmol/L, there was no difference in thirst perception (p=0.98) and none of the participants reported nausea. Despite the identical food/salt intake at both visits, median [IQR] total fluid intake was lower in subjects treated with dulaglutide compared to placebo: 1300ml [887-1600] versus 1600ml [1000-1725], p= 0.06. Similarly, median [IQR] urine output was reduced in dulaglutide versus placebo treated participants: 1250ml [975-2075] versus 1675ml [1400-2037], p=0.04.

Conclusion:
GLP-1 analogues such as dulaglutide not only modulate appetite and provide satiety but also reduce fluid intake in healthy volunteers. This is of interest in terms of future therapeutic options for patients with excessive thirst perception (e.g. patients with primary polydipsia).

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Levels of Long-acting Insulin Analogues during and after Exercise in Type 1 Diabetes

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Background/Introduction
The management of endurance exercise in individuals with type-1 diabetes (DM1) still remains challenging. Adaptation of insulin doses is suggested by guidelines to stabilize exercise-associated glycemia . However, there is currently little data on insulin kinetics in the context of exericse. This study aimed at analyzing the course of plasma levels of long-acting insulin analogues in the context of a cycling exercise.

Methods
Insulin levels before, during and 3 hours after a 90 minute cycling session at 50% of peak-oxygen consuption (VO2peak) were analyzed in well controlled individuals with DM1. Seven exercises were performed under insulin detemir, 3 under insulin glargin and 2 under insulin degludec, respectively. Basal insulin was injected into the thigh at the evening before exercise in patient using degludec and twice daily in individuals using glargin and detemir. Exercise was started at 12am, at least 5h after a standardized breakfast. Patients followed their usual insulin dosing regime and blood glucose was stabilized with carbohydrates as needed.

Results
Participant's mean age was 25.2±2.1 years, mean HbA1c was 7.0±0.3 % and diabetes duration was 14.2±3.7 years. Mean total daily insulin-dose was 0.84±0.06 U/kg and average basal insulin dose was 34.3±3.6 U per day. Insulin levels before, during and after exercise were 308.1±42.5 mU/l, 280.1±24.5 mU/l and 191.3±23.1 mU/l for insulin detemir (p= 0.041); 42.9±3.1 mU/l, 38.2±2.7mU/l and 21.2±3.3mU/l for insulin glargin (0.008); 94.5±7.3 mU/l, 89.0±3.4 mU/l and 85.4±12.0 mU/l for insulin degludec (p=0.77), respectively. This corresponds to an insulin-decline during exercise compared to pre-exercise of -9.1% for detemir, -10.9% for glargin and -5.8% for degludec, respectively (p= n.s.). The insulin-decline post-exercise compared to pre-exercise levels was -37.9% for detemir (p=0.033), -50.5% for glargin (p=0.007) and -9.6% for degludec (p=n.s.).

Conclusion
In this exploratory analysis encompassing a limited number of experiments in patients with DM1 we found a significant reduction of detemir and glargin but not of degludec 3 hours after a 90 minutes cycling-exercise compared to pre-exercise values. The course of insulin values during exercise was comparabel for all 3 insulins, speaking in favour of an alteration in pharmacokinetics of detemir and glargin subsequent to the exercise.

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Association of adrenal hormone metabolites and mortality over a 6-year follow-up in COPD patients with acute exacerbation

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Background/Introduction
The release of hormones from the adrenal gland is vital in acute and chronic illnesses such as chronic obstructive pulmonary disease (COPD) involving recurrent exacerbations. Using a metabolomic approach, we aim to investigate associations of different adrenal hormone metabolites with short- and long-term mortality in COPD patients.

Methods
We prospectively followed 172 COPD patients from a previous Swiss multicenter trial. At baseline, we measured levels of a comprehensive spectrum of adrenal hormone metabolites including glucocorticoid, mineralocorticoid and androgen hormones by liquid chromatography coupled with tandem mass spectrometry. We calculated Cox regression models adjusted for gender, age, comorbidities and previous corticosteroid therapy.

Results
Mortality was 6.4% after 30 days and increased to 61.6% after 6 years. Higher initial androgen hormones predicted lower long-term mortality with significant results for dehydroepiandrosterone (DHEA) (adjusted HR 0.82, 95% CI 0.70-0.98, p= 0.026) and dehydroepiandrosterone sulfate (DHEA-S) (adjusted HR 0.68, 95% CI 0.50-0.91, p=0.009). An activation of stress hormones (particularly cortisol and cortisone) showed a time-dependent effect with higher levels pointing towards higher mortality at short-term, but lower mortality at long-term. Activation of the mineralocorticoid axis tended to be associated with increased short-term mortality (adjusted HR of aldosterone: 2.76, 95% CI 0.79-9.65, p=0.111).

Conclusion
Independent of age, gender, corticosteroid exposure and exacerbation type, adrenal hormones are associated with mortality at short- and long-term in patients with COPD exacerbation with different time-dependent effects of glucocorticoids, androgens and mineralocorticoids. A better physiopathological understanding of the causality of these effects may have therapeutic implications.

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Imatinib Exerts Immune-Modulatory Effects on Pro-Inflammatory Macrophages in Metabolic Disease

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Background/ Introduction:
Insulin resistance in metabolic disease is linked to high prevalence of pro-inflammatory macrophages. One option to improve insulin resistance is to therapeutically dampen the activation of such pro-inflammatory macrophages. Imatinib (IM), which is a chronic myeloid leukemia drug, has been shown to improve glycemia and adipose tissue inflammation. Thus, the aim of our study was to assess whether IM exerts direct immune-modulatory effects on macrophages in metabolic disease, thereby potentially improving glycemic control.

