ISPAD 2013

ORAL SESSIONS

Oral Session I: Acute and chronic complications I

O1

Hypoglycemia awareness training in type 1 diabetic patients with hypoglycemia unawareness

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Objectives: In patients with type 1 diabetes (T1D) hypoglycemia unawareness is a serious diagnostic and therapeutic problem. The aim of this study was to determine the effectiveness of hypoglycemia awareness (HA) training in promoting increased awareness of body cues associated with hypoglycemia in patients with T1D.

Methods: In the initial phase of the study 33 of 260 patients with T1D were diagnosed with hypoglycemia unawareness. HA was assessed by questionnaire method using two tests: according to Clark and according to Gold. In this study we evaluated 27 patients, who agreed to participated in HA training. The mean patients' age was 27.5 ± 5.1 yr, mean diabetes duration was 18.3 ± 7.4 yr. Training of HA consisted of reeducation concerning body cues associated with hypoglycemia, particularly subtle and atypical symptoms. Then patients were advised to measure glucose levels regularly and to analyze the body cues in case of low blood glucose results. Frequency of severe hypoglycemia and mean HbA1c for 12 months preceding the training and for 12 following months were compared.

Results: After the training, 13 patients (48.1%) showed improvement in hypoglycemia perception. No difference in age, diabetes duration, incidence of severe hypoglycemia, and HbA1c was found before HA training between patients with improvement and patients without HA improvement. After the training, in patients with HA improvement, incidence of severe hypoglycemia was reduced compared with the preceding period (0.46 vs. 1.46/patient/year; $p = 0.02$) and a tendency for improved HbA1c was observed (7.24 ± 1.30 vs. 7.54 ± 1.44, $p = 0.22$). In patients without HA improvement, incidence of severe hypoglycemia (1.86 vs. 2.14/patient/year, $p = 0.56$) and HbA1c (7.0 vs. 7.0, $p = 1.00$) remained unchanged.

Summary: HA training was effective in nearly half of patients. Improved HA was associated with decrease in severe hypoglycemia incidence and with a tendency for metabolic control improvement.

O2

Impact of a French national campaign of information on the frequency and severity of ketoacidosis (DKA) at diagnosis of type 1 diabetes in children and adolescents

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Introduction: We report the effect of 2 yr of a national campaign of information on the prevalence of diabetic ketoacidosis (DKA) in children and adolescents.

Methods: The following data were collected over 3 yr in 146 pediatric centers, for each new type 1 diabetes (T1D) patient (<15 yr): age, sex, duration of symptoms, patient's route to the hospital, clinical and biological signs, and family history of T1D. DKA was defined as pH < 7.30 or bicarbonate <15 mmol/L; severe DKA as pH < 7.10 or bicarbonate <5 mmol/L. After 1 yr of data collection, a campaign of information for families and health professionals aimed at reducing the delay to diagnosis and the rate of DKA. Data were compared between the year before (Yr 0) and the first 2 yr of campaign (Yr 1 and Yr 2).

Results: The results concern 1299, 1247, and 1204 young people <15 yr (Yr 0, 1, and 2; about two thirds of all new patients at the national level), one quarter being <5 yr. From Yr 0 to Yr 1 and 2, the rate of DKA decreased from 43.9 to 40.5 and 35.1%; severe DKA from 14.8 to 11.4 and 10.6%. For all 3 yr, the frequency of DKA was higher in children <5 yr, in children coming to the hospital at the family's initiative rather than being sent by a pediatrician or an internist, and when there was no family history of T1D. The frequency of DKA decreased more for the severe forms, in children <10 yr, and in patients sent by a pediatrician or coming at the family's initiative. DKA decreased to 22.0% (7.3% severe DKA) when the family had had some knowledge of the campaign (6.6% of families).

Conclusion: DKA is frequent at diagnosis of T1D in children and adolescents but it decreased during the first 2 yr of a national campaign of information, particularly severe DKA. These first years of a national observatory on DKA has allowed to identify some factors associated with the frequency of DKA and to adjust the strategy of the campaign to make it more efficient on morbidity and mortality at diagnosis of T1D.

O3
Lipoatrophy in a large pediatric diabetes outpatient service

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Objectives: While lipohypertrophy at insulin injection sites is a common problem, lipoatrophy (LA) is seen much less frequently. However, over the last years we observed several patients with this complication. This is a systematic analysis of patients with LA.

Results: Retrospective chart review of all 678 patients with type 1 diabetes (T1D) currently treated in our clinic identified a total of 17 patients (7 male) presently having or having been affected by LA in the past (overall prevalence 2.5%). The current age of the affected patients is 14.3 ± 3.7 yr; the age at onset of LA was 11.3 ± 3.7 yr, the T1D duration 5.1 ± 5.5 yr (mean ± SD). An association with insulin analog use has been discussed. Indeed, all patients were using analogs at onset of LA, three of them lispro, the others aspart. Regarding the treatment modality, CSII was overrepresented in patients with LA: 15 of 17 (83.3%). This supports the hypothesis that a constant mechanical element such as a subcutaneous catheter may trigger the development of LA. Eight of the patients with CSII used a teflon catheter and seven used steel needles. Concomitant autoimmune diseases were present in 41.2% of the cases [thyroiditis (n = 4), thyroiditis and coeliac disease (n = 2), celiac disease (n = 1)]. This may support the concept of LA as an autoimmune inflammatory disease of fat.

Treatment: We encouraged the affected patients to change the injection area away from the lipoatrophic sites. Five of them changed the catheter needle from teflon to steel. Three of the patients switched from aspart to lispro. Seven adolescents started a local treatment with cromoglycat cream twice a day with some improvement in some cases. In two patients the skin defect disappeared spontaneously.

Conclusions: Currently there is no established therapy of LA in patients with T1D. Due to the low prevalence of this complication a multicenter collaborative study is needed to improve our knowledge about the causes as well as the treatment options of LA in young people with T1D.

O4
An ISPAD survey on insulin-induced lipoatrophy

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Background and Objectives: Hypersensitivity skin reactions to insulin has dramatically decreased since 1950s, when 50–60 % of the patients were troubled. Recently, some indications on rising prevalence of lipoatrophy (LA) are published. The underlying mechanism could be an immune-complex-mediated inflammatory lesion, possibly activated by the use of insulin analogues and/or CSII.

Methods: A link to a questionnaire was distributed in May 2013 on the ISPAD homepage, making it available for all ISPAD members to report known cases at the clinic, diagnosed with LA years 2010–2012.

Result: Twelve sites from Europe and USA have so far reported their patients with LA. The total number of patients were 4299 of whom 46 patients had LA, mainly on buttocks or abdomen, which gives a percentage of LA in the reported number of patients of 1.1%. The ratio female/male was 28/18. The current mean age of the patients with LA was 12.8 (SD 4.1), mean age at diabetes diagnosis 6.1 (SD 3.3), and mean age at LA diagnosis 9.8 (SD 4.0); 40 patients were treated with insulin pump (=87%). All but one patient were using a direct acting insulin analogue in the pump, Aspart 36 (=78%) or Lispro 9 (20%). Pumps from Medtronic (n = 27), Roche (n = 9), and Animas (n = 4) were used. Most needles were made of teflon (n = 24), the rest steel needles (n = 13), and three cases not reported. The most common length of the needle was 6 mm but needles of up to 17 mm were used. The maximum diameter of LA was 14 cm; 12 of 46 patients (n = 26%) had tried cremor Cromolyn 4%. No other pharmacological treatment was reported and no biopsy had been performed. The insulin analogue had been switched to another analogue on 28% of the patients after the LA diagnosis. In 30% of the patients the atrophy had resolved. Of the six patients on MDI, four used glargin and two NPH insulin.

Conclusion: This ongoing international survey is indicating the need for increased awareness on LA in young patients. Further studies on larger cohorts of patients are necessary.

O5
Lipoatrophy is associated with increased risk of Hashimoto's thyroiditis and celiac disease in female patients with type 1 diabetes

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Objectives: Lipoatrophy (LA) in patients with type 1 diabetes has become rare since the introduction of recombinant insulin preparations. However, potentially in relation to increasing use of CSII and the use of insulin analogues, more cases of LA have been reported over the past few years. The aim of our survey was to identify patients with type 1 diabetes mellitus (T1DM) and LA and to determine whether there is a relation with other autoimmune

diseases such as Hashimoto's thyroiditis or celiac disease. Our analysis addresses the hypothesis that immune-mediated processes may play a causative role in the development of LA, and that autoimmune phenomena may be more prevalent in patients with T1DM and LA.

Methods: In a multicenter setting, a cross-sectional observational survey was performed in patients registered across Germany and Austria in the electronic diabetes database DPV. Currently, 371 centers with 241 650 patients are available for analysis.

Results: Ninety one patients (46 male/45 female) with a mean age of 12.1 yr (range 2.8–48.1) were found to have lipoatrophy (LA+) and were compared with 53 754 age-matched patients without lipoatrophy (LA−). Patients with LA+ were younger at the onset of diabetes (6.3 vs. 8.7 years, $p = 0.002$) and had more episodes of severe hypoglycemia (69.5 vs.12.4 episodes/100 patient years, $p < 0.001$), while HbA1c, frequency of ketoacidosis, and daily insulin dose did not differ between the two groups. Both, Hashimoto´s thyroiditis and coeliac disease were more prevalent in LA+ patients ($p < 0.001$ and $p < 0.001$). Stratified by gender, LA+ was associated with an increased risk of Hashimoto´s thyroiditis and celiac disease only in female patients [odds ratio (OR) = 2.5, $p = 0.003$ and OR = 3.1, $p = 0.02$]. This association persisted after adjustment for current age, duration of diabetes, and calendar year of treatment (OR = 2.7, $p = 0.002$ and OR = 3.5, $p = 0.01$).

Conclusions: This survey supports the hypothesis that an immune complex-mediated inflammatory process may play a role in the development of LA.

O6

Celiac disease is a risk factor for microvascular complications in patients with type 1 diabetes: longitudinal follow-up of 54 488 patients from the German/Austrian DPV multicenter survey

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Background: The association between type 1 diabetes (T1D) and celiac disease (CD) is well known. A recent study from Sweden showed that a diagnosis of CD for more than 10 yr is a risk factor for the development of diabetic retinopathy. Therefore, the aim of this study was to evaluate whether patients with T1D and CD are at increased risk for microvascular complications.

Methods: Data from 54 488 patients (52% male) with T1D diagnosed <20 yr of age from 357 centers from Germany and Austria were included in the analysis.

Results: 1.3% of the patients had biopsy proven CD; 8.3% had positive CD antibodies and/or clinical symptoms of CD; 90.4 % were CD negative (negative antibodies, negative biopsy, or no clinical signs). Patients with biopsy proven CD and patients with positive antibodies and/or clinical symptoms were defined as CD+ group and were compared with the CD− group; 40 283 patients were screened for retinopathy; 25% of the patients from the CD+ group had retinopathy after 26.6 yr, and after 33.7 yr in the CD− group ($p < 0.0001$). At the age of 25 years, 76.1% of the CD+ group had no retinopathy in contrast to 89% of the CD− group. Using a Cox regression model, CD increases the relative risk for retinopathy by 22%, further risk factors are smoking, HbA1c > 7.5%, and diabetes onset during puberty; 41 589 patients were screened for nephropathy; 25% of the patients from the CD+ group had nephropathy after 17.3 yr compared with 20.7 yr in the CD− group ($p < 0.0001$). Using a Cox proportional model the relative risk for nephropathy is increased by 32% in the CD+ group. Further risk factors are HbA1c > 7.5% and hypertension.

Conclusion: CD increases the risk for microvascular complications in patients with T1D. Therefore, screening for CD is important. The impact of a gluten free diet on the subsequent risk of microvascular complications needs further investigations.

O7

This abstract has been withdrawn.

O8

Inverse relationship between increased glomerular filtration rate and C-peptide level at diagnosis of type 1 diabetes in children and adolescents

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Objectives: To study the relationship between glomerular filtration rate (GFR), C-peptide level, age, and other parameters at diagnosis of type 1 diabetes.

Methods: We determined GFR (by IV injection of 51Cr-EDTA), glycated hemoglobin (HbA1c), C-peptide level, body mass index (BMI) SDS and the loss of weight in 495 children and adolescents (231 females) at diagnosis of type 1 diabetes. Linear and multiple regression analysis were used to test for the associations between GFR and other parameters.

Results: In the 495 diabetic patients, GFR (mean ± 2DS) was increased at 158 ± 77 ml/min/1.73 m^2, normal values being 127 ± 38 ml/min/1.73 m^2 ($p = 0.0001$). In 36% of the patients, GFR was superior to upper normal limit (165 ml/min/1.73 m^2). GFR was significantly negatively correlated with age ($p < 0.001$) and C-peptide level at diagnosis ($p = 0.001$), and positively correlated with weight loss at diagnosis ($p = 0.02$). There was no significant correlation with gender, HbA1c, and BMI SDS. The multiple regression analysis showed that age ($\beta = -1.459$, $p = 0.001$) but especially C-peptide level ($\beta = -7.036$, $p = 0.05$) were independently and negatively related to GFR ($r^2 = 0.04$).

Conclusions: This study shows that, at onset of type 1 diabetes, higher the GFR, younger the age and lower the C-peptide level. Young age and low C-peptide level are bound to a faster course

of β-cell destruction. This hyperfiltration is independent of gender, BMI, and HbA1c at diagnosis. A longitudinal long-term follow-up, during many years, should be necessary to clarify the eventual role of glomerular hyperfiltration, associated with lowest C-peptide level at diagnosis of diabetes in the development of later nephropathy. It has been largely shown that the initial hyperfiltration normalized with good glycemic control. The preventive role of C-peptide administrations needs to be evaluated.

Oral Session II: Acute and chronic complications II

O9

Therapeutic inertia: underdiagnosed and undertreated hypertension in children participating in the T1D Exchange Clinic Registry

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Objectives: While detection and control of elevated blood pressure is an important aim of therapy of youth with type 1 diabetes (T1D), adherence to and implementation of these treatment guidelines in pediatric diabetes practices has not been established. An aim of this study was to compare prevalence of physician-diagnosed hypertension (HTN) vs. the frequency of documented elevated blood pressure (BP) levels at the time of enrollment of children and adolescents in the T1D Exchange Clinic Registry (T1DX). We also assessed the frequency and efficacy of angiotensin-converting enzyme-I (ACE-I)/angiotensin receptor blocker (ARB) treatment in this large population.

Methods: This analysis included 11 607 youth participating in the T1DX, aged 3 to <18 yr, with T1D duration ≥1 yr. Prevalence of clinically diagnosed HTN, documented BP ≥95th percentile at study entry, ACE-I or ARB therapy, and microalbuminuria (MA) were extracted from medical charts.

Results: HTN was diagnosed in 1% (112/11 607); whereas, a diastolic or systolic BP ≥95th percentile for age, gender, and height was recorded in 12% (1300/11 607) of participants. The prevalence of a systolic or diastolic BP ≥95th percentile was 12, 11, and 12% in <10, 10 to <13 and the 13 to <18 yr group, respectively, while the prevalence of diagnosed HTN was 0.2, 0.3, and 2% for the same respective age groups. Among those with a clinical diagnosis of HTN, only half were receiving ACE-I/ARB therapy. For those where albuminuria status was known (n = 7275), MA was seen in 19% with and 4% without a clinical diagnosis of HTN (adjusted $p < 0.001$). A higher A1c also was observed in those with HTN (9.2 ± 1.9%) compared with non-HTN children (8.5 ± 1.5%, adjusted $p < 0.001$).

Conclusions: Even in centers that specialize in the treatment of children and adolescents with T1D, HTN is likely to be markedly underdiagnosed and ineffectively treated. The relatively low numbers of hypertensive children receiving ACE inhibition and reaching BP goals identifies an important area for improving the care of children with T1D.

O10

Serum endothelial monocyte activating polypeptide II levels in children and adolescents with type 1 diabetes mellitus: relation to micro-vascular complications

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Objectives: We determined serum endothelial monocyte activating polypeptide II (EMAP II) in children and adolescents with type 1 diabetes and assessed its relation to inflammation, glycemic control, and micro-vascular complications.

Methods: This cross sectional study included 60 type 1 diabetics compared with 30 healthy controls. Patients were subjected to history with special emphasis on disease duration and insulin therapy, clinical examination, and laboratory assessment of high-sensitivity C-reactive protein (hs-CRP), HbA1c, and the presence of micro-vascular complications including diabetic nephropathy. Serum EMAP II was measured by enzyme-linked immunosorbent assay.

Results: EMAP II levels were significantly increased in patients with micro-vascular complications (1539 ± 321.5 pg/mL) and non-complicated patients (843.6 ± 212.6 pg/mL) compared with healthy controls (153.3 ± 8.3 pg/mL) with highest levels found in complicated patients ($p < 0.001$). EMAP II was increased in diabetic patients with microalbuminuria compared with normoalbuminuric patients and controls ($p < 0.001$). Significant positive correlations were found between EMAP II levels and body mass index, random blood glucose (RBG), HbA1c, serum creatinine, fasting lipids, urinary albumin excretion (UAE), and hs-CRP ($p < 0.05$). Multiple regression analysis showed that RBG, HbA1c, UAE, and hs-CRP were independently related to EMAP II ($p < 0.001$). ROC curve analysis revealed that the cutoff value of EMAP II at 1075 pg/mL could differentiate complicated from non-complicated cases with a sensitivity of 93%, specificity of 82%.

