ISPAD2011

ORAL SESSIONS

Oral Session I: Acute and Chronic Complications

O/1/WED/01

Early neurographic abnormalities precedes symtomatic neuropathy in type 1 diabetes – a 13-year follow-up study

J. Ludvigsson[1], J. Wahlberg[2], N. Alstrand[2] & L. Hyllienmark[3]
[1]*Linköping University, Div of Pediatrics, Dept Clin Exp Medicine, Linköping, Sweden,* [2]*Linköping University, Linköping, Sweden,* [3]*Karolinska Institute, Stockholm, Sweden*

Overt neuropathy with symptoms is uncommon in children and adolescents with Type 1 diabetes (T1D), but may be preceded by a subclinical form which can be detected by studies of nerve cnduction.

Objectives: To elucidate if subclinical electrophysiological abnormalities can predict symptomatic neuropathy in patients with T1D.

Methods: Fifty-nine patients (34 males, 25 females) , with age <15 years at diagnosis of T1D were examined twice with a mean follow-up time of 13 years. From disease onset all patients were treated with multiple insulin-injection therapy or insulin pump. Duration of diabetes at second examination was 20 ± 5.4 years. The first examination included motor nerve conduction velocity (MCV), compound muscle action potential in peroneal and median nerves and sensory nerve conduction velocity and nerve action potential in sural and median nerves. The second examination included also assessment of quantitative sensory thresholds, neuropathy impairment assessment and neuropathy symptom assessment (NSA). Symptomatic neuropathy was defined as NSA of ≥1.

Results: At second examination symptomatic neuropathy was found in 12/59 (20%) of patients. Patients with symptoms had lower peroneal and median MCV at baseline ($P < 0.05$). Patients with symptoms had a higher weighted mean HbA1c than asymptomatic patients, 8.0 ± 0.6 vs. 7.2 ± 1.0% $P < 0.002$ A combination of long-term HbA1c ≥7.0% and a significant (>2 SD) decrease in peroneal MCV at baseline increased the risk of symptoms at follow-up (odds ratio = 21; $P < 0.0001$).

Conclusions: Overt neuropathy with symptoms is preceded by a subclinical form detectable by studies of nerve conduction, and related to higher HbA1c. Despite modern intensive treatment symptomatic neuropathy is seen in 20 percent of patients after 20 years of type 1 diabetes.

O/1/WED/02

Retinal vascular geometry predicts incident renal dysfunction in young persons with type 1 diabetes

P.Z. Benitez-Aguirre[1,2], M.B. Sasongko[3,4], M.E. Craig[1,2,5], A.J. Jenkins[6], J. Cusumano[1], N. Cheung[3], T.Y. Wong[3,7] & K.C. Donaghue[1,2]
[1]*The Children's Hospital at Westmead, Institute of Endocrinology and Diabetes, Westmead, Sydney, Australia,* [2]*University of Sydney, Discipline of Paediatrics and Child Health, Sydney, Australia,* [3]*The University of Melbourne, Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Australia,* [4]*Gadjah Mada University, Department of Ophthalmology, Faculty of Medicine,, Yogyakarta, Indonesia,* [5]*University of New South Wales, School of Women's and Children's Health, Sydney, Australia,* [6]*The University of Melbourne, Department of Medicine, St Vincent's Hospital, Melbourne, Australia,* [7]*National University of Singapore, Singapore Eye Research Institute, Singapore, Singapore*

Aim: To examine the relationship between retinal vascular geometry parameters and development of incident renal dysfunction in young people with type 1 diabetes.

Methods: A prospective cohort study of 511 adolescents with type 1 diabetes (T1DM) of at least 2 years duration, normal albumin excretion rate (AER) and free of retinopathy at baseline attending an Australian tertiary-care hospital. AER was quantified using 3 overnight timed urine specimen collections and early renal dysfunction defined as AER >7.5 μg/minutes. Retinal vascular geometry [including length to diameter ratio (LDR) and simple tortuosity (ST)] was quantified from baseline retinal photographs. Generalized estimating equations were used to examine the relationship between incident renal dysfunction and baseline venular LDR and ST, adjusting for age, diabetes duration, HbA1c, blood pressure, BMI and cholesterol.

Results: At baseline diabetes duration was 4.8 [interquartile range 3.3–7.5] years. After a median 3.7 [2.3–5.7] years follow-up, 34% of participants developed incident renal dysfunction. In multivariate analysis, higher baseline retinal venular LDR (Odds Ratio 1.48, 95% CI 1.05–2.10; 4th vs. 1–3 quartiles) and lower venular ST (1.51, 1.06–2.13; 1st vs. 2–4 quartiles) predicted incident renal dysfunction.

Conclusions: Retinal vascular geometry predicted early renal dysfunction in young people with T1DM of short duration. Abnormal retinal vascular geometry may reflect systemic adaptation to an early diffuse endotheliopathy caused by the diabetic milieu. Retinal vascular geometry may be a useful tool to identify individuals at high risk of renal disease early in the course of diabetes.