Methods:
Murine macrophages were isolated, *in vitro* activated to a pro-inflammatory (M1) phenotype (by LPS/ IFNγ) and treated with or without IM (1μM). To assess IM's effect on insulin resistance and macrophages *in vivo*, obese (HFD) and diabetic (HFD and streptozocin 180mg/kg i.p.) mice were treated with oral IM (100mg/kg) or water. To translate our findings to human metabolic disease, human monocytes were isolated from lean donors (BMI 18-25 kg/m^2), adequately (aDM; HbA1c 7.0%) and inadequately (iaDM; HbA1c>12%) controlled diabetics, activated (by LPS/ IFNγ) and treated with IM. Macrophage activation was assessed by gene and protein expression of pro-inflammatory markers.

Results:
In vitro, imatinib reduced pro-inflammatory gene and protein expression in M1-activated macrophages (both TNFα and IL-6 p<0.01). *In vivo*, IM-treated mice showed improved insulin sensitivity, while glucose tolerance was unchanged. Peritoneal macrophages as a direct readout for imatinib's effect on macrophages *in vivo* showed metabolic reprogramming and dampened pro-inflammatory gene expression, which went along with reduced inflammation in peripheral tissues (adipose tissue TNFα and IL-6 p< 0.05, liver CD68 and TNFα p< 0.05). In line with that, the human study revealed that IM attenuated gene expression of TNFα and MCP-1 in non-activated and activated monocytes from both lean and aDM. In activated monocytes from iaDM, however, IM was unable to dampen the same pro-inflammatory markers.

Conclusion:
Taken together, imatinib specifically dampens pro-inflammatory macrophages leading to reduced inflammation in peripheral tissues. Immune-modulation as exemplified by IM might be a useful strategy in patients with inflammation-mediated insulin resistance.

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The role of liver specific ASK1 in obesity induced insulin resistance

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Background/Introduction
Non-alcoholic fatty liver disease (NAFLD) is a progressive chronic disease that is strongly associated with metabolic disorders such as obesity, insulin resistance and type 2 diabetes, with a high risk for progression to liver fibrosis. Although apoptosis signal-regulating kinase 1 (ASK1) maintains cellular heomostasis by regulating apoptosis, inflammation and tumorigenesis via downstream activation of JNK and p38 MAPK, the role of liver-specific ASK1 in obesity related hepatic fat accumulation and insulin resistance remains to be fully elucidated.

Methods
We generated hepatocyte-specific Ask1 knockout mice to investigate the molecular mechanism underlying the involvement of Ask1 in the regulation of glucose and lipid metabolism.

Results
Here we report that hepatocyte specific-Ask1 knockout mice develop severe hepatic steatosis and liver fibrosis. Similarly, mice treated with an Ask1 inhibitor exhibited both increased lipid droplet accumulation and liver triglyceride (TG) content. Notably, deletion of Ask1 resulted in an increased collagen deposition, upregulated expression of fibrosis markers and impaired autophagy. We also show that Ask1 induces autophagy in cultured hepatocytes while increased lipid droplet accumulation was observed in parallel to decreased autophagy in Ask1 depleted hepatocytes.

Conclusion
This study pinpoints a beneficial function of ASK1 for the prevention of obesity-associated hepatic steatosis and liver fibrosis through induction of autophagy that may have translational therapeutic implications to tackle NAFLD and liver fibrosis.

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Design and development of ACTH antagonist as a potential treatment option for blocking excess androgens caused by 21-hydroxylase deficiency

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Background/Introduction:
Adrenocorticotropic hormone (ACTH) is a 39 amino acid polypeptide secreted from anterior lobe of pituitary and regulates glucocorticoid secretion. It binds to MC2R receptor and stimulates cortisol secretion from the zona fasciculata of the adrenal gland. Cortisol, in turn have negative feedback and regulates the synthesis and secretion of ACTH. Excess ACTH secretion is associated with a wide range of diseases including congenital adrenal hyperplasia (CAH). Classic CAH due to 21-hydroxylase (21OH) deficiency causes a reduction or loss of cortisol synthesis. The negative feedback is removed causing excess ACTH leading to excess adrenal androgens production due to the location of 21-hydroxylase enzyme blockage in steroid synthesis pathway. This high level of androgens compromises growth and fertility in CAH patients. Here we aim to design ACTH antagonists for cutting off this abnormal adrenal androgen production by blocking the ACTH/MC2R receptor.

Methods:
3D structure model of MC2R and ACTH was built by using YASARA and WHATIF programs and further optimization was done by molecular dynamic (MD) simulations. In-silico docking of ACTH to MC2R was performed by AutoDock VINA to calculate contact points and several key residues were selected for designing inhibitors. These peptides were commercially synthesized.
In-vitro cellular binding and signalling assays were performed to test the potency of these designed peptides. OS3 cells transfected with the receptor constructs (human MC2R and CRE-luc reporter plasmids) was used and experiments were performed 36 hours after transfection. Cyclic AMP(cAMP) generation upon receptor activation was measured by dual luciferase assay (Promega). The potential to shift the ACTH concentration response curve (CRC) was evaluated to characterize antagonist activity of designed peptides.

Results:
Activation and inhibition of MC2R by designed peptides was tested at 500nM and the assay results confirmed the bioinformatics prediction. Mutation in the core sequence (M4, R8) of ACTH abolished MC2R activation as predicted. The mean EC50 and EC80 concentrations of ACTH were 0.37 nM and 1.5 nM respectively for MC2R expressing OS3 cells. The potency of the designed peptides was tested at single concentration of 1 micomolar peptide together with the EC80 concentration of ACTH. cAMP response of unstimulated cells was used as control. Among these, one lead peptide inhibitor was identified. In order to determine the effect of peptide antagonist on the EC50 of ACTH, a concentration response curve(CRC) of ACTH was made on transfected cells. Half log shift in ACTH CRC was observed with 500 nM of this peptide. Assays to confirm binding and specificity of this peptide are ongoing.

Conclusion:
We used structure guided aproach to design several peptide inhibitors to compete with ACTH and one compound consistently shifted the ACTH CRC to right showing antagonism. New series of peptides are now designed using this information and assays to characterize them are underway. This study could be useful in ACTH/MC2R antagonist development and blocking MC2R could be a novel aproach for development of medical treatment for CAH.