Conclusions: Elevated EMAP II may be involved in the mechanism of vascular endothelial damage in type 1 diabetics. Hyperglycemia and dyslipidemia may be significant factors contributing to increased EMAP-II levels. EMAP II is closely related to inflammation, glycemic control, and albuminuria level of patients. Thus, it could be considered a reliable marker for micro-vascular complications to identify those at high risk of developing diabetic kidney disease later in life.

O11

Increased cardiovascular disease risk factors, especially in girls: a nationwide, population-based study of children and adolescents with type 1 diabetes

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Introduction: Type 1 diabetes (T1D) is a known risk factors for cardiovascular disease (CVD) and is associated with excess cardiovascular morbidity and mortality, and more so in females.

Objectives: To describe additional CVD-risk factors in a nationwide population-based cohort study of children and adolescent with T1D.

Methods: CVD risk factors as defined by ISPAD/ADA were examined in children and adolescents with T1D in all the pediatric clinics in Norway (n = 27). In 2012, 2528 patients participated in an annual examination, 1321 boys and 1207 girls. Mean age was 12.9 yr (1.9–23.5), mean diabetes duration was 5.4 yr (0.1–17.7) and mean HbA1c was 8.6% (5.4–16.6); 97% were using four or more insulin injections daily, and 64.3 % used insulin pumps.

Results: CVD risk factors are shown in Table 1; 91% had 1≥ additional CVD risk factor. 53% of the participants had 2≥ CVD risk factors; 21% had 3≥ CVD risk factors, 5% had 4≥ CVD risk factors. HbA1c and low-density lipoprotein (LDL)-cholestrol

Table 1. CVD risk factors

Risk factors	Boys n (%) 1277 (52.4)	Girls n (%) 1162 (47.6)	p Value	Total n (%) 2439
CVD*	178 (13.9)	178 (15.3)	ns	359 (14.6)
Diabetes*	347 (27.2)	338 (29.1)	ns	685 (28.1)
HbA1c > 7.5%	996 (78.0)	956 (82.3)	ns	1952 (80.0)
LDL > 2.6 mmol/L	359 (28.1)	500 (43.0)	0.0001	859 (35.2)
HDL < 1.1 mmol/L	88 (6.9)	51 (4.4)	0.01	139 (5.7)
Blood pressure >90th perc	66 (5.2)	56 (4.8)	ns	122 (5.0)
BMI Z-score†	50 (3.9)	19 (1.6)	0.001	69 (2.8)
Persistent microalbuminuria‡	8 (0.6)	9 (0.9)	ns	17 (0.7)
Smokers	9 (0.7)	18 (1.5)	0.049	27 (1.1)

*Positive family history (in first and second degree relatives). CVD events before 60 yr of age.
†BMI Z-score defined as +2 SD.
‡Persistent microalbuminuria is defined as U-ACR in 2 of 3> 2.5 mg/mmol.

above target were found in 80.0% and 35.2%, respectively. Girls had significantly more CVD risk factors than boys ($p < 0.01$).

Conclusions: One or more CVD risk factors are common in youths with T1D. This is particularly high in females and needs to be addressed in our clinical work.

O12
Assessment of left ventricular dysfunctions in children with type 1 diabetes mellitus

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Introduction: Diabetes mellitus is associated with long-term damage, dysfunction, and failure of various organs especially the eyes, kidneys, heart, and blood vessels. Abnormalities of left ventricular (LV) function primarily reflected a diastolic abnormality which was an early sign of diabetic cardiomyopathy, and had been shown to precede systolic dysfunction in diabetic patients.

Objectives: Aim of the work was to detect early left ventricular dysfunctions in children with type 1 diabetes mellitus (T1DM) and their correlation with the glycemic control of these children.

Subjects and methods: This study included two groups: group I included 46 children who were diagnosed as type 1 diabetic patients, and group II which included 23 apparently healthy, age, and sex matched children as a control group. They were subjected to thorough history taking, clinical examination, and laboratory investigations including total serum cholesterol and triglycerides. LV functions were assessed by resting trans thoracic echocardiography (TTE) and tissue doppler imaging (TDI).

Results: There were significant higher diastolic indices by both TTE and TDI in type 1 diabetic children than the control group. Diagnosis of definite left ventricular diastolic dysfunction was detected in five (10.9%) diabetic children by TTE and in seven (15%) diabetic children by TDI. Finally, there were insignificant associations between duration of the disease, hypoglycemic attacks, diabetic ketoacidosis (DKA), systolic and diastolic blood pressures, HbA1c% levels, and different echocardiographic, tissue Doppler parameters.

Conclusion: Alteration of myocardial function induced by diabetes mellitus (DM) may begin earlier than was generally thought and these changes might be not correlated with duration of diabetes nor glycemic control. Children and adolescents with T1DM already have significant changes in myocardial diastolic function of the LV and seem to be at risk of developing further cardiac dysfunctions.

O13
Long-term effects of intensive treatment in type 1 diabetes on all-cause mortality, cardiovascular mortality, and morbidity in cardiovascular disease: a long-term follow-up study

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Objectives: To investigate outcomes regarding mortality and morbidity in the Stockholm Diabetes Intervention Study (SDIS) cohort.

Methods: In SDIS 102 type 1 diabetes patients were randomly assigned to receive either intensified insulin treatment (ICT = 48) or standard treatment (ST = 54) for 7.5 yr. The ICT group gained significantly lower HbA1c throughout the study; 27–29 yr after study start data were extracted from the Swedish Death Register and the Swedish National Inpatient Register (IPR) regarding all-cause mortality, mortality in stroke, myocardial infarction (MI), and kidney failure and morbidity in MI, stroke, and peripheral vascular disease/foot ulcers. HbA1c, total cholesterol, blood pressure, microalbuminuria, smoking habits, and use of antihypertensive and lipid-lowering agents were collected from patient's medical records. HbA1c was analyzed in 3-yr periods from 1996 to 2010. The study was ethically approved.

Results: Mean age at diabetes diagnosis was 13.9 yr; 54% in the ICT group vs. 85% in the ST group received hypertensive treatment, $p = 0.01$. Mean HbA1c levels were significantly lower in the ICT group from 1996 to 1998; 66 vs. 71 mmol/mol, $p = 0.02$, but not in any of the following years. Twenty-two patients died during the observation time; 7 in the ICT vs. 15 in the ST group (Incidence risk 14.6 vs. 28%, $p = 0.11$). For cardiovascular mortality five patients died in the ICT vs. 10 in the ST group, $p = 0.277$, and for cardiovascular morbidity there were 13 patients in the ICT vs. 18 in the ST group, $p = 0.52$ (Fig. 1).

Conclusions: We found no significant long-term differences in mortality or morbidity, however, a tendency towards fewer deaths were seen in the ICT group. The small cohort size limits our result, but nearly 30-yr follow-up time and the initial randomization strengthen the findings that a limited time of improvement in glycemic control may influence long-term survival.

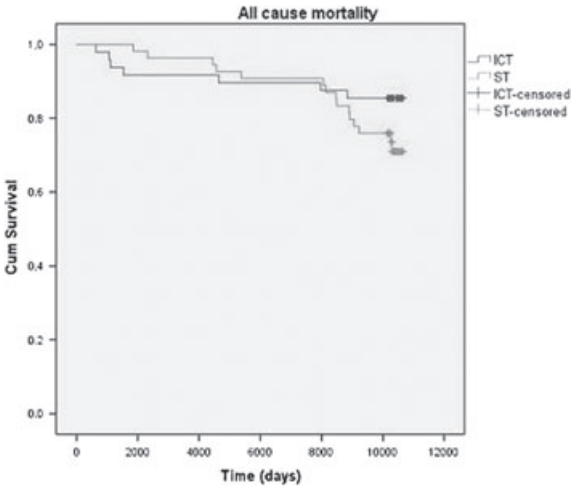

Fig. 1. All-cause mortality.

O14
NGAL and cystatin C as early markers of diabetic nephropathy in patients with type 1 diabetes mellitus

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Objectives: Diabetic nephropathy (DN) is one of the most severe complications of type 1 diabetes (T1D) and until nowadays its early diagnosis is based on microalbuminuria (MA) assessment. In this study we aimed to explore the use of new biomarkers of renal injury, such as neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C (CysC) for the early identification of DN in young patients with T1D.
Methods: Sixty T1D patients, aged 5–22, were included in this prospective cross-sectional study. Along with standard blood and urine chemistry, serum NGAL levels by means of immunoenzymatic assays and serum levels of CysC by nephelometry were measured twice in a time interval of 12–15 months. Glomerular filtration rate (GFR) was calculated with the revised Schwartz bedside formula (eGFR) and the more recently suggested by Schwartz et al. eGFR-formula with CysC (CysC eGFR).
Results: Both NGAL and CysC were found to correlate negatively with the eGFR ($p = 0.05$, $r = -0.25$ and $p = 0.01$, $r = -0.33$, respectively) and positively correlated to the serum creatinine ($p = 0.01$ $r = 0.34$ and $p = 0.006$, $r = 0.37$, respectively). Moreover, NGAL was positively correlated with the CysC value ($p = 0.0005$, $r = 0.49$), the systolic arterial pressure(SAP) ($p = 0.004$, $r = 0.39$) and negatively correlated with the CysC eGFR ($p = 0.01$, $r = -0.33$). The mean value of NGAL was increased at the second measurement performed 12–15 months after the first test ($p = 0.03$). Neither NGAL nor CysC concentrations were correlated with the Tanner stages of puberty.
Conclusions: NGAL and CysC, known markers of renal injury, are found to correlate with the renal function decline in T1D patients suggesting that they may be early markers of DN. The fact that they do not correlate with pubertal Tanner stages implies that they are not influenced by hormonal factors intervening during puberty. These findings suggest that early assessment of these markers may unmask the endothelial dysfunction in T1D patients before overt MA and renal impairment become obvious.

O15
Mannose-binding lectin as a marker of micro- and macro-vascular complications in young type 1 diabetics

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Objectives: We determined mannose-binding lectin (MBL) levels in 80 type 1 diabetics compared with 40 healthy controls as a marker for diabetic micro- and macro-vascular complications and assessed its relation to inflammation, glycemic control, and carotid intima media thickness (CIMT).
Methods: Laboratory assessment of high-sensitivity C-rective protein (hs-CRP), HbA1c, urinary albumin excretion (UAE), and serum MBL was performed. CIMT of the common carotid artery was assessed using high resolution ultrasonography. Patients were prospectively followed up for a mean period of 17 ± 4.3 months for progression in renal disease.
Results: Baseline MBL levels were significantly increased in patients with and without micro-vascular complications compared with controls with highest levels found in complicated patients. Follow-up MBL levels were markedly elevated in complicated than non-complicated patients or baseline levels. Baseline and follow-up MBL levels were elevated in diabetics with or without microalbuminuria compared with controls and also, in progressors from normoalbuminuria or microalbuminuria to a higher albuminuria level than non-progressors with the highest levels in progressors to macroalbuminuria. Cutoff value of MBL at 1520 ng/mL could differentiate complicated from non-complicated cases with high sensitivity and specificity. High-sensitivity C-rective protein (hs-CRP) levels showed no significant difference between progressors or non-progessors. CIMT was significantly higher in patients with micro-vascular complications than non-complicated or controls. Regression analysis showed that serum creatinine, UAE, hs-CRP, and CIMT were independently related to baseline MBL levels in diabetics.
Conclusions: Serum MBL levels are elevated in complicated diabetics and significantly related to inflammation and metabolic control. The positive correlation between MBL and CIMT could consider it a potential marker of progression of diabetic kidney disease and would help to identify patients at risk of developing cardiovascular complications.

O16
Sleep abnormalities and serum orexin-A in children with type 1 diabetes

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Objectives: The aim of the study was to examine sleep structural changes and their correlations to orexin-A serum concentration in children with type 1 diabetes (DM).
Methods: Thirty-two prepubertal boys (9–12 years) with DM and control subjects (20 age-matched healthy boys) underwent overnight polysomnography (PSG). Serum orexin-A concentration was determined by enzyme immunoassay (EIA).
Results: We revealed a reduction of latent periods of all stages of non-rapid eye movement sleep (NREM) in diabetic patients ($p = 0.04$) and increased percentage time of rapid eye movement sleep (REM, $p = 0.03$) compared with non-diabetic controls. DM boys demonstrated the increased number of microactivities ($p = 0.03$) and increased total duration of the waking time during sleep than in controls ($p = 0.005$). Patients with diabetes showed the high frequency of breathing disorders which corresponded to mild degree of sleep apnea/hypopnea syndrome (AHS, $p = 0.01$). The oxygen saturation parameters in diabetic boys were lower ($p = 0.002$) and index of desaturation events in diabetes was higher during NREM ($p = 0.019$) and REM ($p = 0.007$) compared with non-diabetic controls. The mean orexin-A level in the blood serum of patients with diabetes was significantly higher compared with the control group ($p = 0.0001$). A positive correlation with age ($p = 0.04$) and with duration of diabetes ($p = 0.044$) was found. DM patients found strong negative correlation between the level of orexin A and latency period of slow-wave stages in NREM ($p = 0.01$), duration of REM ($p = 0.03$), duration of motions ($p = 0.03$), the level of saturation in the slow-wave phase ($p = 0.04$) and in REM ($p = 0.03$).
Conclusions: The sleep architecture in children with DM, according to PSG, has a number of features reflecting its possible value as a predictor of initial stages of diabetic brain damage. These results suggested that the orexin system may be involved in pathogenesis of sleep disorders in diabetes. The serum orexin-A level may be able to be used as objective marker diabetic central nervous system (CNS) complications.

Oral Session III: Obesity, puberty, and type 2 diabetes

O17

Data analysis for mother–daughter dyads: understanding and capitalizing on dependencies in data in behavioral studies of individuals with diabetes

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Introduction: In behavioral science research phenomena under study are interpersonal in terms of interactions and relations between individuals. Unfortunately, research has often focused on the individual, largely due to culture/research discipline but also prevailing statistical methods. Standard statistical methods assume that the data from each individual in the study are independent (i.e., unrelated) to the data from every other individual under study.
Objectives: Dyadic data analysis works to understand the non-independence between and within dyads, pairs of individuals that are inherently related (due to kinship) and distinguishable (e.g., mother and child, husband and wife, twins).
Methods: In this presentation we will illustrate dyadic analysis using data from the mother–daughter of the READY-Girls Study as an exemplar and will provide the statistician's perspective, which complements the researcher/clinician viewpoint on the topic of adolescent PC presented in 'Mother-Daughter Team Approach for Starting Preconception Counseling at Puberty in Girls with Diabetes: Implications for Dyadic Analyses and Clinical Practice'.
Results: Through dyadic analyses significant associations were found between mothers' and daughters' beliefs and attitudes regarding communication and intention to seek preconception counseling ($p < 0.05$).
Conclusion: When the unit for analysis is the dyad, one should take into account the natural dependencies arising between both members of the dyad. This is particularly true when conducting research in pediatric and adolescent diabetes populations, where parents can influence health behavior and outcomes in youth with diabetes.

O18

Cord blood adipokines in offspring of normal weight, obese, or gestational diabetic mothers

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Purpose: To determine the umbilical cord levels of adipokines at birth in the neonates born from mothers with obesity or gestational diabetic mothers (GDM) in comparison with those offspring from normal pregnancy. Associations between adipokines and maternal or neonatal anthropometric parameters and gravidity were also assessed.
Methods: Umbilical cord blood samples were obtained from 49 neonates at birth. Adipokines were determined by enzyme-lined immunosorbent assay.
Results: Neonates born from obese mothers had higher umbilical cord leptin levels in comparison with neonates born from normal weight mother (7.40 ± 6.60 and 3.32 ± 4.38 ng/mL, $p = 0.046$), no difference between the GDM group and normal pregnancy. The levels of adiponectin and resistin did not differ among three studied groups. In whole studied subjects, cord leptin positively correlated with maternal pregestational BMI and weight at delivery. Cord leptin levels were also positively associated with neonatal birth weight and neonatal birth length. Moderate correlation was observed between cord adiponectin and resistin, however, these two aidpokines did not correlate with any maternal and neonatal anthropometrics. When stratified by gravidity, the cord levels of leptin were significantly higher in women with medium gravidity compared with those who had low gravidity.
Conclusions: These results supported the important role of leptin in the regulation of fetal growth; the absence of association in adiponectin and resistin with neonatal and maternal profile need further investigation.

O19

Metabolic syndrome and impaired glucose metabolism prevalence in overweight children and adolescents in Lithuania

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Background: Clustering of symptoms called as metabolic syndrome (MS) increases the risk for cardiovascular diseases. The ability of components of MS in childhood to predict adult disease makes detection of pediatric MS a promising way to identify children who would most benefit from early interventions to prevent morbidity in adulthood.
Objectives: To assess the prevalence of MS and impaired glucose metabolism [IGM: fasting hyperglycemia, impaired glucose tolerance (IGT), or diabetes] in overweight Lithuanian children and adolescents.
Methods: Two hundred six overweight and obese (BMI over 85 and 97 percentile, respectively) 10–17-yr-old children and adolescents from Kaunas region, Lithuania, were included in the study. Study sample consisted of 86 males and 120 females, median age 13.23 yr (9.87–17.51), median pubertal stage 3 (1–5). Participants underwent anthropometric, blood pressure measurements, oral glucose tolerance, and lipid profile tests. MS was diagnosed according to International Diabetes Federation (IDF) consensus for MS in children. IGT was diagnosed according to ISPAD criteria.
Results: MS was established in 17.6% of subjects (in 21.3% of males and in 15.3% of females). IGM was found in 9.5% of subjects: fasting hyperglycemia in 5.5% (3.7% in males and 6.7% in females), IGT – in 3.5% (3.7% in males and 3.4% in females) and diabetes was diagnosed in one female (0.5% of studied cohort).
Conclusion: MS and IGM prevalence in Lithuanian overweight and obese children and adolescents was evaluated for the first time and appeared to be somewhat lower compared with recently published data from other populations (MS prevalence 16–44%, IGT and diabetes prevalence 6.5 and 0.7%, respectively).

O20
Normalized f-insulin and OGTT in adolescents with severe obesity after gastric bypass surgery

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Objectives: In parallel to the 'epidemic' of obesity we also come across adolescents and children developing impaired glucose control or even overt type 2 diabetes (T2D). We wanted to assess the effect of gastric bypass surgery in adolescents with severe obesity on glycemic control.

Methods: Eighty-one adolescents, 53 female, with a mean (SD) age 16.5 (1.18) yr and a mean(SD) BMI 45.5 (6.05) kg/m^2 underwent gastric bypass surgery during 2006–2009 in a Swedish national study; 81 controls were prospectively identified in a national registry for obesity and all subjects were assessed 5 yr after surgery.

Results: After 5 yr, the mean BMI was 32.3 (6.1) kg/m^2 in operated vs. 41.1 (10.2) in controls. Mean fasting p-glucose were 4.91(0.3) mmol/L and 4.89 (0.5), f-insulin 4.21 (2.3) mU/L and 15.43 (10.6) ($p = 0.02$) and HbA1c were 32.7 (10.1)% and 37.0 (4.5) in operated and controls, respectively. The mean fasting insulin fell significantly by 25.4 (19.8) mU/L from baseline to 5 yr in operated subjects. At oral glucose tolerance test (OGTT), operated patients had a mean f-glucose of 5.23 (0.49) mmol/L and 2-h glucose of 4.16 (0.97), while controls had 5.42 (0.75) and 7.59 ($p < 0.0001$). Impaired fasting or 2-h glucose at OGTT was seen in 12 operated vs. 0 controls at baseline. At 5 yr the corresponding figures were two and six in the groups. The OGTT indicated T2D in one subject at baseline in operated group. At 5 yr one subject had T2D by OGTT criteria in the control group.

Conclusions: Most adolescents and young adults with severe obesity had and maintained a fasting glucose level and HbA1c within normal ranges over 5 yr. However, controls demonstrated pathological fasting insulin levels and OGTT after 5 yr in contrast to patients having undergone gastric bypass surgery who seem to normalize glycemic control.

O21
Epigenetic marks at 5–7y predict adiposity throughout childhood (Early Bird Study)

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Objectives: Obesity is the most important factor underlying the rise in childhood diabetes, and susceptibility may be largely epigenetic. Epigenes are chemical switches (methylations) that alter gene expression. Early environmental exposures are known to modify the risk of obesity, but epigenetic association has so far been based on single measurements at time points that are distant from either the health outcome, or the environmental exposure. Crucial evidence from longitudinal studies linking events over time is lacking.

Methods: We undertook longitudinal analysis of DNA methylation in the peroxisomal proliferator-γ-co-activator-1α promoter (PCG1α) in blood samples obtained every year for 9 yr from 40 children (20 boys). Seven CpG loci were sequenced which have been shown previously to be hypermethylated and associated with decreased PGC1α expression in overweight subjects. The association between methylation of PGC1α at 5–7y and adiposity (DEXA % fat) between 9–14y was modeled using generalized estimating equations, taking into account gender, pubertal timing, and physical activity.

Results: Methylation of CpG loci at 5–7y showed temporal stability, and predicted future adiposity. Thus (i) longitudinal tracking coefficients ($p < 0.001$ for all loci) were such that methylation at 5–7y predicted 77–88% of the variation in methylation at 14y. (ii) For each unit of methylation at 5–7y, adiposity differed by 0.63–1.25%. (iii) Methylation of one site alone (CpG4) at 5–7y predicted 10% of the variation in adiposity at 14y (a 10-fold greater prediction than FTO).

Conclusion: PCG1α is central to energy homeostasis through regulation of mitochondrial function, pancreatic β-cell function, and adipogenesis. Longitudinal collections of DNA are unusual, and these findings are novel. They suggest that early methylation of PCG1α may have a functional role in the later development of obesity, and that such epigenetic marks in early childhood may have predictive value.

O22
Leptin and adiponectin levels in children with type 1 diabetes mellitus vs. their healthy siblings

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Objectives: Adipose tissue is an active endocrine organ that is known to produce and secrete a variety of humoral factors known as adipokines. Adiponectin and leptin are considered to be among the most important adipokines. The aim of this study was to determine adiponectin and leptin levels in children with type 1 diabetes mellitus (T1D) in relation to incidence of T1D and study the impact of age, gender, and body mass index (BMI).

Methods: Data was derived from a population-based registry of diabetic children (DanDiabKids) from 1997 to 2005; 482 children with newly diagnosed T1D and were prospectively studied with serum levels of adiponectin and leptin within 3 months of diagnosis; 479 healthy siblings were chosen as a control group.

Results: Leptin levels were significantly lower in children with T1D (RR 0.74, $p = 0.003$) and they were significantly lower the first 2 d after onset of insulin treatment compared with samples taken later (RR 0.32, $p < 0.0001$). Leptin levels increased significantly from 1997 to 2005 in patients and siblings. A significant increase was found with age in children with T1D and siblings together or in siblings alone, but not in the case group alone. Our study also showed a gender difference with lower levels of leptin in boys (RR 0.52, $p < 0.001$). There was a significant decrease in adiponectin levels with increasing age and from 1997 to 2005 in the patients, and levels were lower the first 4 d after diagnosis. No significant difference of adiponectin levels regarding case-status or gender was seen. Both adipokines showed a significant correlation with BMI in children with T1D.

Conclusion: There is an increase in leptin levels and a decrease in adiponectin levels in children with or without T1D from 1997 to 2005, indicating an increased inflammation or increase in adipocytes parallel with the increasing incidence of T1D among children.

O23
Clinical and metabolic characterization of pediatric patients with type 2 diabetes newly diagnosed

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Objectives: To describe the clinical and biochemical phenotype in pediatric patients with type 2 diabetes mellitus (T2DM) at diagnosis.
Methods: We performed a cross-sectional study in children and adolescents with T2DM with <1-month of diagnosis who attended the diabetes clinic at the Hospital Infantil de Mexico Federico Gomez in Mexico City. A total of 30 patients aged 8–16 yr were recruited. A sample of venous blood was obtained after a 12-h fast in order to determine concentrations of glucose, insulin, total cholesterol, HDL-C, LDL-C, triglycerides, and HbA1c values. We measured waist circumference, weight, height, systolic and diastolic blood pressure, sexual maturation stage, disease onset, and questioning family history of T2DM. We obtained measures of central tendency and dispersion, and data were processed with SPSS V 20.0.
Results: Out of the total population studied, 50% were females, the clinical and biochemical characteristics are shown in Table 1. 53% of the patients had clinical manifestation of disease, 16.7% for positive laboratory tests and 30% with diabetic ketoacidosis. 70% had family history of T2D in second grade and 33.3% the mother was affected. 60% had morbid obesity (BMI > p99) despite lost weight before diagnosis.
Conclusions: Our results show that T2DM are associated with a greater degree of metabolic alterations. Also, the relationship between the severity of obesity and T2DM is evident. Given the close relationship between obesity, and T2DM it is imperative to implement prevention, diagnosis, and early treatment measures for obesity and T2DM involving all sectors of society.

Table 1. Anthropometric measures, blood pressure and metabolic profile of children with T2DM

Features	Total n = 30
Age (years)*	12.8 ± 2.6
Anthropometric	
Weight (Kg)*	61.1 ± 2.3
Height (cm)*	153.4 ± 14.7
BMI (kg/m^2)*	25.2 ± 5.7
WC (cm)*	85.2 ± 15.1
Blood pressure (mmHg)	
Systolic*	102.5 ± 10.4
Diastolic*	64.1 ± 7.9
Metabolic (mg/dL)	
HbA1c%	9.7 ± 3.6
Glucose†	300.0 (171–1000)
Insulin (μU/mL)	10.9 (2.9–143)
C-peptide (ng/mL)	2.5 (0.1–14.1)
HOMA-IR‡	3.4 (0.97–33.98)
Total-C*	172.8 ± 35.6
LDL-C†	101.5 (58–156)
HDL-C†	35.5 (20–69)
Triglycerides†	129.0 (56–496)
ALT (UI/L)†	53.5 (30–147)
ALT (UI/L)†	26.5 (12–80)

*Values are means ± SD.
†Values are media (min–max).
‡HOMA-IR: [(fasting glucose (mg/dL)(fasting insulin (μU/mL)/405)].

O24
Frequency of type 2 diabetes detected by urine glucose screening program in the Tokyo Metropolitan Area has been increasing in recent 5 yr, in particular among primary school children

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Objectives: We have detected many cases with childhood type 2 diabetes (T2D) by urine glucose screening program in Tokyo since 1974. We analyzed change of frequency in T2D detected by the screening system during 1974–2010.
Methods: A total of 10 508 073 children, 7 137 378 in primary school children (PSC) aged 7–12 yr and 3 370 695 in junior high school children (JHSC) aged 13–15 yr, were screened to detect childhood diabetes. Subjects, who had a positive result in urine glucose and had glucose intolerance in fasting PGs level and/or on OGTTs, were diagnosed as having diabetes. In these patients, T2D was identified on the basis of having obese, sings of insulin resistance, strong family history of T2D, and showing negative for antibodies against pancreas.
Results: (i) Two hundred seventy-nine children, 61 in PSC and 218 in JHSC, were identified as having T2D, thus, the frequencies of T2D/year/100.000 school children were 2.65 in the total, 0.85 in PSC, and 6.47 in JHSC, respectively. (ii) The frequency of T2D significantly increased after 1980s, and it was of interest that the frequency in 2005–2010 (3.40) was proved to be highest during the study period. (iii) The frequencies of T2D in JHSC was not statistically changed during the study period, while those of PSC in 1996–2000 (1.48) and in 2005–2010 (1.71) significantly increased as approximately five times as that observed in 1974–1980 (0.27).
Conclusions: We found notable increase in frequency of T2D in recent 5 yr in particular among PSC in Tokyo. Ministry of Health and Labor in Japan reported that children aged 10–12 yr have a highest frequency of obesity rather than JHSC and high school adolescents after 2000, in particular this trend is evident children residing in Tokyo. This result could be one of the reasons for significant increase of frequency in PSC in Tokyo.

Oral Session IV: Diabetes care, education and psychological issues I

O25

The SWEET-Project 2006–2012: data analysis from 741 to 5749 patients per year – improving average glycemic control and completeness of monitoring

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Objectives: 'SWEET' is an acronym derived from 'Better control in Pediatric and Adolescent diabetes: Working to crEat cEnTers of Reference' and is based on a partnership of established national and European diabetes organizations (www.sweet-project.eu) led by ISPAD. Data in participating centers were directly extracted from 2006 ongoing from local electronic health records.

Methods: The SWEET Online platform allows presently 14 centers from 13 countries to connect to one unified anonymized diabetes database. Aggregate data are de-identified and exported for longitudinal health and economic data analysis.

Results: The number of patients and patient visits increased from 2006 (n = 741) to 2012 (n = 5749), currently including 8500 patients and 105 373 patient-visits overall. For example, patients with a valid HbA1c in the data base rose from 704 (mean H bA1c: 8.1%) in 2006, to 1109 (8.1%) in 2007, 1371 (8.2%) in 2008, 1867 (8.2%) in 2009, 2838 (8.0%) in 2010, 5185 (7.9%) in 2011, and 5551 (7.9%) in 2012. The percent of patients within the target HbA1c range <7.5% increased steadily: 33% (2010), 35% (2011), and 37% (2012). Over time the completeness of data increased from 83 to 98% (HbA1c), 75 to 89% (height), 77 to 91% (weight), 50 to 65% (blood pressure), 12 to 19% (microalbuminuria screening), and 30 to 41% (hyperlipidemia screening).

Conclusions: Ongoing collection of benchmarking data motivates centers to improve data collection and reflects improving glycemic control in most participating European pediatric diabetes centers. While the degree of completeness is close to 90% or above for HbA1c, weight, and height, the assessment of diabetes-associated co-morbidities leaves much room for improvement. It remains to be clarified if these deviations from current ISPAD guidelines is a problem of data collection or comorbidity assessment and is caused by structural difficulties or lacking reimbursement.

O26

Weight gain and glycemic control in children with type 1 diabetes mellitus treated with 2 different basal bolus insulin regimens

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Objectives: (i) To evaluate the rate of overweight/obesity and change in body mass index (BMI) over 2 yr following diagnosis in children with type 1 diabetes mellitus (T1D) treated with basal bolus regimen (glargine and short-acting insulin) using fixed insulin dose for consistent carbohydrate (Fixed Regimen) and basal bolus regimen using insulin to carbohydrate ratio (Ratio Regimen). (ii) To evaluate glycemic control in children with T1D treated with Fixed Regimen and Ratio Regimen.

Methods: Data at diagnosis and clinic visits of 136 consecutive patients (age <19 yr) with newly diagnosed T1D at Nationwide Children's Hospital from July 2007 to June 2008 were analyzed. Patients were randomly treated with either the Fixed Regimen or Ratio Regimen.

Results: The rate of overweight and obesity increased significantly from 26.2% at baseline to 53.3% at 1 yr and to 42.5% at 2 yr ($p < 0.05$) in ratio group. The rate of obesity increased significantly from 9.5% at baseline to 26.7% at 1 yr and to 22.5% at 2 yr ($p < 0.05$) in Ratio group. There were no significant differences in HbA1c at each visit in each group. For the entire cohort, the rate of overweight and obesity increased from 27.8 to 42.2% at 1 yr ($p = 0.0002$), and to 40.8% at 2 yr ($p = 0.0009$). The rate of obesity increased from 15.9% at baseline to 23.7% at 1 yr ($p = 0.0195$), and to 22.4% at 2 yr ($p = 0.09$).

Conclusions: Children with T1D in our cohort had a higher rate of obesity than the national average (23.7 vs. 17%). The rate of overweight and obesity at 1 and 2 yr after diagnosis was significantly increased in T1D children treated with insulin to carb ratio, but no significant change in those treated with fixed insulin dose. There were no significant differences in HbA1c between groups. This study emphasizes the need to monitor weight gain in children with T1DM and to investigate the contributing factors of obesity and to optimize interventions to prevent overweight and obesity.

O27

HbA1c tracking' and bio-psychosocial determinants of glycemic control in children and adolescents with type 1 diabetes in the North of Scotland: retrospective cohort study and multi-level analysis

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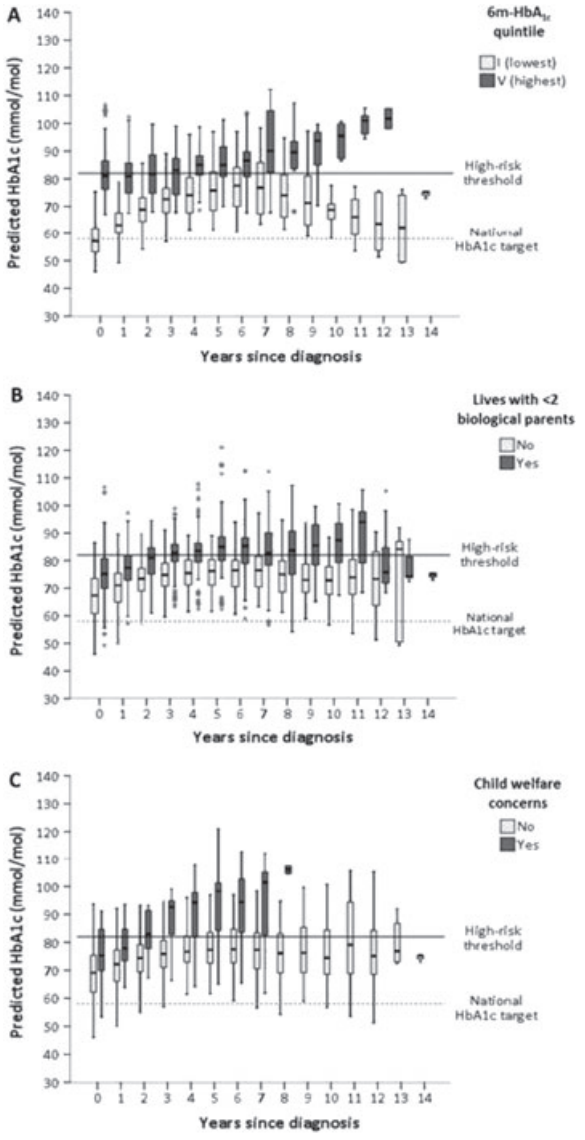
Objectives: To explore the association between HbA1c 6 months after diagnosis (6m-HbA1c) and long-term glycemic control in children with type 1 diabetes, accounting for other bio-psychosocial determinants.



Methods: We followed a retrospective cohort of 155 children and adolescents (≤16 yr) from the North of Scotland, diagnosed between January 1993 and August 2011, and receiving care between January 2008 and August 2012 (N = 3121 clinic reviews). Multi-level analysis identified the fixed effects of 6m-HbA1c on HbA1c trajectories after adjustment for auto-regression, random-effects, and covariates. Patterns of glycemic control were identified by cluster-analysis.