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IL-6-type Cytokine Signalling in Adipocytes induces GLP-1 Secretion

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Background/Introduction
High production and release of interleukin-6 (IL-6) from adipose tissue may contribute to the dys-regulated metabolism in obesity and its associated diseases. In order to activate the intracellular signalling pathway, the IL-6 ligand/receptor complex associates with a homodimer of glycoprotein 130 (gp130), which is a common signal transducer of all IL-6-type cytokines. Using adipocyte-specific gp130 knockout mice we recently showed that IL-6-type cytokine signalling in adipocytes induces FFA release from visceral adipocytes thereby promoting obesity-induced hepatic insulin resistance and steatosis. In addition, IL-6-type cytokines may increase the release of leptin from adipocytes, thereby inducing GLP-1 secretion and, thus potentially improving β-cell function. Herein, we aimed to test the possible role of adipose IL-6-type cytokine signalling in the regulation of insulin secretion

Methods
Mice were either fed a chow (12% kcal from fat) or high-fat diet (HFD, 58% kcal from fat) for 12 weeks. Gucose metabolism was assessed by oral and intraperitoneal glucose tolerance as well as intraperitoneal insulin tolerance tests. Plasma leptin, GLP-1 and insulin levels were measured in systemic circulation and leptin release was assessed in isolated adipocytes of epididymal fat depots. Insulin secretion was analyzed in isolated pancreatic islets incubated in medium containing 2.8 mM or 16.7 mM glucose. GLUTag cells were treated with or without recombinant leptin (0.1 μM) or with supernatant of isolated adipocytes. Gene expression was assessed by real-time RT PCR. Insulin levels were assessed by ELISA, active GLP-1 and leptin levels were determined using MSD technology.

Results
Adipocyte-specific gp130 knockout mice on a high fat diet for 12 weeks showed impaired glucose tolerance when compared to control littermates. In addition, circulating leptin, GLP-1 and insulin levels were reduced. In line, adipocytes isolated from knockout mice revealed reduced leptin release, and collected supernatant induced lower GLP-1 release from GLUTag cells, paralleled by blunted expression of Pcsk1, the gene encoding PC1/3, which controls GLP-1 production. Moreover, intestinal Pcsk1 expression was decreased in HFD-fed knockout mice. Importantly, the GLP-1 receptor antagonist exendin 9-39 blunted impaired glucose tolerance in adipocyte-specific gp130 knockout mice. Ex vivo, glucose and GLP-1 stimulated insulin secretion was not affected in islets of knockout mice, further suggesting that an impaired incretin function constitutes the observed metabolic phenotype.

Conclusion
Adipocyte-specific IL-6-type cytokine signalling induces GLP-1 release in obesity to enhance insulin release thereby counteracting insulin resistance.

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Outcome after preoperative Immunonutrition in Head and Neck Squamous Cell Carcinoma Patients

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Background/Introduction
Perioperative disease-related malnutrition results in compromised wound healing, reduced immunologic functions, increased susceptibility to infections and decreased tolerance to further treatment, leading to a prolonged hospital stay and a poorer prognosis. Patients with head and neck squamous cell carcinoma (HNSCC) are specifically at risk for nutritional deficiencies. The aim of the study was to evaluate the effect of preoperative immunonutrition (IN) on postoperative short-term outcomes in patients with HNSCC undergoing elective oncologic surgery.

Methods
Single centre before and after study was conducted to compare clinical outcomes of consecutive patients before (control group) and after implementation (intervention group) of preoperative IN, given for 5 days preoperatively. We used regression models adjusted for important outcome predictors to compare length of hospital stay (LOS), local infections and general complications (Buzby and Dindo classification).

Results
A total of 411 patients were included (control group: 209, intervention group: 202). The LOS was significantly lower in patients receiving IN compared with the control gorup (median 6 vs. 8 days, $p < 0.001$). Local wound infections were significantly reduced after IN was implemented (7.4% vs. 15.3%, p=0.006). Specifically, there was a significantly lower rate for local wound complications, such as abscesses (4. 5% vs. 7. 7%, p=0. 031) and fistulas (3. 5% vs. 6. 2%, p=0. 009). Subgroup analysis showed more pronounced effects in patients with previous irradiation and extensive surgeries.

Conclusion
Data about the impact of preoperative IN on postoperative outcome in HNSCC patients are scarce. Patients receiving preoperative IN had a shorter LOS and a lower rate for wound infections and local complications compared with control group, whose effects remained robust after a multivariate adjustment. Further randomized controlled trials may be needed to confirm our results and to give evidence based recommendations.

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Design and Interim Evaluation of a Smartphone App for Overweight Adolescents Using the Behavioural Health Intervention Platform MobileCoach*

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Background/Introduction
Obesity in Swiss youth has stabilized at about 19%, yet simple and novel methods are needed to reach overweight adolescents living at distance from therapy centres or suffering from other barriers impeding the adherence to multimodal therapy programs, e.g. stressful life conditions. Though the number of digital health interventions is increasing, the effects in reaching long term health goals mostly remain unproven. The aims of the present study are to design a health app for overweight adolescents and to test, whether it supports their motivation to participate in an intervention including relaxation and activity exercises.

Methods
Based on the open source platform mobile-coach.eu, which has been successfully used for various behavioural health interventions in public health, a mobile chat app with game character was designed for Android smartphones. It included one chat channel with a text-based healthcare chatbot (THCB) and pre-defined answer options, a second chat channel for a direct communication between patients and health professionals and sensor integration such that patient's activities can be monitored by health professionals. This THCB intervention uses encrypted communication and data storage in Switzerland and, with the support of a virtual coach, encourages patients to achieve daily challenges, e.g. 6000 steps per day, breathing exercises for relaxation or photos of eating or family situations, in order to earn virtual rewards. Physicians perform four on-site and two telephone consultations during 24 weeks, and 2 follow up visits until 12 months, while all visits are on-site in the treatment-as-usual.