Results: 6m-HbA1c was positively associated with diabetic ketoacidosis at diagnosis, shorter duration of partial-remission, female gender, and psycho-social adversity. In multi-level analysis the effects of 6m-HbA1c on subsequent HbA1c trajectories remained significant after adjusting for patient and observation level predictors. An increase in 6m-HbA1c of 10 mmol/mol was associated with an average increase in HbA1c levels of 5.3 (95% CI: 4.5–6.2) mmol/mol ($p < 0.001$) throughout follow-up. Coefficients for linear and quadratic growth identified sustained effects of 6m-HbA1c on glycemic control ($p < 0.001$). Higher average levels or accelerated increases in HbA1c were associated with: age at diagnosis; autoimmune thyroid disease; falling BMI (in girls > boys); onset of mental health problems; adverse life-events; living with greater than two biological parents; child welfare concerns; neighborhood deprivation; and clinic non-attendance. Cluster-analysis identified groups with '*poor*' or '*deteriorating*' control, characterized by: older age at diagnosis; multiple psycho-social adversities; and maladaptive healthcare use (Fig. 1).

Conclusions: Early HbA1c predicted future glycemic control across childhood. Control was further modified, by biological factors, psycho-social adversity, and patterns of healthcare contact.

O28

Self-measured blood glucose values vs. simultaneous laboratory-obtained glucose-concentrations in children and adolescents with type 1 diabetes – an analysis of glucose meter accuracy and its impact on metabolic control based on a German/Austrian pediatric diabetes registry

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In patients with type 1 diabetes (T1D) self-monitoring of blood glucose (SMBG) is essential. The quality requirements for SMBG-devices are specified in the standard DIN EN ISO 15197:2003; a new, tightened draft version is available.

We compared the SMBG-values of children/adolescents with T1D with laboratory-obtained glucose levels measured in parallel and studied possible effects on HbA1c-values and hypoglycemia-rates. The DPV ('Diabetes patients observational study')-database was searched according to the criteria 'T1D/ <18 yr/ time period 2004-12/ parallel measured blood glucose values available', resulting in 9163 patients. In Clarke (Parkes) error grid analyses the percentages of SMBG-values (means) in zone A were between 91.9 and 95.6% (92.5–95.6%) over the years 2004–12. Gender, duration of diabetes, or age did not influence the proportion of zone A-values significantly. 91.5–95.3% of the SMBG-measurements met the current DIN standard (requirement >95.0%). The proposed new DIN-version's criteria could not be met: 82.9–89.3% of the SMBG-values fell within the required range of tolerance. For a linear regression, 8760 SMBG-values (most current measurement per patient) were divided into quartiles according to their deviation from the laboratory-obtained glucose levels: 'far too high' (Q1)/ 'too high' (Q2)/ 'too low' (Q3)/ 'far too low' (Q4). Too low SMBG-values resulted in significantly higher HbA1c-values (comparison of Q1/Q4: $p = 0.0002$; Q2/Q4, Q3/Q4: $p < 0.0001$, respectively). A Poisson regression with 9163 glucose pairs revealed a significant influence on the frequency of severe hypoglycemia, especially with coma (comparison of Q1/Q2: $p = 0.0383$; Q1/Q3: $p = 0.0001$; Q1/Q4: $p = <0.0001$). In summary, we could show that the currently used SMBG-devices barely fulfill the actual but not at all the planned ISO standard criteria. Deviations of the SMBG-values from the 'true' glucose levels have a negative impact on metabolic control and contribute to dangerous hypoglycemic events.

O29

Blood glucose and C-peptide in healthy school-children in relation to their physical activity: a part of the prospective longitudinal ABIS cohort

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Introduction: The incidence of type 1 diabetes (T1D) increased rapidly during the 90s and early 2000 parallel to an increase in weight of children, which fits with the beta cell stress hypothesis suggesting that increased insulin demand might contribute to T1D. As, in addition, physical activity might have decreased we wanted to investigate if lower physical activity further increases beta cell stress already in children.

Participants and methods: A subgroup of school children from the prospective cohort ABIS (All Babies in Southeast Sweden) were asked to participate in some extra tests; 199 children (100 girls and 99 boys) in two communities (130 from Linköping and 69 from Kalmar) participated at age 8, and 107 children from one of the communities (Linköping) participated in a follow-up at age 12 (51 girls and 56 boys). Physical activity was objectively measured as average daily steps (by pedometers), and also subjectively estimated by questionnaires. We used anthropometric data and measured HbA1c, C-peptide, f-glucose, HOMA-IR, and HOMA-B.

Results: Low physical activity was related not only to anthropometric measures but also to insulin resistance and β-cell stress. Thus the more daily steps the lower BMI ($p < 0.02$), lower waist circumference (8 yr: $p < 0.02$; 12 yr $p < 0.001$), lower C-peptide ($p < 0.03$ resp < 0.001), HOMA IR ($p < 0.03$ resp < 0.001), and HOMA β ($p < 0.03$ resp $p < 0.001$). The connection was especially pronounced in boys, who were more physically active than girls both at 8 and 12 yr of age ($p < 0.001$).

Conclusions: Already in young children low physical activity is related not only to body measures, e.g., increased waist circumference but also to insulin resistance, increasing the load on the β-cells. Facilitating physical activity in children might decrease the risk of diabetes, both type 1 and type 2.

O30

Moderate to vigorous physical activity (MVPA) is associated with lower fasting glucose in overweight and obese children and adolescents

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Background and objectives: Increased habitual physical activity (PA) can be protective against development of type 2 diabetes. In children, the intensity of PA conferring improved glycemia is unclear. Our objective was to evaluate effects of PA on fasting glucose and insulin resistance (IR).

Methods: Total PA was assessed in overweight/obese children age 8–18 yr using doubly-labeled water (non-resting energy expenditure: NREE). MVPA values were defined according to previously established cutoffs (>2295 counts/min) using an accelerometer worn for 7 d. Glucose and insulin measures were determined through fasting venous blood samples. IR was calculated as HOMA-IR (glucose mmol/L × insulin mU/L)/22.50). Body composition was assessed by air displacement plethysmography. Linear regression models with interaction between the independent variables and PA were performed.

Results: Mean age was 13.2 ± 2.4 yr, BMI 27.2 ± 5.9 kg/m^2, MVPA 45.1 ± 26 min/d. For the entire group, lower FM was associated with lower fasting glucose ($p = 0.05$) with a positive interaction with MVPA such that those with lower MVPA demonstrated increasing fasting glucose for increasing fat mass (FM) compared with those with higher MVPA ($p = 0.04$). No interaction was found for MVPA, FM, and HOMA-IR. Likewise, total time spent in PA was not associated with glucose or IR.

Conclusions: A larger proportion of time spent in regular MVPA may provide a protective effect against high fasting blood glucose associated with increasing fat mass in overweight/obese children. This effect may occur via insulin-independent mechanisms.

O31

Increase in physical activity is associated with lower HbA1c levels in children and adolescents with type 1 diabetes: results from a cross-sectional study based on the Swedish pediatric diabetes quality registry (SWEDIABKIDS)

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Objectives: Physical activity is an important part of diabetes management. However, studies concerning the relation between physical activity and metabolic control have shown conflicting results. In this study we wanted to evaluate the effect of physical activity (PA) on metabolic control, measured by glycosylated hemoglobin (HbA1c) in a large cohort of children and adolescents with type 1 diabetes.

Methods: Cross-sectional analysis of data from 4655 patients in 2010–2011, comparing HbA1c values with levels of physical activity. Data were obtained from the Swedish pediatric diabetes quality registry, SWEDIABKIDS. The patients were 7–18 yr of age, had type 1 diabetes and were out of remission. The patients were grouped by frequency of physical activity lasting at least 30 min each week as follows: PA0, none, PA1, less than once a week, PA2, one to two times per week, PA3, three to five times per week, and PA4, every day.

Results: The frequency of physical activity was lower for older children and adolescents ($p < 0.001$), mean age varying from 13.5 yr in PA4 to 15.9 yr in PA0. Mean HbA1c level was higher in the least active group [PA0: 70 ± 15 mmol/mol (8.5% ± 1.4)] than in the most active group [PA4: 61 ± 13 mmol/mol (7.8% ± 1.2)] ($p < 0.001$). Linear regression showed an inverse dose–response association between physical activity and HbA1c (β: −2.7, 95% CI: −3.0 to −2.3, $p < 0.001$). This effect was found in both sexes and all age groups, apart from girls aged 7–10 yr ($p = 0.252$). Multiple regression

analysis revealed that the association remained significant (β: −2.0, 95% CI: −2.4 to −1.7, p < 0.001) when adjusted for disease duration, insulin dose, insulin methods, and hypoglycemia.
Conclusions: This study indicates that a higher level of physical activity results in better metabolic control. More studies with objective methods in large populations are required to confirm the inverse dose–response relationship between physical activity and HbA1c.

O32
mHealth in diabetes management – the BLink experience

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Objectives: We analyzed the effect of a closed-loop diabetes decision support system (BLink®). Blood glucose data were synchronized by smartphone with a web-based personal health record (PHR), linked to the electronic medical record system (EMR).
Patients: We included 29 patients with T1DM, mean age 15 yr (11–20 yr), mean diabetes duration 4.7 yr (0.6–13 yr). All patients were on MDI. HbA1c ranged from 68 to 110 mmol/mol (4.6–2.9%), mean 68 mmol/mol (8.3%).
Methods: Patients used a Glucomen LX Plus® meter, an Android smartphone (Samsung Galaxy Y®) and an individual PHR-account (Patient1®). Data transfer from meter to smartphone was via bluetooth, then to the PHR as encrypted internet data and to the EMR (Norma®) by a VPN connection. Patients could contact a help-desk for technical problems. These were logged in a FAQ database about the most common errors and their solutions. At the start and after 3 and 6 months, patients and diabetes nurses filled out questionnaires about the usability of the system.
Results: Patients encountered minimal technical problems, the majority caused by human error. Four patients did not complete the study. The mean number of blood glucose measurements (nBG) was 25 ± 10 wk. nBG did not change significantly after 3 and 6 months. Mean HbA1c decreased from 68 mmol/mol (8.3%) to 65 mmol/mol (8.1%). A positive correlation was found between nBG and HbA1c, corresponding to previous reports. nBG did not correlate with age, diabetes duration, or gender. There was a positive evaluation on the usability of the system in patients and diabetes nurses. The fixed-format of data presentation highly facilitated the communication with our diabetes team.
Conclusion: BLink® empowers patients in closer monitoring of their blood glucose by facilitating trend-analysis and communication with their caregivers, and this effect continues after 6 months. Furthermore, it enhances the uniformity of the data presentation, thus improving the workflow of the health professionals.

Oral Session V: Diabetes care, education and psychological issues II

O33

Higher glucose concentrations following protein and fat rich meals: results of a pilot study in adolescents with type 1 diabetes (The Tuebingen Grill Study)

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Background: Traditionally, insulin dosage is adjusted according to the estimated carbohydrate amount of meals. However, it is generally accepted that protein and fat also influence blood glucose though the magnitude of these influences is unknown.
Objectives: To investigate the influence of a fat and protein-rich meal on glucose concentrations in adolescent patients with T1D.
Patients and methods: Fifteen adolescent (two female) patients, mean age 16.8 (SD 2.9) yr, HbA1c 6.9 (SD 0.6)%, insulin dose 0.9 (SD 0.3) IU/kg/d, with T1D were investigated. On two consecutive days they received a standard evening meal (SM) with fat 19 g = 30 kcal%, protein 28 g = 20 kcal%, carbohydrate 70 g = 50 kcal% and a fat protein rich (FPM) evening meal with fat 52 g = 40 kcal%, protein 110 g = 40 kcal%, carbohydrate 70 g = 20 kcal%. Insulin adjusted for carbohydrate amount was injected with the individual carbohydrate bolus and remained identical when switching from SM to FPM. Glucose was measured continuously with the Enlite Sensors and the Guardian System (Medtronic) overnight during the following 12 h after the meal.
Results: Glucose area under the curve (AUC) for SM was 1400 (SD 580) mg/dL/12 h and for FPM 1967 (SD 394) mg/dL/12 h ($p < 0.05$). There was a significant difference in the AUC between 4 and 12 hours after the meal. Maximal AUC difference was 6 h after the meal. Glucose concentrations in the morning (12 h after the meal) differed: 91 (SD 34) mg/dL after SM and 153 (SD 60) mg/dL after FPM ($p < 0.05$). For SM 31% of glucose levels were <80 mg/dL and 24% >150 mg/dL, for FPM it was 3 and 48%.
Conclusion: In adolescents with T1D, glucose concentrations are significantly higher following a fat and protein rich meal. This effect is detectable up to 12 h after the meal. Subsequent studies will investigate how this effect can be reduced by additional insulin administration.
Supported by the Arbeitsgemeinschaft für Pädiatrische Diabetologie and Medtronic.

O34

Healthy and unhealthy eating behavior in adolescents with type 1 diabetes: the role of depression and HbA1c

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Objectives: To examine if adolescents with type 1 diabetes (T1D) differ in healthy and unhealthy eating behavior from peers without a chronic disease. In the group adolescents with T1D we further investigated if adolescents with suboptimal/poor metabolic control differed in eating behavior from adolescents with optimal metabolic control, and if adolescents with and without elevated levels of depressive symptoms differed in eating behavior.
Methods: One hundred fifty-one adolescents with T1D (mean 14.9 ± 1.7 yr) and a comparison group (CC) (N = 122) reported their healthy and unhealthy eating behavior on the Health Behavior in School-aged Children (HBSC) questionnaire. They also reported their depressive symptoms on the Children's Depression Inventory (CDI). Recent HbA1c was recorded from medical charts.
Results: Adolescents with T1D differed from the comparison group in the more structural use of diet soda ($p = 0.000$) and eating breakfast ($p = 0.007$). No differences in unhealthy eating behaviors were found. Adolescents with suboptimal or poor HbA1c (>58 mmol/mol) reported significantly more unhealthy eating behavior, namely dieting to lose weight ($p = 0.002$), compared with adolescents with optimal HbA1c (<58mmol/mol). Adolescents with elevated levels of depressive symptoms (CDI > 13) significantly more often skipped lunch ($p = 0.000$) and dinner ($p = 0.006$) and insulin boluses or injections to control weight ($p = 0.000$), than adolescents without elevated levels of depressive symptoms.
Conclusions: Overall, adolescents with T1D do not differ in healthy and unhealthy eating behavior from peers without a chronic disease. However, in the group adolescents with T1D some differences in eating behavior were found depending on the risk group they belonged to (optimal HbA1c or not, and depressive or not). Dieting to lose weight was especially related to suboptimal/ poor HbA1c. Skipping lunch meals and insulin boluses or injections to control weight was especially related to elevated levels of depressive symptoms.

O35

Are we using current up-to-date evidence in the delivery and documentation of sick day management education to children and adolescents with type 1 diabetes?

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Objectives: To improve the delivery, documentation, and understanding of sick day management amongst children, adolescents, and families diagnosed with type 1 diabetes by reviewing educational practices.
Methods: The project used a pre/post-intervention audit design looking at six audit questions developed from the evidence. Twenty randomly selected patient charts were reviewed looking at educational practices of credentialed diabetes educators and how their practice aligned with the audit questions. Postimplementation audit chart review was undertaken to see if practice change had occurred (n = 20). A literature review on sick day education (SDE) revealed professional guidelines for managing sick days, however, did not reveal any dosing tables adapted for patient use for managing periods of ketosis. Such a tool was developed and used to enhance teaching. Ethical approval was received from the relevant HREC.
Results: Improvements in compliance with best practice were seen across all six audit questions as follows: (i) SDE given to all patients, preimplementation 90% postimplementation 94%; (ii) SDE given within 6 months of diagnosis, pre- 90% post- 94%; (iii) easy to use sick day/ketone table used to support SDE, pre- 5% post- 43%; (iv) SDE documented reflecting what was taught, pre- 0% post- 37%; (v) patient understanding evaluated, pre- 0% post- 50%; and (vi) SDE

given is activity based, pre- 0% post- 43%. This illustrates significant changes to practice were attained.
Conclusions: Developing an educational, engaging, personally relevant program to address sick day management in type 1 diabetes is an important issue given the rising incidence of admissions with diabetic ketoacidosis in Australia across this age range. Results show that by reviewing the evidence and using audit and feedback changes to practice can be introduced. Incorporating the use of a sick day/ketone insulin dosing table developed for patient use and point of care reminder assisted with practice change.

O36
Improving outcomes for adolescents with type 1 diabetes: results from the Kids In Control OF Food (KICk-OFF) trial

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Objectives: KICk-OFF (KO) is a 5 d group self-management education course for 11–16 yr-old with type 1 diabetes. The aim of this cluster randomized trial was to assess whether the course improved biomedical and psychological outcomes over 2 yr.
Method: Four hundred thirty-six participants were recruited from 31 UK centers, randomized to control (n = 14) or intervention (n = 17). Randomization was stratified by level of pre-existing education delivery (low/medium/high). Control centers continued their usual care and education. Children in KO centers attended one of the 31 KO courses. Primary predefined outcome measures were HbA1c, generic (PedsQL-G) and diabetes specific (PedsQL-D) quality of life measured at 6, 12, and 24 months. Secondary outcomes included BMI, DKA, and hypoglycemia rates. Analysis was by whole group and three baseline HbA1c subgroups.
Results: Baseline data were collected on 396 participants: demographics were similar in both arms. Compared with controls, at 6 months the KO group showed significant improvement in PedsQL physical, social, and psychosocial scores. Diabetes symptoms significantly improved at 6 months ($p = 0.008$) and treatment adherence improved in KO arm at 12 months ($p = 0.02$) and 24 months ($p = 0.029$). Overall HBA1c did not significantly change over time. However the sub-group with an HbA1c of >80 mmol/mol at baseline showed a steady improvement in mean HbA1c for KO compared with controls (Mean diff KO – Control: 6 months 2.2 (CI: −3.3, 7.6; $p = 0.44$); 12 months 0.5 (CI: −5.9, 6.9; $p = 0.88$); 24 months −8.55 (CI: −16.4, −0.7; $p = 0.03$).
Conclusion: Participation in KICk-OFF resulted in significantly improved psychological outcomes at 6 months, improved diabetes symptoms and adherence to treatment. For those with the poorest control at baseline, glycemic control improved during the 2 yr of the study for KICk-OFF participants compared with controls, reaching significance at 24 months. This, if sustained, is likely to reduce their risk of long-term complications.