Results
Twenty-two patients (39 % girls) were included at 4 months' evaluation (15 THCB minus 2 dropouts for psychiatric reasons; 7 controls). At start, age and BMI-SDS were not significantly different: 14.2 years, range 11.9 – 17, and 2.56 SD, range 1.7 – 3.5. Almost 70% of the patients have at least 4 conversational turns with the THCB per day and 37% of the daily challenges are completed successfully in month 4, compared to 89% and 62%, resp., after 1 month. Only during the first month, open chat questions, mainly on technical issues, took place in 3.4% of roughly 13.000 conversational turns.

Conclusion
As described in other studies, compliance with digital health services decreases after 1 month, but remained much higher than in our own pre-study (70 % versus 15 %). This may be explained by the rewarding game system, the peer character of the THCB and the perceived usefulness of the THCB integrated in the personalized smartphone. Further analyses will explore, whether THCB usage is associated with positive health effects.

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Childcare correlates of physical activity, sedentary behavior, and adiposity in preschool children (SPLASHY)

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Background/Introduction
The childcare (CC) environment can influence young children's physical activity (PA), sedentary behaviour (SB), and adiposity. However, there is lack of knowledge regarding the impact of sociocultural correlates on these health outcomes. The aim of the study was to investigate a broader range of CC correlates of PA, SB and adiposity in a large sample of 2-6 years-old preschoolers.

Methods
84 CC participated in the Swiss Preschoolers' Health Study (SPLASHY). Based on the socio-ecological model of health behavior, 35 potential CC correlates were selected according to the following domains: demographic/biological, psychological/cognitive/emotional, behavioural, socio-cultural, and physical environment. PA was measured by accelerometry. Outcome measures included total PA (TPA), moderate-to-vigorous PA (MVPA), SB, BMI, and skinfold thickness (SF). PA measures consisted of both PA during CC days (full day attendance) and overall PA (including all days, both home and CC days).

Results
476 preschool children (mean age 3.9±0.7 yrs; 47% girls, 23% overweight and obese) participated in the study. Using multiple regression analysis, we identified the following CC correlates for higher TPA, higher MVPA or lower SB during CC days: older age, sex (boys), more frequent child-initiated interactions during CC, mixing different ages within a group, and the presence of a written PA convention in the CC (all p≤0.02). For higher overall TPA and/or MVPA or lower overall SB including both home and CC days correlates were: older age, sex (boys), more frequent child-initiated interactions during CC, mixing different ages within a group, parental PA involvement in the CC, and having a larger surface area in CC (all p≤0.046). Correlates for lower SF were: sex (boys), and parental PA involvement in the CC (all p≤0.02) and for lower BMI only increased age (p=0.001) was a correlate.

Conclusion
More frequent child-initiated interactions and mixing different ages in CC, the presence of a written PA convention and/or a larger CC surface are correlates of PA and SB during CC days, and mostly also for overall PA. Parental involvement in CC PA projects was a correlate for reduced body fat. In Switzerland, demographic/biological, psychological, and sociocultural factors are CC correlates of preschooler's PA, SB, and adiposity.

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Is Testing for Postprandial Hyperinsulinemic Hypoglycemia after Gastric Bypass necessary?

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Background/Introduction
Bariatric surgery is the most efficient and only durable treatment of severe obesity [1][2]. Whatever surgery is provided to a patient, it changes anatomy and function of the gastrointestinal and humoral system. Standard Roux-en-Y gastric bypass (RYGB) takes an intermediate position in the risk benefit ratio and is the operation of choice for thousands of patients. RYGP is safe and has been performed for decades. Most long-term sequels are well known and require a lifelong patient follow-up [1]. One increasingly reported complication is the postprandial hyperinsulimic hypoglycemia (pHH). As it can cause life threatening emergencies without warning symptoms, provocative testing can detect patients at risk. The objective of this study was to determine the prevalence of pHH after RYGB with or without symptoms of hypoglycemia.

Methods
Observational cohort study of consecutive, unselected patients 11 to 28 months after uncomplicated laparoscopic standard RYGP. In order to simulate normal habits all patients received a carbohydrate rich standardized solid mixed meal. Insulin and glucose were measured at 30, 60, 90, 120 and 150 minutes thereafter. Symptoms were recorded and classified as autonomous or neuroglycopenic. Patients with hypoglycemia, defined as blood glucose of < 3.3 mmol/L (60 mg/dL), were tested a second time within a week with a protein rich standardized solid mixed meal.

Results
A total of 113 consecutive, non-selected patients were included. Total postoperative weight loss was 33.97 ± 9.3%. In 24.8% of patients glucose dropped to less than 3.3 mmol/L (60 mg/dL), 13.8% to less than 3.0 mmol/L (55 mg/dL) after the carbohydrate solid mixed meal in contrast to only one patient after a protein rich meal (0% with less than 3.0 mmol/L (55 mg/dL)). Only 40.7% showed hypoglycemic symptoms. One patient needed emergency treatment after sudden loss of consciousness 80 minutes after the carbohydrate meal. Asymptomatic patients carry a significant risk ($p < 0.01$) for pHH.

Conclusion
pHH after RYGB can be life threatening and occur without warning symptoms. Therefore, testing all patients is necessary. How, when and how often remains to be investigated. A standardized solid food test is an option close to daily life situations and patients can be counselled according to the obtained results.

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Vitamin D Deficiency in the Swiss Sunny Lounge?

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Background/Introduction
With increasing age the synthesis of vitamin D (VitD) decreases1. According to the Swiss nutrition report of 2012 the intake of VitD with food is on average low by 100 IU (target 800 IU). The aim of our study was to evaluate the prevalence of Vit D deficiency in the Italian Region of Switzerland (Tessin) and possible seasonal fluctuations. Furthermore, we analysed clinical data (age, sex, main diagnosis, comorbidities and number of drugs) as indicators for VitD deficiency.

Methods
VitD values were measured in older internal medicine patients (>69 yrs) entering the emergency unit of the regional of Bellinzona, once in spring and once in autumn. 25OH-VitD and others hydroxylated metabolites were measured in serum according to an immunoassay test. Patients with an already substituted VitD deficiency or with VitD associated diseases were excluded.

Results
107 patients were included, 58 patients during the spring period and 49 during autumn. In the spring group 98% (n=57) of the patients showed a VitD deficiency (<50 nmol/L). From this group 31% (n=18) of the patients showed a VitD insufficiency (25-50 nmol/L) and 67% (n=39) a severe VitD deficiency (<25 nmol/L). During the autumn period 63% (n=31) of the patients revealed a VitD deficiency. Of this group 47% (n=23) presented a VitD insufficiency and 16% (n=8) a severe VitD deficiency. In neither season we could demonstrate a significant correlation between age, sex, main diagnosis, comorbidities or number of drugs and VitD deficiency.

Conclusion
A VitD deficiency in older internal medicine patients is very often and shows a seasonal fluctuation. None of the tested clinical data showed a significant correlation with VitD deficiency. On these grounds and according to the recommendations of the FOPH, a prophylaxis with 800 IU VitD daily in all older people is reasonable, especially in the winter. Such a prevention measure is cost-efficient, easy, safe and effective.

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Are patients affected by mitochondrial disorders ar nutritional risk?

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Background/Introduction
Patients suffering from mitochondrial disorders (MD) frequently present gastrointestinal complaints, mainly gastrointestinal dysmotility, that interfere with their food intake. Deterioration of their nutritional state may worsen the course of the disease. Our aims were to evaluate a simple screening tool to identify nutritional risk and to perform an extended nutritional assessment to explore the potential presence of deficiencies in this population compared to controls..

Methods
A prospective cohort study comparing outpatients with MD to matched healthy controls was conducted. Nutritional screening and full nutritional assessments were performed, including quantitative and qualitative dietary habits (7-day food recall), body function and composition, resting energy expenditure and quality of life (QoL) measurements. Blood and 24-hour urine analyses were performed in the patient group.

Results
Twenty-six subjects were included: 11 in the patient group and 15 in the control group. No patient was screened as malnourished according to the NRS-2002, but compared with controls, they had a lower muscle mass (p=0.13), reduced handgrip strength (p=0.07), significant changes in QoL and pathologic creatinine height index, which indicate malnutrition. The patients also had a significantly lower protein intake (p=0.01).

Conclusion
According to the current definition from the international societies of clinical nutrition and metabolism, all patients fulfilled the criteria for manifest malnutrition. Thus, the usual nutritional screening tool is less sensitive for chronically ill outpatients. These results provide a rationale to increase protein intake and adapt patients' energy supplies to improve bodily symptoms and QoL.

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Metabolomic markers of oxidative stress are associated with clinical outcomes in Patients with Community Acquired Pneumonia

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Background/Introduction
Oxidative stress is a modifiable risk-factor in inflammation and infection causing damage to human cells. As an adaptive response, cells catabolize Tyrosine to 3-Nitrotyrosine (3-NT) by nitrosylation. We investigated whether a more efficient reduction in oxidative stress, mirrored by a lowering of Tyrosine, and an increase in 3-NT and the Tyrosine/3-NT ratio was associated with better clinical outcomes in patients with community-acquired pneumonia (CAP).

Methods
We measured Tyrosine and 3-NT in CAP patients from a previous Swiss multicenter trial. The primary endpoint was adverse outcome defined as death or ICU admission within 30-days; the secondary endpoint was 6-year mortality.

Results
Of 278 included CAP patients, 10.4% experienced an adverse outcome within 30 days and 45.0% died within 6 years. A more efficient nitrosylation of Tyrosine was associated with a lower risk for adverse outcome as evidenced by a (sex-, gender- and comorbidity-) adjusted odds ratio of 0.44 (95%CI 0.19 to 0.99, p=0.049) for 3-NT and an adjusted odds ratio of 0.90 (95%CI 0.78 to 1.04, p=0.16) for the Tyrosine/3-NT ratio. Similar results were found for 6-year mortality with higher 3-NT levels (adjusted hazard ratio 0.81, 95%CI 0.50 to 1.11, p=0.185) and a higher Tyrosine/3-NT ratio (adjusted hazard ratio 0.96, 95%CI 0.91 to 1.01, p=0.072) showing trends towards improved survival.

Conclusion
Increased nitrosylation of Tyrosine to 3-NT is associated with better clinical outcomes at short- and long-term in CAP patients. Whether therapeutic modulation of the Tyrosine/3-NT pathway has beneficial effects should be evaluated in future studies.

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Investigating representativeness of SwissDiab participants vs non-participants at baseline

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Background/Introduction
The Swiss Diabetes Registry (SwissDiab) is a longitudinal observational study of patients with diabetes regularly seen and treated at Swiss tertiary diabetes care centres. The aim is to evaluate the current standard of diabetes care in Switzerland, including the distribution and progression of vascular complications, medication use, quality of life, and costs. The aim of the current project was to investigate the representativeness of the participants enrolled in SwissDiab to the non-participating background patient population at the Clinic of Endocrinology and Diabetology at the Cantonal Hospital of St. Gallen. This information is important to understand to what extent results emanating from SwissDiab are generalizable to the background patient group at large at a tertiary diabetes care centre.

Methods
The project was designed as a retrospective cross-sectional study, based on the SwissDiab participants enrolled between 01.01.2010 and 31.12.2016 and the non-participating patients treated during the same time period consenting to their data being used for this project. Descriptive characteristics of participants were retrieved from the SwissDiab baseline visit. For non-participants, data were collected from the patient clinical records ±6 months from the date the patient declined to participate in SwissDiab or the decision was made that the patient was not eligible for participation. Basic descriptive characteristics were compared stratified by diabetes type (type 1/DM1; type 2/DM2). Two-sided Wilcoxon rank-sum test was used for continuous and Chi-Square test for categorical variables. P-value ≤0.05 was considered statistically significant.