O37
International Diabetes Federation (IDF) Life for a Child (LFAC) index of diabetes care for children and youth

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Objectives: The objective of the LFAC Index of Diabetes Care for Children and Youth is to provide a standardized, reproducible measure that can be used globally to document and compare critical factors influencing outcomes.
Methods: The Index consists of 36 multiple choice questions and is completed by a key person aware of the standard of care in each country. Minimum score is 0, maximum 130. The Index was sent to 43 countries in which LFAC operates, as well as 33 others.
Results: Responses were received from 40 LFAC countries and 19 others (income levels: 18 low, 17 lower-middle, 10 upper-middle, and 14 high). Total raw scores for low-income countries were from 16–67; lower-middle 16–77; upper-middle 36–90; and high 71–128. Of 35 low/lower-middle income countries, only 2 (6%) had full government provision of human insulin and 1 (3%) of blood glucose test strips. In the others, non-government support was required. Nine (25%) had ≥10% usage of insulin pens. Only two (6%) had >5% of families with glucagon access and six (17%) urine ketone strips; 19 (54%) had home refrigerator access of <33%. HbA1c testing was available in 33 (94%), 15 (42%) with point-of-care testing. Most common insulin regimens were twice daily mixed or regular/NPH. Eight (22%) predominantly used multiple daily injections; 16 (45%) had pediatric endocrinologists. Access to nurse educators, dietitians, appropriate education resources, 24-h phone service, and complications screening was, if present, mostly limited to major centers. Long travel times were common. Deaths from misdiagnosis of diabetic ketoacidosis were highly likely in 12 countries (36%). In comparison, governments in high-income countries generally provide all components of comprehensive care.
Conclusion: In many low-income countries, major challenges remain in access to insulin and other supplies. Continued health professional training and mentoring is integral to optimizing outcomes in each country.

O38
Normalizing: adolescent experiences in living with type 1 diabetes

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Objectives: The purpose was to gain a greater understanding, from the adolescent's perspective (ages 11–15), of their experiences living with diabetes, associated challenges and management issues. The aim was to build a theoretical paradigm that captured the main categories and behaviors in the experiences of adolescents and provided much needed information and hypotheses to support interventional design.
Methods: Classical grounded theory with constant comparative analysis using gerund coding was utilized with 15 interviews.
Results: The substantive theory that was developed was '**normalizing**'. Normalizing is defined as the ability of adolescents to integrate diabetes into the background of their daily life by creating routines to make diabetes 'part of me'. The conceptual codes that describe normalizing include: (i) 'recognizing life is changing', (ii) 'taking action to prevent a crisis', (iii) 'disclosing to engage support', (iv) 'taking on the burden of care', (v) 'accepting the 'new normal'', and (vi) 'hoping for a normal future'. Normal developmental tasks are closely related to each step of this normalizing process and help to explain why adolescents struggle with diabetes during adolescence.
Conclusions: Needle fear, moving through transition to self-care, conflict with parents, and the interactions, reactions, and emotions of others were key processes that affect the ability to normalize. Strategies to manage diabetes include: maintaining motivation, building trust, and learning to cope. Supportive behaviors of parents,

peers, teachers, and others were helpful. When researchers and clinicians view this stage as an attempt to normalize their life, it places a positive perspective on this process with a focus on wellness and maintaining a normal life rather than on illness. This creates opportunities to provide education and interventions to help adolescents normalize, and assist their parents, peers, schools, and communities to help them normalize as well.

O39
Psychosocial functioning is not associated with current glycemic control in preadolescence

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Objectives: Adolescents with T1DM have a higher prevalence of depression and other psychosocial problems than healthy adolescents, and psychosocial problems are a known predictor of poorer glycemic control in adolescence. However, psychosocial functioning and its association with glycemic control in middle-childhood have not been thoroughly studied. This study assessed both adaptive and maladapti.

Table 1. Comparison between T1D and T1D + AN, or T1D + BN/BED

Adjusted estimates	T1D	T1D + AN	T1D + BN/BED
HbA1c (mmol/mol)	68.7 ± 0.1	71.1 ± 1.8	81.8 ± 2.1*
Daily insulin dosage (units/kg)	0.85 ± 0.002	0.77 ± 0.026*	0.79 ± 0.031
Insulin pump (%)	25.0	18.6	16.0*
Pathological insulin injection sites (%)	35.2	45.5*	48.9*
Hypoglycemia with coma (per pat. year)	0.02 ± 0.001	0.05 ± 0.018*	0.04 ± 0.020
Ketoacidosis (per pat. year)	0.07 ± 0.002	0.12 ± 0.028*	0.14 ± 0.038*
Retinopathy (%)	2.1	1.3	5.8*
Inpatient care (per pat. year)	0.6 ± 0.01	1.0 ± 0.09*	1.3 ± 0.13*
Hospital duration (days per pat. year)	2.4 ± 0.01	8.5 ± 0.25*	10.5 ± 0.36*

Conclusions: In pediatric and young adult females with T1D, EDs are probably underestimated. However, they are associated with a worse metabolic control and a negative effect on the course of diabetes. Diabetologists should be aware of comorbid EDs in T1D in order to refer patients to psychological consultations in time and to offer maybe new treatment options, e.g., continuous glucose sensors.

O40
Life chances (''*Lebenschancen*'') of young adults with onset of type 1 diabetes during childhood

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Objectives: The concept of ''Life chances'' introduced by Max Weber, describes the likelihood, that an individual is able to satisfy one's needs. Young adults with T1DM face several life-tasks. In a cross-sectional study the socioeconomic, emotional and overall health status of 19–30 year old adults with T1DM and predictors of their HbA1c and QoL are assessed.

Methods: In 26 diabetes practices (Lower Saxony) all adults (19–30 yrs, onset of T1DM < 18 yrs) were invited to answer questionnaires on their demographic, educational, occupational, and diabetes specific status, their emotional well-being (WHO-5) and diabetes specific distress (PAID).

Results: Among 306 participants (47% female; age 24.1 ± 3.5 yrs; diabetes duration 11.7 ± 5.8 yrs; 43% CSII) 20% reported of a physical co morbidity, 11% of a psychological disorder, and 33% of a severe life event (past 12 months). Mean HbA1c was 8.3 ± 1.6% (CSII 8.0 ± 1.4 vs. MDI 8.4 ± 1.8; $p = 0.02$). Severe life events and psychological disorders predicted HbA1c (each $p < .001$), but not co morbidity. Mean score of WHO-5 was 13.5 ± 0.3 with 15.4% of young adults scoring < 8 (indication for depressive disorder). Mean score of PAID was 26.8 ± 20 with 25% of the participants experienced serious distress (> 39 cut off score). Stress was mainly connected to ''worrying about future'', and ''feeling guilty''. Both psychological measures were associated with HbA1c ($r = -0.14$; $r = 0.23$). All participants graduated from school, 49% with high school graduation, only 6% were unemployed. These data point to a higher educational level and lower rate of unemployment compared to the regional background population.

Conclusions: Despite the chronic disease the majority of young adults solved the age specific life-tasks successfully with good/acceptable metabolic control. About 25% were affected by anxiety of late complications, depressive mood, low confidence in self-management and/or reduced quality of life. They require specific advice to better cope with T1DM.

Oral Session VI: Diabetes care, education and psychological issues III

O41

Parental burnout in relation to sociodemographic, psychosocial and personality factors as well as disease duration and glycemic control in children with type 1 diabetes mellitus

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Objectives: To be a parent of a chronically ill child sets new demands on the parental role. We have recently shown that the frequency of burnout symptoms is doubled, 42.9 % vs. 20.5 % ($p < 0.001$), in mothers of children with Type 1 Diabetes compared to control mothers (Acta Paediatr 2010;99(3):427–32). The aim in this study is to examine associations between burnout and sociodemographic, psychosocial, personality, medical factors in parents of children with T1DM.

Methods: 252 parents of children with T1DM participated in a population-based study. We used self-report questionnaires to assess symptoms of burnout and background factors. To analyse associations between burnout and demographic, psychosocial, personality and medical variables we used Chi-Square test, Kruskal-Wallis test and Mann-Whitney's U-test.

Results: Psychosocial background factors were significantly associated with burnout in parents, whereas there were no associations between sociodemographic or medical factors and burnout. For both genders parental burnout was associated with low practical social support (mothers $p < 0.02$, fathers $p < 0.04$), lack of leisure time (m $p < 0.03$, f $p < 0.01$), and a perception that the child's disease affects everyday life (m $p < 0.00$, f $p < 0.06$). Self-esteem based on performance ($p < 0.00$), and high need for control ($p < 0.00$) were risk factors for maternal burnout.

Conclusion: In the screening of risk factors for long-term stress in parents of children with T1DM we should recognize parents' attitudes and psychosocial issues. In clinic consultations we need to pay attention to the day-to-day life circumstances in the support of these parents. Certain factors were associated only for mothers; personality traits may indicate a link between maternal parenting and burnout. Continued research about the causal relationship between the parental responsibility, psychosocial factors and gender aspects of burnout is warranted. Support program for affected parents should be evaluated.

O42

Experience of a stressful life event increases the risk for childhood type 1 diabetes: the ABIS population-based prospective cohort study

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Objective: To prospectively investigate the association between childhood type 1 diabetes (T1D) and the experience of serious life events in the family before diagnosis.

Methods: The population-based All Babies In Southeast Sweden (ABIS) cohort invited all babies born between Oct 1st 1997 and Oct 1st 1999 in southeast Sweden. Our study sample includes n=10445 who participated in at least one of the follow ups at 2–3 years, 5–6 years, 8 years and 10–13 years, n=58 children later got T1D. Age at diagnosis of T1D was obtained from the national register SweDiabKids at 31 Dec 2012. Experiences of serious life events (SLE) both for the child and for the parent were assessed separately by two questions followed by checklists consisting 7 to 14 specified events. SLE for the parent were assessed at all four follow-ups, and SLE for the child at all except 2–3 years in questionnaires completed by one of the child's parents.

Results: Experience of a serious life event for the child previous in childhood was associated with higher risk for later diagnose of T1D (hazard ratio = 2.3; p = 0.01). A serious life event experienced by one parent was significantly associated to diagnosis when reported the last 3 years before diagnosis of T1D (hazard ratio = 2.2; p = 0.03).

Conclusions: Consistent with previous results from several retrospective studies, this first prospective study concludes that experience of a serious life event in the family seems to be one factor that can contribute to the development of type 1 diabetes in children.

O43

Italian translation, cultural adaptation and validation of the PedsQL™ 3.0 Diabetes Module (PedsQoLDM) questionnaire in children and adolescents with type 1 diabetes (T1DM) and their parents

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Objective: To assess reliability and validity of the PedsQL™ 3.0 Italian version after cultural adaptation. Items were: "Diabetes symptoms", "Treatments barriers", "Treatment adherence", "Worry" and "Communication".

Methods: In a multicenter study the PedsQL™ 3.0 was administered to 172 Italian children and adolescents (C&A) with T1DM aged 5–18 years and 104 parents (P) by trained psychologists after translation in Italian according to the MAPI Institute algorithm.

Results: Data completeness was optimal. Item internal consistency was satisfied at 89% for the C and 100% for the P proxy-report scales. Discriminant validity was satisfied for 71% of C&A and for 82% of P. Adequate Cronbach´s α coefficient >70% was found for items of both reports, other than those for all the sub-scales in the C self-report scales (range 0.61 - 0.67), and for the "Diabetes symptoms", "Treatment barriers" and "Communication" sub-scales of patient

proxy-report scales. For the test-retest reliability, the Pearson correlation coefficients (PCC) and ICCs ranged from 0.66% to 0.82% for all subscales of the C self-report; only the ''Worry'' subscale had a value < 70%. PCC ranged from 37% to 99%, the ICCs ranged from 31% to 99% for the P proxy-report. All sub-scales coefficients were > 70%. Factor analysis showed that the PedsQoLDM for C self-report could be summarized into 10 components, explaining 62% of the variance. For the P proxy-report statistical analysis selected 9 factors which explained about 68% of variance. The external discriminating validity and responsiveness were compared across gender, age, time since diagnosis and HbA1c mean values. Differences in ''Treatment adherence'' and ''Communication'' were observed for age ≤7 years, and in ''Treatment adherence'' for time since diagnosis ≤1year.

Conclusions: Italian translation of the PedsQL™ 3.0 is easy to understand and reduces cultural biases supporting its use as an outcome measure for diabetes cross-national clinical trials/ research.

O44

Quality of life of 11- to 17-year-olds with early onset type 1 diabetes and mental health problems

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Objectives: To evaluate quality of life (QoL) in youths with mental health problems (MHP) and early onset type 1 diabetes (T1DM) compared to representative non-diabetic peers with MHP in Germany.

Methods: The 11- to 17-year old participants were diagnosed with T1DM when they were younger than 5 years of age (N=629, 54% boys, mean age 15.3 years (standard deviation 1.7), diabetes duration 12.5 (1.6) years, HbA1c 8.3% (1.3)). Data on MHP and QoL were compared with those of a representative German sample (KiGGS study, N=6813, 51% boys, age 14.6 (2.0) years). The participants answered the strengths and difficulties questionnaire (SDQ). Youths with abnormal scores in at least 2 of the 5 SDQ-subscales (emotional symptoms, hyperactivity, conduct problems, peer relationship problems, prosocial behaviour) were considered to have mental health problems. QoL was assessed by means of the KINDL-R self-report questionnaire (scale 0–100, higher values in the total score and the subscales indicate higher QoL). Multivariable regression analyses were performed adjusted for age group and gender. Results are reported as adjusted mean differences between groups (regression coefficients (β) and standard errors (SE)).

Results: The proportion of youths with MHP was 5.3% in the patient group and 3.7% in the general population (OR=1.5 (95%-CI 1.0-2.1), p=0.067). Youths with T1DM and MHP scored lower in the KINDL-R subscales physical well-being (β=−16.1 (SE 3.6), p< 0.001), family (β=−11.2 (4.6), p=0.015), friends (β=−9.2 (4.0), p=0.023) and in the KINDL-R total score (β=−7.4 (2.3), p=0.001) than peers with MHP, while there were no differences in the subscales emotional well-being, self-esteem and school.

Conclusions: Compared with the general population with MHP, the QoL of young people with diabetes and MHP is more severely impaired. This observation calls for early prevention and intervention as part of paediatric diabetes long term care.

O45

The analysis of quality of life parameters in adolescents with type 1 diabetes

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Objective: To estimate the parameters of quality of life (QOL) in type 1 diabetes (MD1 type).

Materials and Methods: The study group was included 42 adolescents (15 ± 0,9 years). Duration of diabetes 2–7 years (4,6 ± 1,4 years). We conducted general examination and psychological questionnaire ADDQoL.

Results: The mean level of QOL was 1,38 ± 1,0 points. The majority of patients (67%) rated their QOL as ''very good'' and ''good'', 62% of the patients stated that if they did not have diabetes, QOL ''would be better''. MD1 type has a negative impact on all aspects of life (−2,8 ± 0,8). The most negative effect was noted in (−4): professional life, travel, freedom of choice of food and drinks. To a lesser extent diabetes affects (−2) freedom of movement family life, outside, motivation, the reaction of others, confidence in the future, financial position, living conditions. It was found that diabetes has a more pronounced effect on the QOL of boys than girls (p = 0,045).Boys often showed a decrease in the scales: of travel (−5.9), freedom of choice of food (−5.8), of beverages (−5.8), professional life (−5), free time (−4, 8), confidence in the future (−4), physical condition (−4), confidence (−3.9), social services (−3.5), wealth (−3.5), freedom of movement (− 3). While the girls are most reduced following indicators: professional life (−2.8), freedom of choice of food (−2), leisure (−1.8), appearance (−1.8), the scope of travel (−1.7), social services (−1.5), freedom of movement (−1.4), physical condition (−1.3).The study found relationship between the level of glycemia (p = 0,042), HbA1c (p = 0,02), duration of disease (p = 0,036) with the aspects of quality of life, according to a ADDQoL.

Conclusions: 1. MD1 type has a negative impact on all aspects of quality of life.

2. We found gender differences, providing a more pronounced effect on the QOL of boys over girls.

3. The level of blood glucose, HbA1c, duration of disease affects the quality of life.

O46

Characteristics of type 1 diabetes in 223 females with clinically recognized comorbid eating disorder identified among 24,399 female paediatric and young adult type 1 diabetes patients

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Objectives: To compare diabetes treatment and complications in female paediatric and young adult type 1 diabetes (T1D) patients with and without comorbid eating disorder (ED).

Methods: The multicentre, prospective German/Austrian diabetes patient registry (www.d-p-v.eu) was searched for the diagnosis of comorbid ED in T1D. Until March 2013, 24,399 female T1D patients aged 8-< 30 years (median[Q_1;Q_3]:16.1[13.0;17.9]), with documented insulin dosage, weight, height, and with no coeliac disease were registered. In 132 females (17.3[15.7;18.8] yrs.) the additional diagnosis anorexia (AN) was documented; bulimia (BN) or binge eating disorder (BED) in 91 females (17.7[16.6;20.2] yrs.). Multivariable regression models adjusted for age and diabetes duration were created; adjusted estimates were calculated. Statistical package: SAS 9.3.

Results: 0.9% of females with T1D revealed a clinically recognized comorbid ED. The table summarizes the comparisons between T1D and T1D+AN, or T1D+BN/BED (*p< 0.05). In T1D with ED, HbA1c was higher and complications were on average more common.

Conclusions: In paediatric and young adult females with T1D, EDs are probably underestimated. However, they are associated with a worse metabolic control and a negative effect on the course of diabetes. Diabetologists should be aware of comorbid EDs in T1D in order to refer patients to psychological consultations in time and to offer maybe new treatment options e.g. continuous glucose sensors.

Adjusted estimates	T1D	T1D+AN	T1D+BN/BED
HbA1c [mmol/mol]	68.7±0.1	71.1±1.8	81.8±2.1*
Daily insulin dosage [units/kg]	0.85±0.002	0.77±0.026*	0.79±0.031
Insulin pump [%]	25.0	18.6	16.0*
Pathological insulin injection sites [%]	35.2	45.5*	48.9*
Hypoglycemia with coma [per pat. year]	0.02±0.001	0.05±0.018*	0.04±0.020
Ketoacidosis [per pat. year]	0.07±0.002	0.12±0.028*	0.14±0.038*
Retinopathy [%]	2.1	1.3	5.8*
Inpatient care [per pat. year]	0.6±0.01	1.0±0.09*	1.3±0.13*
Hospital duration [days per pat. year]	2.4±0.01	8.5±0.25*	10.5±0.36*

[Comparison between T1D and T1D+AN, or T1D+BN/BED]

O47
Associations between individual depressive symptoms and HbA1c are different between teenage boys and girls with DM1

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Objectives: Earlier studies have found that depression is associated with higher levels of HbA1c. Yet, depression is a heterogeneous concept consisting of a variety of symptoms that reflect emotional problems. Therefore the relationship between individual depressive symptoms and blood glucose regulation (HbA1c) is examined in teenage boys and girls with T1D.

Methods: One hundred fifty-one adolescents with T1D aged 12–18 yr (65 boys: mean 15 ± 2 yr and 86 girls: mean 15 ± 2 yr) reported their depressive symptoms on the Children's Depression Inventory (CDI). The 27-items refer to cognitive, affective, and behavioral depressive symptoms. Recent HbA1c was recorded from medical charts. Separate regression analyses for boys and girls were performed to examine the association between each individual depressive symptom and HbA1c, adjusting for age.

Results: The depressive symptoms self devaluation ($\beta = 0.25$, $p = 0.02$), suicidal ideation ($\beta = 0.22$, $p = 0.05$), negative body image ($\beta = 0.32$, $p = 0.00$), and disobedience ($\beta = 0.29$, $p = 0.04$) were significantly related to higher HbA1c values in girls. The depressive symptom pessimistic worrying ($\beta = 0.28$, $p = 0.04$) was significantly related to higher HbA1c values in boys. The total number of depressive symptoms was not significantly related to HbA1c in both boys ($\beta = 0.01$, $p = 0.93$) and girls ($\beta = 0.17$, $p = 0.11$).

Conclusions: Several individual depressive symptoms were related to higher HbA1c levels. The association between depressive symptoms and HbA1c differed between boys and girls. Negative body image was especially related to less optimal HbA1c in girls, pessimistic worrying was especially related to suboptimal HbA1c in boys. Further study of these individual depressive symptoms, both in research as well as in clinical practice is relevant, in order to find a specific entrance for psychological treatment that may be associated with both a better mood and more optimal blood glucose regulation in both boys and girls with T1D.

O48
The use of a brief psychological screening tool to screen for disordered eating in adolescents with type 1 diabetes

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Objectives: Adolescents with type 1 diabetes have an increased risk of developing a range of psychological issues. This study assessed if a brief screening measure of psychopathology was associated with disturbed eating behaviors and cognitions in adolescents with type 1 diabetes.

Methods: In this cross-sectional study, 119 adolescents with type 1 diabetes (55% female, average age 15.5 ± 1.5 yr) completed two self-administered questionnaires. The Strengths and Difficulties

Questionnaire (SDQ) assessed common emotional and behavioral symptoms. The Eating Disorder Inventory-3 Risk Composite (EDI-3RC) assessed risk for disordered eating. In addition, data were collected from the adolescent's medical records: including height, weight, glycosylated hemoglobin (HbA1c), and duration of illness. Clinical case status was defined as a borderline or abnormal if the SDQ $\geq$ 13 for females and $\geq$15 for males (1). 'At risk' status for an eating disorder was determined using an EDI-3RC cutoff score of $\geq$48 (2). Independent sample t-tests compared the mean scores for the EDI-3RC and glycemic control between the SDQ clinical case status groups. The Mann–Whitney test was used to compare non-parametric data. Statistical significance was set at 0.05 values for all tests.

Results: SDQ clinical case status was associated with significantly higher scores on the EDI-3RC ($p < 0.001$) which remained consistent for females ($p < 0.001$) but not for males. SDQ clinical case status was associated with poorer glycemic control ($p = 0.005$) and showed 100% sensitivity and 71% specificity for determining at risk disordered eating status with the EDI-3RC.

Conclusion: This study found high SDQ scores were significantly associated with disordered eating and poor glycemic control, providing evidence for the use of the SDQ as a brief screening tool in adolescent diabetes clinics. More specific screening for disordered eating in females is advised if borderline/high SDQ scores are seen.

References

1 Mellor, 2006
2 Garner, 2004

Oral Session VII: Diabetes epidemiology and monogenic forms of diabetes

O49

Gender differences: a higher proportion of girls have poorer metabolic control during adolescents and as young adults

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Objectives: To study HbA1c values in patients with type 1 diabetes during adolescence, and in young adults between 18–41 yr of age, aiming to compare metabolic control between boys and girls.

Methods: Data on HbA1c on 4250 patients (54% boys and 46% girls) at 12–17.99 yr of age registered in the Swedish pediatric national quality registry, Swediabkids, and further on followed in the National Diabetes Registry (NDR), at 18–41 yr of age, was used. Fifty percent of the patients were diagnosed before 10 yr of age and had a diabetes duration >15 yr. HbA1c values were categorized into three groups; <57 mmol/mol, 58–78 mmol/mol, and >78 mmol/mol.

Results: Girls had a higher mean HbA1c in Swediabkids (69 mmol/mol) compared with boys (66 mmol/mol). This difference was not seen in NDR (69 compared with 68 mmol/mol). Furthermore among the patients with HbA1c < 57 mmol/mol in both Swediabkids and NDR only 34% (139/407) were girls compared with the group that had HbA1c above 78 mmol/mol in both Swediabkids and NDR where 52% (197/381) were girls ($p < 0.001$).

Conclusions: In this large population-based study using national quality registries data both from childhood and young adults, a remarkable gender difference is shown with girls presenting a poorer metabolic control during adolescence. Furthermore, girls constitute a larger proportion of those with high HbA1c both during adolescence and later as young adults. Next step is to explore if these girls have a higher frequency of late complications.

O50

Mortality in patients diagnosed with diabetes during childhood in Northern Ireland, UK

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Objectives: To examine mortality rates and causes of death among patients diagnosed with type 1 diabetes before their 15th birthday in Northern Ireland.

Methods: A cohort of 3129 patients from the population-based Northern Ireland Childhood Diabetes Register was included in the study. Of these 2503 were prospectively registered cases diagnosed with type 1 diabetes since 1989, while the remaining 626 were existing patients at that date known to pediatricians in Northern Ireland. Deaths were identified through the Health Service Central Register and the underlying cause, coded according to ICD-9 (1981–2000) or ICD-10 (2001–2012), retrieved from the Registrar General's Office. Expected numbers of deaths were calculated from Northern Ireland mortality rates by the person years approach, and standardized mortality ratios (SMRs) calculated as the ratio of observed to expected deaths.

Results: There were 39 755 person-years of follow-up (mean 12.7 yr per patient) with 245 patients (8%) lost to follow-up through emigration. In total 59 patients had died by the end of follow-up in December 2012 compared with 19.9 deaths expected giving an SMR of 296 (95% confidence interval 230–382). The female SMR of 535 (361–764) based on 30 deaths was significantly higher than the male SMR of 203 (136–291) based on 29 deaths. The SMR was similar in categories of disease duration. A total of 23 of 59 deaths (39%) were directly attributable to acute complications of diabetes, while another five deaths (8%) were attributable to late complications. There was a small, non-significant excess of deaths due to accidents or violence (14 observed vs. 11.7 expected), but no excess was observed in the number of suicides/deaths with undetermined intent (4 observed vs. 4.6 expected).

Conclusions: Subjects with type 1 diabetes diagnosed under 15 yr of age had three times the mortality risk of the population. Nearly half of the deaths were due to acute or chronic complications of diabetes.

O51

Variations in cumulative incidence of the association between celiac disease and type 1 diabetes in Northern Italy (Bologna, Florence, Genoa, Turin, and Trento)

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Objectives: The association between type 1 diabetes (T1D) and celiac disease (CD) has been known for more than 40 yr. As compelling evidence suggests that the single incidences of T1D and CD are widely increasing, we aim to evaluate the fluctuations of their association reporting an up-to-dated cumulative incidence in Northern Italy.

Methods: All newly diagnosed T1D patients (pts) from January 2005 to December 2012 were tested and annually screened for CD antibodies in five Paediatric Diabetes Care Centres in Northern Italy. Pts underwent a duodenal biopsy to confirm the diagnosis (according to Marsh classification).

Results: 1355 pts with a new T1D diagnosis were studied; 109(8%) were affected by CD: 22 (20.1%) were diagnosed for CD before T1D (mean interval 5.4 ± 4.6 yr, max 18.4 yr), 55 (50.4%) were found positive for CD-related autoantibodies at T1D onset, 21 (19.2%) during the first 2 yr of follow-up, 9 (8.2%) after 2 yr of follow-up (max 4 yr 3 months), in two cases (1.8%) N/A. 485 pts were diagnosed for T1D between January 2005 and December 2007, ensuring at least 5 yr of follow-up (mean follow-up 6.31 yr) and 37 were affected by CD: in 1 (2%) CD was diagnosed before T1D, in 21 (56,7%) CD autoantibodies were positive at T1D onset, in 5 (13.5%) during the first 2 yr of follow-up, in 9 (24.3%) after 2 yr of follow-up (max 4 yr 3 months), in 1 case (2.7%) N/A. At CD diagnosis 64.3% of T1D pts was asymptomatic, 27.4% reported gastrointestinal symptoms, and 8.3% presented atypical symptoms. The point prevalence at December 2012 was 9.8% with local differences: Bologna 12.8%, Trento 12.1%, Florence 11.6%, Genoa 8%, and Turin 6.8%.

Conclusions: Although the increasing incidence of T1D and CD, whole cumulative incidence and prevalence of their association in Northern Italy did not differ than previously reported, still in the

upper range. We found significant differences between the centers, the highest peak in Bologna. The majority of CD cases were diagnosed at T1D onset or during the first years of follow up.

O52

Two cases of diabetic ketoacidosis in HNF1A-MODY linked to severe dehydration: is it time to change the diagnostic criteria for MODY?

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Background: HNF1A-MODY is a monogenic form of non-insulin-dependent diabetes caused by heterozygous mutations in the *HNF1A* gene. Diabetic ketoacidosis is presumably lacking in these patients because they do not have absolute insulinopenia. According to the current criteria, a history of diabetic ketoacidosis is an exclusion criterion for genetic testing for MODY.

Case report: We describe two unrelated probands aged 17 (patient 1), and 24 yr (patient 2) with genetically confirmed HNF1A-MODY caused by heterozygous mutation p.Arg272His, and p.Ser142Phe, respectively. Both patients displayed positive family history of diabetes, and were negative for pancreatic autoantibodies. They developed severe diabetic ketoacidosis several years after the diagnosis of diabetes. Both patients were treated with insulin but their metabolic control was poor (HbA1c 15%, 140 mmol/mol and 13%, 119 mmol/mol, respectively) due to non-compliance and missed insulin injections. In both patients, diabetic ketoacidosis followed a course of recurrent vomiting with dehydration and prerenal acute kidney injury. Their glycemia, blood pH, and base excess at admission were 97 mmol/l (1748 mg/dL), 6.80, and −33 mmol/L (patient 1) and 34 mmol/L (613 mg/dL), 7.03, and −14 mmol/L (patient 2).

Conclusions: The two demonstrated cases of diabetic ketoacidosis in poorly controlled patients with HNF1A-MODY may have implications both for the need of adequate patient education, and for individual assessment of the indication criteria for genetic testing, as – although the molecular-genetic diagnosis of MODY diabetes has direct implications for patient treatment – most cases of MODY remain misclassified.

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O53

A case of relapsing 6q24-related diabetes successfully treated with a DPP4 inhibitor

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Objectives: To explore the possibility of DPP4 inhibitors for the treatment of relapsing 6q24-related diabetes.

Patient and methods: Patient: A 21-yr-old male. History: Born after 37 wk of gestation with the birth weight of 1660 g. Hyperglycemia noted at day 7 and was treated with insulin until 7 mo of age. Oral GTT returned to normal at 1 yr 3 months. After an uneventful interval, glycosuria was noted at 12 yr of age. Initially treated with an alpha glucosidase inhibitor, HbA1c remained at 6.3–7.1%. After 18 yr of age, HbA1c started to creep up to constantly over 7% which was associated with decreasing C-peptide. He remained non-obese throughout the course.

Diagnosis: (i) Methylation-specific PCR. Genomic DNA was extracted from peripheral blood leukocytes. After treatment with bisulfite, methylation-specific PCR was conducted to amplify the differentially methylated region (DMR) at 6q24 transient neonatal diabetes critical region. The results suggested paternal dominance at 6q24. (ii) Comparative genomic hybridization. A CGH array analysis using the Sure print G3 array (Agilent) revealed an amplification of the chromosomal region spanning the PLAGL1 gene located within the 6q24 critical region. Intervention: Under the diagnosis of relapsing 6q24-related diabetes, a DPP4 inhibitor, alogliptin 25 mg qd, was initiated. The rationale for this choice was; (i) the diabetes could be due to decreased insulin secretory capacity rather than due to insulin-resistance, therefore sulfonylureas might be eventually deleterious to beta cell function (ii) an *in vitro* study suggested a possible efficacy of incretins for this condition.

Results: After the initiation of alogliptin, his HbA1c dropped and constantly remained below 6.3%.

Conclusions: At present, there is no consensus treatment for relapsing 6q24-related diabetes. Our results suggest that DPP4 inhibitors could be a useful first-line treatment for these patients.

O54

De novo mutations of *GCK*, *HNF1A*, and *HNF4A* may be more frequent than assumed: possible implications for genetic testing

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Objectives: According to the current guidelines, genetic testing for maturity-onset diabetes of the young (MODY) should be performed only in families with a positive history of diabetes. However, *de novo* mutations have been reported anecdotally. We aimed to systematically revisit a large collection of MODY patients to determine the minimum prevalence of *de novo* mutations in the most prevalent MODY genes (i.e., *GCK*, *HNF1A*, and *HNF4A*).

Methods: Joint analysis of 922 patients from two national MODY centers identified 150 probands (16%) who came from pedigrees that did not fulfill the criterion of two generations with diabetes but did fulfill the remaining criteria. The *GCK*, *HNF1A*, and *HNF4A* genes were analyzed by direct sequencing.

Results: Mutations in *GCK*, *HNF1A*, or *HNF4A* genes were detected in 58 of 150 subjects lacking the positive family history of diabetes. Parents of 28 probands were unavailable for further analysis, which left the question of their mutation origin open. Of the remaining 30 families, in 19 probands the mutation was inherited from an asymptomatic parent, whereas in 11 probands the biological parents were negative for the respective mutation; thus the mutations arose *de novo*. This finding represents 7.3% of the 150 families without a history of diabetes and 1.2% of all of the referrals for MODY testing.

Conclusions: We demonstrated that *de novo* mutations account for a significant number of MODY probands. Our findings indicate that the testing of carefully selected individuals without a family history of diabetes could lead to genetic confirmation of the diagnosis and that these patients could benefit from the advantages of tailored therapy. Supported by grant (Transendogen/26240220051) by the ERDF and Scientific Grant Agency of the Ministry of Education, Science, Research, and Sport of the Slovak Republic (2/0151/11) and by grants from the Czech Ministry of Health (NT11402 and MH CZ - DRO, University Hospital Motol, Prague, Czech Republic 00064203).

O55
Neonatal diabetes in Ukraine

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Objectives: The aim of this study was to determine the clinical and genetic features of neonatal diabetes (ND) in Ukraine.
Methods: In 2012, according to the Ukraine Pediatric Diabetes Register the number of children 0–17 y.o. with DM type 1 was 8148 (10.26 per 10 000 pediatric population), and number of children with ND was 29 (0.04 per 10 000). Among these children, we investigated 24 children (82.7%): 10 children with onset of DM before 6 months (group 1) and 14 - before 9 months (group 2).
Results: In group 1 we found genetic mutations at all children: in two cases – *6q24*, in four – *KCNJ11*, in three – *ABCC8*, and in one – *GLIS3* gene. In group 2 we found genetic mutations only in 21.4% of children: in one case – *KCNJ11* and two cases – *INS* gene. All children with *KCNJ11* and *ABCC8* mutations were successfully transferred on SU treatment. Initially was omitted fast-acting insulin. At the start of transferring process the daily dose of SU was divided into four to five doses, but after 3 months of SU treatment – into two to three doses. Also we analyzed data at children with detectable genetic mutations that have been successfully transferred on SU and in those without them (Table 1).