Results
Baseline data was available for 614 SwissDiab participants and 80% (n=400) of the non-participating patients agreed to their data being included in this study. No significant difference in age, blood pressure, and proportion of patients with a BMI ≥25 kg/m2 was observed between SwissDiab participants and non-participants, regardless of diabetes type. In both DM1 and DM2, the non-participant group presented with a higher HbA1c compared to the study participants (median [IQR] 8.5% [7.0-9.9] vs 7.4% [6.8-8.0], P-value <0.0001, and 8.0% [7.0-9.4] vs 7.1% [6.6-7.9], P-value <0.0001, respectively). Smoking and lower educational level were also more common in the non-participant group compared to the participant group, regardless of diabetes type (all P-values ≤0.05). In DM1, non-participants (n=74) were older at the time of diagnosis (27.5 yrs [15-40] vs 18 yrs [12-34], P-value=0.04) and tended to have a higher migration background (28% vs 18%, P-value=0.053) than participants (n=245). In DM2, non-participants (n=326) had a lower BMI (31.0 kg/m2 [27.7-34.3] vs 32.1 kg/m2 [28.4-36.5], P-value=0.008), shorter diabetes duration (8 yrs [4-15] vs 12 yrs [6-18], P-value <0.0001), a more frequent migration background (51 % vs 34%, P-value ≤0.0001), and included proportionally more females (36% vs 29%, P-value=0.04) and less participants with a family history of the disease (55% vs 68%, P-values <0.0001) compared to participants (n=369).

Conclusion
The results show some differences in basic descriptive characteristics between SwissDiab participants and non-participating patients, with the latter group tending to present with a worse overall clinical risk profile. This knowledge in turn will be valuable for the interpretation of future research findings emanating from the SwissDiab Study. Our study also highlights a need to understand to what extent the observed differences between participants and non-participants influence diabetes self-care and management, e.g. in terms of adherence and efficiency of medical treatment and progression of disease.

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Incidence of type 2 diabetes, hypertension, and dyslipidemia in metabolically healthy obese and non-obese: The Colaus Study

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Background/Introduction
Metabolically healthy obese (MHO) individuals are devoid of many metabolic abnormalities, but how this condition is maintained over time remains debated. The objectives of this study were to assess the prevalence of metabolically healthy obesity and the incidence of hypertension (HTN), dyslipidemia, and type 2 diabetes mellitus (T2DM) in MHO as compared with metabolically healthy non obese (MHNO) over time.

Methods
Prospective, population-based study including 3148 participants (50.2±10.0 years; 1824 women) free from metabolic syndrome at baseline and examined after a follow-up of 5.5 years and 10.7 years on average. At each follow-up, prevalence of MHO, MHNO, metabolically unhealthy not obese (MUNO), and metabolically unhealthy obese (MUO), as well as of HTN, dyslipidemia, and T2DM, was calculated and stratified by sex, age group, and education.

Results
At baseline, 179 (5.7%) MHO participants were identified, of which 62 (34.6%) and 79 (44.1%) remained MHO at 5.5 and 10.7 years follow-up, respectively. At 5.5 years follow-up, MHO participants were more likely to develop low HDL or be on hypolipidemic medication [multivariate-adjusted OR (95% CI): 1.56 (1.02-2.38)], dyslipidemia [1.94 (1.33-2.82)], and high triglycerides [2.07 (1.36-3.14)] than MHNO. At 10.7 years follow-up, MHO participants were significantly more likely to develop T2DM [3.44 (1.84-6.43)], dyslipidemia [1.64 (1.14-2.38)], and low HDL or be prescribed hypolipidemic medication [1.57 (1.08-2.27)] than MHNO. Conversely, no differences were found regarding incidence of hypertension.

Conclusion
A considerable fraction of MHO individuals lose their status over time, and in metabolically healthy adults, obesity confers a higher risk of developing dyslipidemia and T2DM.

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Physiological stress measures in preschool children and their relationship with body composition and behavioral problems

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Background/Introduction
The relationship between physiological stress measures and weight or behavioral problems in older children remains controversial and data in young children are lacking. The aims of the study were to investigate the relationship of physiological stress measures with body composition and behavioral problems in predominantly healthy preschool children using different stress measures.

Methods
476 healthy children aged 2-6 yr in 84 child care centers participated in the SPLASHY study. Physiological stress measures of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal axis (HPA) were assessed using saliva (diurnal salivary alpha amylase (sAA; ANS) and salivary cortisol (HPA)), nail clips (cortisol), and overnight electrocardiogram for heart rate variability (vagal tone; ANS). Health outcome measures included children's body composition (BMI, skinfold thickness) and behavioral problems (emotional problems, behavioral problems, conduct problems, and hyperactivity problems using the Strengths and Difficulties Questionnaire).

Results
Vagal tone, was inversely related to BMI and to body fat. Vagal tone was also inversely related to emotional problems and to peer problems. Diurnal sAA levels were related to hyperactivity problems and moderated the relationship of diurnal salivary cortisol with hyperactivity problems. Cortisol levels in saliva or nails were not related to body composition or behavioural problems.

Conclusion
n young children, measures of the ANS stress system were related to both body composition and behavioral problems. These results might highlight the protective role particularly of the parasympathetic nervous system early in life.

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Obesity-Protected Mouse Models are protected from HFD-induced Increase of Inflammatory Intestinal Macrophages

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Background:
Besides the well-established role of chronic inflammation, studies have shown gastrointestinal (GI) alterations in metabolic disease, such as altered gut microbiota, increased pro-inflammatory cytokines and macrophages as well as translocation of bacteria and endotoxin. However, the mechanism linking GI alterations and metabolic disease remains elusive. These GI alterations and macrophages' crucial role in systemic inflammation could indicate that intestinal macrophages (iMϕ) are the critical link between environmental stress - like high fat diet - and metabolic disease.