Comparison between groups

	No mutations (n = 11)	KCNJ11 or ABCC8 mutations (n = 8)	p
Onset of DM (days)	254 (240; 263)	85.5 [75.7; 92.2)	p = 0.0008
Weight (g)	3355 (3200; 3550)	2625 (2525; 2822)	p = 0.01
DDI at onset of DM (U/kg)	0.6 (0.5; 0.85)	1 (0.85; 1)	p > 0.05
DDI at the time of the survey (U/kg)	0.8 (0.6; 0.83]	0.6 * (0.56; 0.67)	p > 0.05, *p = 0.04
HbA1c (%)	10.0 (9.1; 10.4)	7.1 (6.5; 7.5)	p = 0.008
Neurological disorders (%)	8.3	42.8	
Relatives with DM	41.7% (DM 1)	0	

p, between groups; *p, within group with mutations.

Conclusions: Every child with DM onset before 9 months should undergo genetic testing for ND.

O56
Neonatal diabetes in premature infants

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Objectives: Prematurity (gestation <37 wk) affects up to 12% of births and hyperglycemia is a common complication usually attributed to inadequate pancreatic development rather than neonatal diabetes due to a monogenic cause. No studies have investigated patients with neonatal diabetes who were born prematurely. We aimed to assess the clinical characteristics and genetic etiology of preterm patients with neonatal diabetes.
Methods: We studied an international cohort of 750 patients with diabetes diagnosed before 6 months of age. We compared the genetic etiology and clinical characteristics of 146 patients born prematurely (<37 wk) and compared them to 604 born ≥37 wk.
Results: A defined genetic etiology was found in 97 of 146 (66%) preterm infants compared with 501 of 604 (83%) born ≥37 wk, $p < 0.0001$; 36of 97 (37%) preterm infants had a potassium channel mutation. Chromosome 6q24 imprinting abnormalities (27 vs. 12%, $p = 0.0001$) and *GATA6* mutations (9 vs. 2%, $p = 0.003$) occurred more commonly in pre-term than term infants whilst mutations in *KCNJ11* were less common (21 vs. 34%, $p = 0.008$). The preterm patients with an identified mutation were diagnosed later than those without an identified mutation 35 (34–36) wk [median (interquartile range)] vs. 31 (28–36) wk, $p < 0.0001$.No difference was seen in other clinical characteristics of preterm patients with and without an identified mutation [age of presentation, 1.0 (0.1–4.0) vs. 0.7 (0.1–3.5), $p = 0.99$], birth weight SDS [−1.28 (−2.27 to 0.43) vs. −1.06 (−1.98 to −0.20), $p = 0.48$], time to referral for genetic testing [19(4–212) vs. 8(4–42), $p = 0.10$].
Conclusions: Patients with neonatal diabetes can be born pre-term, especially those with 6q24 abnormalities or *GATA6* mutations. A genetic etiology is more likely in patients with less severe prematurity. Prematurity should not prevent referral for genetic testing as the 37% patients with a potassium channel mutation will be sulfonylurea responsive.

Oral Session VIII: Genetics and immunology

O57

Enterovirus RNA in longitudinal blood samples from children at the highest genetic risk of type 1 diabetes, and the development of islet autoimmunity: the MIDIA study

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Objectives: Our aim was to investigate the association between enterovirus and islet autoantibodies in a Norwegian high-risk cohort study. Only a few similar molecular longitudinal studies are available, with positive results seemingly limited to the Finnish population that shares several important characteristics with the Norwegians.
Methods: Children with the highest HLA-DQ-DR-encoded type 1 diabetes risk formed the Norwegian birth cohort MIDIA ('Environmental Triggers of Type 1 Diabetes'). Their serial blood samples were tested for autoantibodies to insulin, GAD65, and IA-2. Among 911 children at risk, 48 cases developed positivity for two or more autoantibodies. Two controls from the cohort were closely matched to each case. Enterovirus was tested in RNA obtained from frozen cell packs after removal of plasma, using a meticulously controlled reverse transcriptase TaqMan real-time PCR.
Results: Enterovirus RNA was observed in 15% of the 778 tested blood samples. Positivity for enterovirus in blood was not associated with the appearance of islet autoantibodies, as demonstrated in a logistic regression model with random intercept: OR = 1.01, 95% CI 0.58–1.79, p = 0.96 for the enterovirus positivity in the sample with first islet autoantibodies or in preceding samples. Similarly, no significant association was found in analyses restricted to high levels of enterovirus RNA, or to shorter time windows.
Conclusions: We observed no link between enterovirus RNA in blood and the development of islet autoimmunity in a large Norwegian cohort with homogeneously high genetic risk. Of note, the detection method and the RNA source yielded high enterovirus positivity rates, rendering our study higher power than earlier publications. Our negative finding does not exclude an existence of a diabetogenic virus genotype responsible for only a small proportion of infections – genotyping of enteroviruses in blood is therefore warranted, although it is technically extremely difficult.

O58

Functional and expressional characterization of human islets at onset of type 1 diabetes – results from the DiViD study

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Objectives: The understanding of the pathogenesis of type 1 diabetes (T1D) remains limited partly due to lack of studies of pancreatic tissue at diagnosis. One aim of the Diabetes Virus Detection Study (DiViD), the first pancreatic study of live patients with newly diagnosed T1D, was to characterize the pancreatic islets to understand the pathogenic processes leading to beta-cell destruction.
Methods: Six patients (24–35 yr) with newly diagnosed T1D were included. After informed consent a minor pancreatic laparoscopic tail resection was performed. In this part of DiViD, islets were isolated and their insulin secreting function and expression of inflammatory-related proteins were studied.
Results: Islets from two of the patients secreted high amounts of insulin in response to glucose stimulation showing the biphasic insulin secretion characteristic for healthy islets. Two patients secreted substantial amounts of insulin without the typical biphasic response. One patient showed a severely impaired insulin response and one did not secrete any detectable insulin. Multiplex analysis of 42 cytokines and chemokines in the isolated islets revealed large variations between patients; 25 of the 42 analytes were detected, none deviating significantly from controls without T1D. Notably, IFNg and IL-2 were among the undetected analytes and only low levels of type 1 IFN were detected. CXCL10, implicated in T-cell recruitment in T1D, was detected in islets from three patients. The large variation may be due to wide variation in stages of inflammation of the examined islets.
Conclusions: The demonstration of functional islets in some patients with recent onset T1D is promising for the possible preservation of remaining beta cells by reversing the destructive process at diagnosis. The characterization of inflammatory proteins in islets, together with data from the transcriptome analysis, is unique and will be of great value for future studies of processes occurring in islets in early T1D.

O59

Increased humoral response against *Mycobacterium avium* subsp. *paratuberculosis* in an Italian cohort of children at risk for type 1 diabetes

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Introduction: Type 1 Diabetes (T1D) is an autoimmune disease mediated by a combination of genetic ad environmental factors resulting in T-cell infiltration of the pancreas and destruction of insulin producing beta cells. *Mycobacterium avium* subsp. *paratuberculosis* (MAP), the etiological agent of Johne's disease in ruminants, has been proposed as a new environmental trigger that might contribute to T1D pathogenesis. Recent studies have linked MAP to T1D in a Sardinian population and in a T1D cohort from Continental Italy.
Aim: The aim of this study was to investigate if MAP immunodominant peptides were recognized in children at T1D risk in a pediatric cohort of children from Continental Italy.
Methods: We selected 45 children at risk to develop T1D (based on the presence of risk-HLA genotype and the autoantibodies to pancreatic islet antigens) and 42 age-matched healthy controls (HCs). The cohort was stratified as high risk and medium-low risk based on the number of positive autoantibodies. We tested the presence of antibodies towards two specific MAP peptides, $MAP3865_{125-133}$ and $MAP3865_{133-141}$ respectively, using ELISA. These epitopes

are immunodominant Ab targets within the full-length MAP3865 protein.
Results: ELISA results showed a significant increased humoral response in subjects at risk to develop T1D against both MAP peptides compared with HCs. In particular we found a $MAP3865_{133-141}$ positive response in 21 subjects at risk to develop T1D (46.6%) compared with 2 HCs (4.7%) ($p < 0.0001$) and a $MAP3865_{125-133}$ positive response in 22 subjects at risk to develop T1D (48.8%) compared with two HCs 4.7%, ($p < 0.0001$). When we stratified the subjects based on high and medium-low risk we did not find any difference in MAP positivity between the two groups.
Conclusion: These data significantly associate anti-MAP antibodies presence with a higher risk to develop T1D in genetically predisposed individuals. These results reinforce the hypothesis that MAP may be a potential trigger in T1D.

O60
Does *Helicobacter pylori* infection influence the prevalence of ATP4A autoantibodies in children with type 1 diabetes?

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Objectives: Atrophic body gastritis (ABG) is an autoimmune disease associated with T1DM. ATP4A autoantibodies (aAb) directed towards parietal cells are typical for ABG, present early and persist over time. The study aimed to assess whether *Helicobacter pylori* (Hp) infection might trigger the production of ATP4A aAb in children with T1DM.
Methods: We obtained sera form 70 (38♀) T1DM children (aged 13.2 ± 4.5 yr, T1DM duration 0–16 yr, mean HbA1c at study time $7.83 \pm 1.64\%$), all of them were patients of a regional diabetes clinic in Katowice, Poland. At time of serum collection patients were tested for Hp infection using 13C urea breath test. ATP4A aAb were measured by means of a novel radioimmunoprecipitation assay (RIA) developed and conducted in Barbara Davie Center for Diabetes, University of Colorado Denver, USA.
Results: Hp infection was detected in 23 [32.9% 95 CI (21.9; 43.9%)] and ATP4A aAb in 21 [30%, 95 CI (19.3; 40.7%)] children. The relation between Hp status and ATP4A aAb presence was insignificant. Age, T1DM duration, and HbA1c also did not impact the occurrence of ATP4A aAb. Their prevalence was only gender-dependant with significantly more girls being ATP4A aAb positive [42.1 95 CI (26.4; 57.8%) vs.15.6% 95 CI (3.1; 28.2%), $p = 0.016$].
Conclusions: A significant percentage of T1DM children present ATP4A aAb, with higher prevalence among girls. Hp infection does not seem to trigger the autoimmune process regarding parietal cells in children with T1DM.
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O61
Serum CXC chemokine ligand 10 (CXCL10) in type 1 diabetic children, adolescents, and subjects at high risk of type 1 diabetes

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Introduction: CXCL10 is one of CXC chemokines family secreted from islet cell itself during insulinitis.
Objectives: To assess serum concentration of CXCL10 in newly diagnosed and long-standing type 1 diabetics as well as high risk subjects [positive islet cell (ICA) and Glutamic Acid Decarboxylase (GAD) antibodies] and low risk subjects (negative anti-GAD and ICA autoantibodies) to study the role of CXCL10 in pathogenesis of type 1 diabetes.
Methods: The study included 80 subjects divided into: 40 patients [20 newly diagnosed (diagnosed <6 wk) and 20 with long-standing (diagnosed >5 yr) type 1 diabetics], 20 first degree relatives (10 high risk and 10 low risk subjects), and 20 healthy age and sex matched controls. All were subjected to detailed clinical assessment, mean random blood glucose (MRBG), HbA1c, urinary albumin excretion, and serum level IP-10 by ELISA technique.
Results: Serum CXCL10 level was significantly increased in newly diagnosed diabetic patients and in high risk subjects with positive GAD and ICA auto antibodies (prediabetics) compared with controls ($p = 0.001$), but there was a significant increase in serum CXCL10 level in newly diagnosed patient compared with prediabetics ($p = 0.032$). Newly diagnosed diabetics had significantly increased CXCL10 level than long standing diabetics ($p = 0.001$). Significant negative correlations existed between CXCL10 level and age ($r = -0.377$, $p = 0.003$), BMI ($r = -0.34$, $p = 0.008$) in diabetics with no significant correlation with MRBG or HbA1c ($p = 0.05$). A cutoff value for CXCL10 of >60 pg/mL can differentiate between diabetics and non-diabetic subjects, with sensitivity 87.5% and specificity 100% and between high-risk and low-risk subjects with sensitivity 40% and specificity 90%.
Conclusions: Higher CXCL10 was detected in newly diagnosed diabetics and subjects at 'high risk' of diabetes. Measurement of serum CXCL10 in high risk subjects with positive GAD and ICA autoantibodies may help to predict the development of diabetes.

O62
T-cell autoreactivity at onset of pediatric type 1 diabetes (T1D) is related to adiposity but not residual c-peptide

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Objectives: T-cell reactivity to diabetes-related antigens distinguishes T1D from controls and is thought to precede autoantibody (Ab) detection. The relationship between adiposity and T-cell reactivity has not been examined. Our objective was to assess the relationship between T-cell reactivity to T1D-related antigens and both measures of adiposity (BMIz, waist percentile) and c-peptide in normal and overweight children with new onset T1D.
Methods: Subjects diagnosed with T1D between 12/2004 and 6/2008 were included ($n = 216$): age 1.2–18.9 yr, 92% white, 59% male. T-cell autoreactivity to 10 antigens, Ab (GADA, IA-2A, IAA, and ICA), body mass index (BMI) percentile, waist percentile and c-peptide at onset and 3 months were measured.
Results: Subjects with BMI percentile ≥85th had higher T-cell autoreactivity to two neuronal T1D-associated antigens ($p < 0.05$). Subjects with waist percentile ≥85th had higher T-cell autoreactivity for 8 of 10 antigens, including neuronal, islet, and milk (p values between 0.008–0.036). The cohort was subdivided by Ab and T-cell characteristics (Table 1). The 28 Ab-negative subjects (only one also

Autoantibody and T-cell characteristics

Group	Ab+/T+	Ab−/T+	Ab+/T−	p Value
N	173	27	15	
Age (years) Mean + SD	9.5 + 3.9	11.4 + 3.8	10.3 + 3.7	0.5
C-peptide at onset (ng/mL) Median [interquartile range—IQR]	0.6 [0.25–0.9]	0.8 [0.25–1.8]	0.5 [0.25–0.7]	0.08
Δ3 months C-peptide (ng/mL) Median [IQR]	0.9 [0.2–1.9]	0.87 [−0.1–2.9]	1 [0.7–1.5]	0.8
BMIz at baseline Mean + SD	0.05 + 1.5	0.8 + 1.2*	−0.07 + 1.1	0.046*
BMIz at 3 months Mean + SD	0.8 + 0.9	1.4 + 0.8*	0.6 + 1.1	0.008*
Onset HbA1c% Mean + SD	11.8 + 2.4	12.4 + 2.1	11.9 + 2.5	0.5

T-cell negative) had similar c-peptide levels, but higher BMIz than those with positive Ab.

Conclusions: This is the first observation to link elevated BMI and T-cell autoreactivity in T1D. In overweight new onset T1D children, T-cell autoreactivity is more closely related to measures of adiposity. With one exception, the entire cohort demonstrated islet autoimmunity with similarly low c-peptide levels. Our longitudinal study will assess the ontogeny of T-cell/B-cell antigen spreading.

O63
Insulin resistance, beta-cell function and the effect of non-HLA genetic variants in Finnish DIPP study children with HLA-conferred risk for type 1 diabetes

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Objectives: To study if markers of insulin resistance (IR) show association with diabetes-associated autoantibodies, and the effect of different genetic variants on insulin secretion and development of insulin resistance in children at increased genetic risk for T1D.

Methods: Type 1 Diabetes Prediction and Prevention Project in Finland (DIPP) is a population-based follow-up study of genetically susceptible children to T1D. To date, a total of 1101 intravenous glucose tolerance tests (IVGTTs) have been performed to 492 children in the Turku DIPP center; 92 of these children have been diagnosed with T1D. Insulin resistance values were measured using HOMA-IR (homeostasis model assessment) and beta-cell function was evaluated by first phase insulin response (FPIR). As part of regular follow-up visits, diabetes-associated autoantibodies were analyzed using techniques standardized according to DASP recommendations. Selected non-HLA genetic variants (n = 23) were analyzed in a subcohort of study children. Statistical analyses were performed using RM ANOVA for log-transformed values. The models included the child's progression to diabetes, autoantibody level, genetic variants, and their interaction. In case of positive interaction the progression groups were analyzed separately.

Results: The relationship between IAA and fasting insulin and HOMA-IR levels differed between progressors and non-progressors ($p = 0.002$ for fasting insulin and $p = 0.003$ for HOMA-IR). Progressors' fasting insulin had a strong positive correlation with IAA [$\beta(se) = 0.11$ (0.032), $p < 0.001$]. This association of fasting insulin and IAA can also be seen in HOMA-IR [$\beta(se) = 0.12$ (0.036); $p = 0.002$]. The non-progressors showed no correlation between IAA levels and fasting glucose or HOMA-IR. Analyses of genetic variants are ongoing and results will be reported in the meeting.

Conclusion: Our preliminary findings imply that there is a relationship between IR and serum IAA levels in children who later progress to T1D.

O64
The Euro-WABB registry: differences in prevalence of diabetes between Wolfram, Alström, and Bardet–Biedl syndromes

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Objectives: We aimed to develop a registry for the rare genetic diseases Wolfram (WS), Alström (AS), Bardet–Biedl (BBS), and other diabetes syndromes, containing clinical, genetic diagnostic, and outcome data. The purpose is to establish the natural history of these diseases; to assess clinical management; to characterize cohorts for future clinical trials; and to establish genotype–phenotype relations. This abstract describes the first 178 patients recruited.

Methods: Patients with a confirmed diagnosis (clinical or genetic) were recruited from both within and beyond Europe by their physicians (14 centers across 9 countries). Information was collected for 42 'core' data fields, reached by consensus to differentiate between syndromes. We analyzed prevalence of core clinical symptoms including obesity and diabetes.

Results: The age range was 3–68 yr. There were 82 participants with WS [median age 20 yr (range 5-46 yr)], 56 with AS (17 yr (3–55 yr), 35 with BBS [11 yr (3–29)], 2 with Wolcott–Rallison, 2 with other diagnoses, and 1 with vision and hearing impairment of unknown cause. The prevalences of diabetes and median ages of onset were: WS (78/82; 6 yr); AS (32/56; 13 yr); BBS (5/35; 23 yr); $p < 0.01$ for ages of onset BBS vs. WS and AS combined. The prevalences of obesity and median ages of onset were: WS (2/82; 22 yr); AS (47/56; 1 yr); BBS (32/35; 1 yr); $p < 0.001$ for obesity prevalence WS vs. AS and BBS combined.

Conclusions: The core dataset captured sufficient data to differentiate between diabetes syndromes. Diabetes presented before puberty in WS, was not associated with obesity, and is known to be insulin dependent; whereas it presented during puberty in AS and in young adulthood in BBS, was associated with obesity, and is insulin resistant. The prevalence of diabetes is low in AS and BBS during childhood. Further patient recruitment and longitudinal data collection will use a consensus extended dataset of 400 fields to accurately characterize the phenotypes.

Oral Session IX: Pumps and sensors

O65
The reasons for pump discontinuation in children with diabetes type 1 (T1DM)

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Introduction: Pump discontinuation is rare. It is estimated that only about 4% of patients previously on pumps return to multiple daily injections (MDI).
Objectives: To study the factors that influence the decision to stop continuous subcutaneous insulin infusion therapy (CSII).
Method: Analysis of the anonymous questionnaires indicating factors that influenced pump discontinuation and returning to the MDI.
Results: Respondents: 30 children (17 girls), mean age 14.3 yr (±3.57), at the start of CSII 11.06 yr (±4.01), at discontinuation of pump therapy 13.46 yr (±3.64). CSII term: median duration was significantly longer in boys: 3.28 ± 2.31 vs. 1.27 ± 1.04 yr ($p = 0.01$); mean HbA1c was 8.03 ± 1.03%, with no sex difference. The most often reported disconnection reasons were: a greater sense of illness (93%), difficulty in sports training (70%), worse mood during pump therapy (60%), adhesions and pain at the site of injection catheter (50%), shame (56%), instability of glycemia (46%), the difficulties in controlling glycemia during exercise, fear (43%), high HbA1c (36%), and frequent measurements of glycemia (26%). Problems with technical pump handling, severe hypoglycemia, or ketoacidosis during CSII were not reported. The mean age at the time of the resignation of CSII in those which have marked difficulties in controlling glycemia during exercise was significantly lower than in the children who did not choose this factor: 12.3 ± 3.33 vs. 14.69 ± 2.82 ($p = 0.04$).
Conclusions: The individual psycho-emotional state of the child and appropriate education play the important role at the start and during continuation of CSII.

O66
Can integrated technology improve self-care behavior in youth with type 1 diabetes? A randomized crossover trial of automated pump function

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Objectives: For users of continuous subcutaneous insulin infusion (CSII), achievement of adequate glycemic control remains highly dependent on user behavior. Novel adjunct glucometers have been developed which allow a user's capillary blood glucose (BG) reading to be automatically delivered to their pump using wireless technology, thus removing the necessity of this manual step. This study was designed to assess whether use of an automated integrated blood glucose measurement and insulin pump device, as compared with standard insulin pump therapy and BG monitoring, resulted in higher mean daily frequency of blood glucose measurements recorded in a user's pump after 6 months of use.
Methods: T1DM subjects ($n = 35$) were recruited at a single tertiary-care center for a randomized crossover study. Subjects were randomized to two 6-month phases, to commence using either their own insulin pump, or the automated system. Post-first phase, participants then crossed over to use of the alternative pump. Number of BGs was assessed from pump and glucometer downloads.
Results: Use of the automated insulin pump and meter resulted in a higher number of BGs per day assessed over 6 months of use when compared with users' own insulin pump (5.8 ± 1.7 vs. 5.0 ± 1.9 BGs per day; $p = 0.02$). No difference was observed between groups in HbA1c at 6 months ($7.7\% \pm 0.86$ vs. $8.0\% \pm 1.3$ own pump; $p = 0.38$), total insulin dose (U/kg/day), or number of boluses/day. Users of the automated system were more likely not to recommend the system to others ($p = 0.007$) and comparatively preferred using their own pump ($p = 0.005$).
Conclusions: Use of an automated glucometer/insulin pump resulted in a higher mean number of BGs over 6 months of use when compared with use of an insulin pump where manual entry of BGs is required. This finding did not translate to a difference in HbA1c, indicating the presence of other significant barriers to improved glycemic control in youth using CSII.

O67
Comparison of pump use and outcomes in children under 6 yr of age in the DPV and T1D exchange registries

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Although ISPAD guidelines indicate that clinicians should aim for A1c levels <7.5% in children with T1D, data are limited as to the success in achieving this target, especially in very young patients. The T1D Exchange (T1DX) in the USA and the DPV registry in Germany/Austria collaborated to evaluate this question. Both registries queried their databases regarding clinical characteristics, modes of treatment, and treatment outcomes, in all patients <6 yr of age with ≥1 yr of T1D.
Young children in the T1DX and the DPV had similar clinical characteristics with respect to age, sex, and T1D duration (Table 1). Moreover, total daily insulin dose and frequency of SMBG were nearly identical. Nevertheless, mean A1c was higher, the percentage of patients with A1c < 7.5% was lower and SH was higher in T1DX vs. DPV patients. It is also noteworthy that only 49% of patients in T1DX vs. 77% in DPV were being treated with insulin pump therapy. Within the T1DX cohort, A1c levels were lower in pump (7.9%) than in injection patients (8.5%).
Young patients in the DPV were able to achieve lower A1c levels, with a higher proportion reaching the ISPAD target and less SH than in the T1DX. Increased use of insulin pumps in the DPV cohort appears to be an important factor in differences in treatment outcomes between these two groups. These data support the contention that comparison of diabetes care practices and outcomes in large diabetes registries can provide guidance for optimizing care of children with T1D.

Characteristics of participants

	T1DX (n = 674)	DPV (n = 1019)
Age, years	4.0 (4.0, 5.0)	4.8 (4.0, 5.4)
Sex, % male	58%	53%
T1D duration, years	2.0 (1.0, 2.0)	2.2 (1.6, 3.1)
Percentage on pump therapy	49%	77%
HbA1c, %(mmol/mol)	8.2 ± 1.0% (66.2 ± 10.8)	7.5 ± 0.8% (58.0 ± 9.2)
Percentage A1c < 7.5% (<58 mmol/mol)	22%	57%
Total daily insulin, units/kg/day	0.68 (0.56, 0.83)	0.65 (0.54, 0.78)
SMBG/day	7.0 (5.0, 9.0)	7.0 (5.5, 8.0)
Percentage with ≥1 SH event (seizure/coma) in past year	8%	2%

O68
Glycemic variability in type 1 diabetes: which indicators to use?

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Background: GV is an important parameter of metabolic control in T1D patients. It is a risk factor for significant glucose excursions, especially hypoglycemia, and suspected as involved in the pathogenesis of vascular complications regardless of HbA1c. The association with the alteration of quality of life in T1D patients is also mentioned. Many indicators of GV are available; however, there is no consensus on their practical use.

Objectives: To identify the best indicators of glycemic variability, both for clinical practice and as the endpoints for clinical trials.

Methods: The population is derived from a randomized clinical trial (Start-In!) which assesses the impact of continuous glucose monitoring (CGM) on HbA1c in T1D children and adolescent. During the first 3 months, 141 subjects were wearing a CGM device for more than 90% of the time. Fifteen GV indicators were calculated weekly during these 3 months (BG mean; SD; coefficient of variation-CV; Mean Amplitude of Glycemic Excursion-MAGE; Mean Of Daily Difference-MODD; Continuous Overall Net Glycemic Action-CONGA 1, 2, 4, and 24; J-index; M-Value; GRADE; Low Blood Glucose Index-LBGI; High Blood Glucose Index-HBGI; and Average Daily Risk Ratio-ADRR). Indicators were analyzed using principal component analysis (PCA) and Spearman's correlations.

Results: Three components of the GV were highlighted, possibly representing variability *per se*, magnitude (hypo/hyperglycemia), and temporality (intra/interday) of glycemic excursions. Each of these components explains respectively 66, 18, and 5%, in total 89% of the variance. Spearman's coefficients inside each group of indicators defined by the PCA, greater than 0.70, reinforce the first results. Thus, six indicators appear sufficient to fully describe GV: three descriptive parameters (MAGE MODD, and CV) and three risk indicators (LBGI, HBGI, and ADRR).

Conclusion: Six among 15 GV indicators are able to evaluate the three GV dimensions and should be used as standardized outcomes in clinical trials.

O69
Performance of a continuous glucose monitoring system (CGM) and CGM glucose ranges in youth ages 2–17 yr old

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Objectives: We studied the performance during home use of the Dexcom G4 PLATINUM (DG4P) CGM system in 176 youth, age 2–17 (mean 11.5) from six US centers.

Methods: Youth wore two systems (one blinded and one displayed) on either the abdomen (i) and/or upper buttocks (ii) for 7 d. We compared accuracy vs. SMBG at the different wear sites in young children (2–5 yo), children (6–12 yo), and adolescents (13–17 yo) and examined CGM glucose ranges in different ages.

Results: Most youth (72%) used insulin pumps; mean A1C was 8.2 ± 1.3%; zBMI was 0.5 (range −4.7 to 2.6). With SMBG capillary glucose serving as reference, the DG4P mean absolute relative difference (MARD) was 15% in 16 318 paired sample; results were similar for abdomen (14%) and buttocks (16%). MARD was 17% in 2–5 yo (17.1% A and 15.5% B), 16% in 6–12 yo (14.9% A and 16.5% B), and 15% in 13–17 yo (13.5% A and 15.5% B). The percentages of CGM glucose in various ranges were similar across the three age groups (See Table 1).

Percentage CGM within glucose ranges by age group

Age Group, subjects HbA1C,	CGM glucose range	Mean of %CGM	SD of %CGM
2–5 yo, n = 28, Mean A1C = 7.8%	<3.9 mmol/L (70 mg/dL)	6.3	4.0
	3.9–13.9 mmol/L	65.8	13.0
	>13.9 mmol/L (250 mg/dL)	27.9	11.4
6–12 yo, n = 68, Mean A1C = 7.8%	<3.9 mmol/L	6.0	4.7
	3.9–13.9 mmol/L	70.4	14.5
	>13.9 mmol/L	23.6	14.0
13–17 yo, n = 78, Mean A1C = 8.3%	<3.9 mmol/L	6.3	5.3
	3.9–13.9 mmol/L	69.6	13.7
	>13.9 mmol/L	24.1	13.6

Conclusion: This is largest pediatric CGM performance study to date, and included young children 2–5 yo. DG4P performance compared favorably to the CGM system currently approved for pediatric use. There were minor differences at wear sites with near equivalent performance at the abdomen and buttocks in subjects

2–5 yo and minor differences in older youths. The percentages of glucose in low and high glucose ranges measured by CGM across different age groups were similar.

O70

Measuring glycemic variation: limitations of glycemic datasets

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Objectives: When assessing glycemic variation (GV), investigators need to be cognisant of the limitations imposed by the properties of the glycemic dataset. Datasets may vary in glycemic-point intervals and also in duration from several days to weeks. An inherent limitation is segments of data with absent glucose values, often relating to signal drop-out. We have previously published analyses showing that the accuracy of the most popular GV metrics (MAGE, SD, and CONGA) varies considerably according to the interval of glycemic data points, with reliability falling as the intervals increase to 1 h (MAGE) or 2–4 h (SD and CONGA). The purpose of this study was to assess the impact of the duration of the glycemic dataset upon accuracy in measurement.
Methods: Continuous glucose monitoring (CGM) was carried out for 90 consecutive days in 20 youth with well controlled T1DM (mean Hba1C = 7.6%). GV was measured using standard deviation (SD) with the 90-d GV measure being defined as the 'gold standard'. GV estimates were then calculated using 2, 4, 6, 12, 18, 24, and 30-d duration times. Measurement comparison was assessed between duration intervals using Bland–Altman plots of percentage error of the SD difference, with a difference of ≤10% deemed clinically significant.
Results: Subjects were 35% male, had a mean age of 13.5 ± 2.6 yr and mean duration of diabetes of 5.6 ± 2.7 yr. Mean difference of compared measurement intervals increasingly approximated to the 3-month standard as the duration of use increased. This became clinically accep' at the 12-d interval [mean diff = 6.4% (CI 2.1–10.8)], with increased duration showing continued difference reduction [18-d diff = 4.8% (CI 1.2–8.5); 24-d diff = 2.5% (CI 0.4–4.6); 30-d diff = 1.5% (CI 0.7–3.8)].
Conclusions: When measuring CGM variability, the minimum duration of continued sensor use from which clinically significant inference can be made is 12-d duration.

O71

The predictive low glucose management system in youth with type 1 diabetes during exercise – data from the Pilgrim study

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Objectives: The low glucose suspend (LGS) feature suspends insulin delivery when a preset sensor glucose threshold is reached. In the next generation of artificial pancreas development, the prevention of hypoglycemia with the use of the Predictive Low Glucose Management (PLGM) was evaluated in youths with type 1 diabetes undergoing vigorous exercise.
Methods: The PLGM system is composed of a Paradigm insulin pump, an Enlite glucose sensor, and a Blackberry-based controller. During this study, a 30-min predictive horizon with sensor threshold of 70 or 80 mg/dL was used. Subjects (n = 22) on CSII [5 female, 17 male, age 15 (14–20) years; diabetes duration: 7 (2–14) yr; HbA1c: 8.0 (6.7–10.4)% median(range)] followed an exercise regimen to lower glucose levels, exercising until the PLGM system suspended insulin delivery or until the reference (Hemocue) blood glucose value reached the predictive suspension threshold setting. Prevention of hypoglycemia was defined as reference values remaining ≥63 mg/dL. An experiment was evaluated when either the PLGM-triggered insulin suspension or hemocue was <60 mg/dL.
Results: The hypoglycemic threshold during exercise was reached in 16 of 22 patients with PLGM activating in 15 of 16 successful experiments. Of these 15 experiments, hypoglycemia was prevented in 12 experiments. PLGM threshold was set at 70 mg/dL for two experiments. PLGM threshold was set at 80 mg/dL for 14 experiments. The mean (±SD) sensor glucose at predictive suspension was 92 ± 7 mg/dL resulting in a post suspension nadir (Hemocue) of 77 ± 22 mg/dL. The suspension lasted for 90 ± 35 (range: 30–120) min resulting in a sensor glucose at insulin resumption of 97 ± 19 mg/dL.
Conclusions: These early feasibility data suggest that the PLGM system prevents hypoglycemia by suspending insulin ~30 min before a predicted hypoglycemic event even under the demanding conditions of vigorous exercise.

O72

Reduction in hypoglycemia and no deterioration in A1C with threshold-based sensor-augmented pump (SAP) insulin suspension: ASPIRE in-home

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Objectives: ASPIRE In-Home was a 3-month RCT comparing SAP with threshold suspend (SAP + TS), which stops insulin at a specified sensor glucose (SG) threshold for up to 2 h, to SAP alone (SAP).
Methods: The primary safety outcome was the between-group difference for ΔA1C. Safety data on severe hypoglycemia and DKA was also collected. The primary efficacy outcome was the between-group difference for AUC of nocturnal hypoglycemia (NH) events, measured by Enlite CGM sensors. Subjects with T1D, ages 16–70 who had ≥2 NH episodes in a 2-wk run-in period were randomized to SAP + TS (121) or to SAP (126).

Safety and efficacy outcomes by age

		Age 16–24		Age 25–50		Age 51–70	
		SAP	SAP + TS	SAP	SAP + TS	SAP	SAP + TS
Number of Subjects	Randomization	12	14	78	60	30	52
	3-month	11	14	78	59	27	51
A1C, %	Randomization	7.56 ± 0.97	7.64 ± 0.67	7.20 ± 0.71	7.07 ± 0.73	7.28 ± 0.60	7.25 ± 0.82
	3-month	7.41 ± 0.76	7.41 ± 0.89	7.23 ± 0.68	7.02 ± 0.70	7.19 ± 0.60	7.20 ± 0.81
AUC of NH events, mg/dL × min	Study Phase	1439 ± 1711	1921 ± 2625	925 ± 1117	1528 ± 1912	891 ± 1031	1531 ± 1911

Results: Changes in A1C were similar between groups, meeting the safety outcome. The mean overall AUC of NH events was 980 ± 1200 mg/dL × min in SAP + TS and 1568 ± 1995 mg/dl × min in SAP, meeting the efficacy outcome. The overall number of NH events per patient-week was 1.5 ± 1.0 in SAP + TS and 2.2 ± 1.3 in SAP. No reported DKA occurred during the study. Four severe hypoglycemia events occurred (four subjects), all in the SAP group. The study was not originally powered to look at subgroup analysis by age. In *post-hoc* analysis, the primary safety and efficacy outcomes were consistent across age groups. Indicators of glycemia were least favorable in the youngest age cohort.

Conclusions: ASPIRE In-Home demonstrated that using SAP therapy with the TS feature safely reduced nocturnal and overall hypoglycemia, without deterioration of A1C (Table 1).