Research Design and Method:
IMϕ were isolated from the colon of C57BL/6, CCR2-K/O or germ-free (GF)-mice fed either a high fat diet (HFD: 60 kcal%) or control diet for up to 3 months and characterized by flow cytometry as $CCR2^+$ ("inflammatory" P1-P2, intermediate P3) and $CCR2^-$ resident (anerg, anti-inflammatory P4-P5) subpopulations.

Results:
Mice fed HFD for one week had significantly shorter colon lengths ($p<0.001$) and increased inflammatory iMϕ-subpopulations P1 and P2 compared to chow-fed controls (P1 1.6±0.9 fold, P2 7.2±5.1 fold, absolute numbers P1 $p<0.01$; P2 $p<0.001$, n=19-20), which was evident up to 3 months (P1 2.68±1.6 fold, P2 4.3±2.0 fold). Interestingly, mice with less weight gain under HFD had lower inflammatory iMϕ-subpopulation P1. As GF- and CCR2-K/O mice are typically protected from obesity, we assessed their iMϕ-subpopulation pattern to substantiate the link between inflammatory iMϕ and weight gain. GF-mice had a similar iMϕ-distribution as colonized mice fed chow, albeit at lower absolute numbers. With HFD, however, no increase in P1 and P2 was observed. Furthermore, CCR2-K/O mice lacked inflammatory iMϕ (P1-2) under chow diet. After one week of HFD, however, inflammatory ($Ly6C^{hi}$) iMϕ increased (absolute numbers P1 1.7±1.0 fold, P2 16.6±10.9 fold), but again at ≥10-fold lower absolute numbers than in WT mice.

Conclusion:
We propose that HFD activates intestinal macrophages in a microbiota-and CCR2-dependent manner, which could mediate chronic inflammation in metabolic disease. Mouse models protected from HFD-induced obesity suggest that there is a threshold of inflammatory intestinal macrophages required to elicit metabolic disease.

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Imaging of advanced medullary thyroid carcinoma with the CCK-2 receptor agonist 177Lu-PP-F11N –Preliminary proof of the principle within the "Lumed" study.

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Background/Introduction
Systemic treatment options for patients with advanced medullary thyroid cancer (MTC) have improved with the new molecular targeted therapies, such as Vandetanib. However, these substances show a broad spectrum of side reactions, often leading to discontinuation or dose reduction of the medication. There is, therefore, still an unmet need for an effective systemic therapy. Targeting the cholecystokinine-2 (CCK-2) receptor with radiolabeled gastrin analogues is a potential approach for radionuclide therapy of MTC. The aim of this study is the feasibility testing of targeting CCK-2 receptors with the novel 177Lu labelled gastrin analogue PP-F11N [DOTA-(DGlu)6-Ala-Tyr-Gly-Trp-Nleu-Asp-PheNH2] in six patients with advanced MTC (ClinicalTrials.gov: NCT02088645).

Methods
So far, 4/6 patients fulfilling the inclusion criteria (advanced MTC, Calcitonin > 100 pg/ml and/or doubling time < 24 months) were included in the study. Three of them received already two injections of 1 GBq 177Lu-PP-F11N: one injection without and one with Physiogel (Gelofusin) infusion for the evaluation of a possible strategy for nephroprotection. An additional patient received only one of the two injections until now. Planar scintigraphy and SPECT/CT scans were performed at several time points for up to 72 h post injection in order to calculate tumor- and organ doses using 3D voxel-based dosimetry (STRATOS software). Several vital parameters were measured up to 12 weeks after the second administration of 177Lu-PP-F11N in order to evaluate adverse events.

Results
Apart from self-limiting flushing, nausea and vomiting (grade 1 according to CTCAE version 4.0) at the time of injection, there were no adverse reactions observed. In intensity and duration these reactions were comparable to that of a diagnostic pentagastrin injection. In all patients, radiotracer uptake was visible in recurrent tumor and/or metastases on planar scintigraphic and SPECT/CT images. Due of the high density of CCK-2 receptors in the gastric mucosa, a high intensity of tracer uptake was visible in the stomach. Furthermore, uptake in the kidneys was visible.

Conclusion
The administration of the new CCK-2 receptor ligand 177Lu-PP-F11N was safe in the first four examined patients without serious adverse reactions.
Visualization of metastasized/recurrent disease in all patients proves that the principle of CCK-2 receptor targeting of MTC with this radiopharmaceutical is feasible.
Organs of relevant physiologic uptake, and therefore potential risk organs, are stomach and kidneys.

The potential of radionuclide therapy with 177Lu-PP-F11N can be further evaluated.

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Effect of ferric carboxymaltose on phosphate homeostasis in patients with iron deficiency following bariatric surgery

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Background/Introduction
Iron deficiency secondary to impaired intestinal absorption is a common finding in post-bariatric patients and repetitive parenteral supplementation is frequently required to restore and maintain normal iron levels. Ferric carboxymaltose (FCM; Ferinject) is among the preferred compounds used but may be associated with new-onset hypophosphatemia. Due to the high prevalence of secondary hyperparathyroidism, post-bariatric patients may be particular risk for this important adverse effect. The prevalence and clinical sequelae of hypophosphatemia following i.v. FCM in post-bariatric patients have not yet been studied, however.

Methods
Post-bariatric patients presenting with iron-deficiency (ferritin < 30 mcg/l) scheduled for i.v. supplementation with 500 mg FCM were eligible for this prospective cohort study. A clinical and biochemical assessment was performed before and 1 week after i.v. FCM. The new onset of hypophosphatemia (< 0.8 mmol/l) was the primary endpoint of the study. Oral phosphate supplements were prescribed if plasma phosphate dropped < 0.6 mmol/l and patients were followed until normal plasma phosphate concentrations were restored without supplements. Data are given as mean and 95% CI. A $p < 0.05$ was considered statistically significant and paired t-tests were used as appropriate.

Results
27 patients (22 F, 5M) following Roux-Y gastric bypass surgery were included. The mean age and BMI were 44 years (39-48) and 32.6 kg/m2 (30.5-34.7). 8 subjects (29%, 12-47) developed new-onset hypophosphatemia and the mean decrease in plasma phosphate was 0.34 mmol/l (-0.25- -0.43; $p<0.0001$). A significant 102% (48-157; $p=0.0002$) increase in the fractional urinary phosphate excretion was observed and associated with an increase in plasma intact FGF-23 (+19.8 ng/l; -2-42; $p=0.02$) and PTH (+14.9 ng/l; 2.8-27.1; $p=0.02$) and a decrease in 1,25 (OH)2 Vitamin D (-12.1 ng/l, -26-1.9; $p=0.0001$) concentrations. 6 patients required oral phosphate supplements for a mean duration of 3.3 weeks. We failed to identify any baseline characteristics that predicted the development of hypophosphatemia.

Conclusion
Post-bariatric patients receiving i.v. FCM are at considerable risk of developing clinically significant hypophosphatemia secondary to increased renal phosphate wasting through a mechanism involving FGF-23. Our data suggest that plasma phosphate should be monitored in post-bariatric patients following parenteral iron supplementation with FCM.

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Role of Microglia during Cephalic and Postprandial Phases of Insulin Release in Health and Diabetes

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Background/Introduction
It was recently shown that macrophage-derived IL-1β contributes to the postprandial stimulation of insulin secretion. Indeed, feeding induces a physiologic increase in the number of peritoneal macrophages that secrete IL-1β in a glucose-dependent manner. Postprandial inflammation is limited by normalization of glycaemia.

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

Results
In an ongoing follow up study, we observed that the muscarinic acetylcholine antagonist atropine strongly decreased the IL-1β effect on insulin secretion while darifenacin, a specific muscarinic 3 receptor antagonist that does not cross the blood brain barrier had no effect, suggesting a central neuronal effect. Moreover, purely cephalic stimulation of insulin release in mice increased IL-1β mRNA expression specifically in hypothalamic microglia, an effect that was sustained and even enhanced in the postprandial state. Furthermore, injection of the IL-1 receptor antagonist IL-1Ra reduced the cephalic phase of insulin secretion. IL-1β whole body KO mice also showed reduced insulin levels during cephalic phase compared to WT littermate controls. However, this effect was not seen in LysMCre IL-1β KO mice, that do not express IL-1β in most myeloid lineage cells, with the exception of microglia.

Conclusion
Therefore, we hypothesize that the cephalic and postprandial stimulation of insulin secretion is partly mediated by microglia derived IL-1β.

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Precision medicine for monogenic diabetes: From a survey to the development of a next generation diagnostic panel

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Background/Introduction: Monogenic diabetes (MD) accounts for 1-2% of all diabetes cases. Because of its wide phenotypic spectrum, MD is often misdiagnosed as type 1 or type 2 diabetes. While clinical and biochemical parameters can suggest MD, a definitive diagnosis requires genetic analysis. We conducted a survey among clinicians specialized in diabetes to document the cases with MD. Then, we designed a new diagnostic panel of 42 genes to obtain a comprehensive analytical instrument for the diagnosis of MD.

Methods: Questionnaire: We conducted a survey by sending a questionnaire to the members of the Swiss Society of Endocrinology and Diabetes to collect anonymous data on diabetic subjects with either a clinical suspicion of MD or genetically confirmed MD.
Diagnostic tool (Haloplex technology): This custom assay, designed based on liquid phase capture (Haloplex HS, Agilent, Santa Clara, CA, USA), allows for the trapping of all coding regions of the 42 gene and the respective splicing regions.

Results:
Of 74 clinically suspected MD patients in the survey, 54% had undergone genetic analysis, which was mostly conducted using the classical sequencing method by Sanger. Among the subjects, there were 44 females and 30 males with a median age at diabetes onset of 24.5 years (range 0.03-49). Two subjects had neonatal diabetes (< 6 months of age), 8 had childhood diabetes (≥ 6 months to < 11 years), and 14 had adolescent diabetes (≥ 11 to <18 years). The remaining 50 patients were adults, and 19 (25.7%) were 35 years or older at diabetes onset. The most common recorded mutations were in the *GCK* gene, followed by the mitochondrial genome (m.3243A>G mutation) and the *HNF1B* and *HNF1A* genes. The remaining 46% of patients had only a clinical diagnosis, mostly because genetic analysis was not easily accessible at that time. Here, we developed a new diagnostic panel of 42 genes. The panel was validated with an independent sample of nine known MD patients. We have now analyzed the first 10 consecutive patients with the diagnostic tool and identified a monogenic disease in 50% of the subjects. We found two different variants in the *GCK*, two variants in the *HNF1A* and one in the *ABCC8* genes, all classified as pathogenic or likely pathogenic according to the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology Society. In the other five patients the result remained negative. Interestingly, the *ABCC8* variant was reported to be functionally inactivating and therefore compatible with the transient congenital hyperinsulinism presented by the newborn, this is in contrast to activating *ABCC8* mutations known to cause neonatal diabetes.

Conclusion:
In this clinical survey we confirmed the need for a comprehensive genetic diagnostic test for MD. Our newly developed next generation diagnostic panel shows a pick-up rate of 50% in the first 10 consecutive patients, which is above the published rates of 21.4% to 36.8 % in the UK and 25% to 30% in France. The panel detects missense variants, insertions, and deletions, as well as activating or inactivating mutations, as shown in the newborn patient. The diagnosis of MD is crucial because it dictates treatment, may improve metabolic control and reduce long-term complications as proposed by precision medicine.