O/1/WED/03

An independent effect of parental lipids on the offspring lipid levels in a cohort of adolescents with type 1 diabetes

M.L. Marcovecchio[1], P.H. Tossavainen[1], R.N. Dalton[2] & D.B. Dunger[1]
[1]*University of Cambridge, Department of Paediatrics, Cambridge, United Kingdom,* [2]*King's College London, Evelina Children's Hospital, WellChild Laboratory, London, United Kingdom*

Objectives: Genetic factors modulate lipid levels and an intrafamilial aggregation of abnormal lipid profiles has been reported in the general population. As dyslipidemia is common among young people with type 1 diabetes (T1D) and has been associated with diabetic nephropathy, our aim was to assess whether parental lipid levels were related to lipids and albumin excretion in young offspring with T1D.
Methods: Non-fasting blood samples were collected from 895 offspring, 825 mothers and 582 fathers for a total of 769 mothers-offspring pairs, 548 fathers-offspring pairs and 501 complete trios. Total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol were measured. Three early morning urinary albumin-creatinine ratios (ACR), HbA1c and anthropometric parameters were also assessed in the offspring.
Results: The offspring's mean age (±SD) was 14.4 ± 2.1 years and T1D duration 5.3 ± 3.6 years. The fathers' mean age was 45.5 ± 6.1 years and the mothers' mean age 42.8 ± 5.5 years. After adjusting for the offsprings age, gender, BMI SDS and HbA1c, mean parental lipid parameters were significantly associated with the offspring's lipids.
In contrast, no significant association was found between parental lipids and the offsprings ACR (all P > 0.05). However, mothers of offspring with microalbuminuria (n = 96) had a higher prevalence of low HDL-cholesterol than mothers of normoalbuminuric offspring (n = 673): 6.3% vs. 2.1%, P = 0.03.

	Mean parental lipids (n = 501)	Paternal lipids (n = 548)	Maternal lipids (n = 769)
Total cholesterol	β = 0.27; P < 0.001	β = 0.25; P < 0.001	β = 0.16; P < 0.001
Triglycerides	β = 0.15; P = 0.001	β = 0.16; P < 0.001	β = 0.06; P = 0.14
HDL-cholesterol	β = 0.37; P < 0.001	β = 0.28; P < 0.001	β = 0.27; P < 0.001
LDL-cholesterol	β = 0.33; P < 0.001	β = 0.28; P < 0.001	β = 0.18; P < 0.001

[Multiple regression analysis]

Conclusions: Parental lipid levels were independently associated with the same traits in the offspring, suggesting a role of genetic and/or shared environmental factors in modulating the metabolic profile of adolescents with T1D. In addition, decreased maternal HDL-cholesterol was related to microalbuminuria in the offspring.

O/1/WED/04

Hyperandrogenism and insulin resistance are associated with cardiac autonomic dysfunction in peri-pubertal girls with type 1 diabetes

Y.H. Cho[1], M.E. Craig[1,2,3], S. Srinivasan[1], A. Chan[1], J. Cusumano[1] & K.C. Donaghue[1]
[1]*The Children's Hospital at Westmead, Institute of Endocrinology and Diabetes, Sydney, Australia,* [2]*University of Sydney, Discipline of Paediatrics and Child Health, Sydney, Australia,* [3]*University of New South Wales, School of Women's and Children's Health, Sydney, Australia*

Objectives: To examine the role of hyperandrogenism, insulin resistance and glycemic control on cardiac autonomic function in peripubertal girls with type 1 diabetes (T1D).
Methods: We assessed 129 girls with T1D (age 8–18 years) for clinical/biochemical features of hyperandrogenism/insulin resistance: BMI SDS, acanthosis, waist:height ratio (WHR), sex hormone-binding globulin level (SHBG) and microvascular complications. An ECG-recording over 20-minutes using LabChart measured mean resting heart rate (HR) and HR variability parameters: standard deviation of mean NN intervals (SDNN), where NN = adjacent QRS-complexes, root mean squared difference of successive NN-intervals (RMSD)- an estimate of overall HR variability and lower:higher frequency (LF:HF) ratio- an estimate of sympathetic/parasympathetic balance. Associations between hyperandrogenism/insulin resistance and HR variability parameters were examined using multiple linear regression.
Results: Median age was 15.1 years [IQR 13.3–16.0], diabetes duration 6.9 years [4.2–10.0], 97% used intensive insulin therapy (50% CSII), median total daily insulin dose was 0.95 U/kg/day [0.76–1.21], median HbA1c was 8.4% [7.5–9.5], 46% were overweight (BMI > 85th centile), 48% had WHR $\geq$0.5 and 21% had acanthosis. Higher baseline HR was associated with higher HbA1c (β 2.6, 95% CI 0.6–4.5; P = 0.01). Lower SDNN was associated with higher HbA1c (β –4.4, –8.6 to –0.2; P = 0.04) and lower SHBG (β 0.2, 0.1–0.4; P < 0.01), lower RMSSD with lower SHBG (β 0.4, 0.2–0.6; P < 0.001) and higher LF:HF ratio with higher HbA1c (β 0.2, 0.1–0.3; P < 0.001) and weight SDS (β 0.2, 0.1–0.4; P = 0.01).
Conclusions: Almost half of adolescent girls with T1D are overweight with higher WHR, which potentially imposes additional cardiovascular risk. Lower SHBG, an index of insulin resistance, and higher HbA1c may identify adolescents who are at risk of early cardiac autonomic dysfunction, a marker of long-term cardiovascular morbidity and mortality in adults.

O/1/WED/05

The importance of glycaemic control for development of microangiopathy in type 1 diabetes – the VISS-project (vascular diabetic complications in Southeast Sweden)

M. Nordwall[1], M. Abrahamsson[2], M. Dhir[2], M. Fredrikson[3], J. Ludvigsson[3] & H.J. Arnqvist[3]
[1]*Linköping University, Div of Pediatrics,Dept of Clinical and Experimental Medicine, Linköping, Sweden,* [2]*Department of Ophthalmology, Vrinnevi Hospital, Norrköping, Sweden,* [3]*Linköping University, Clinical and Experimental Medicine, Linköping, Sweden*

Objectives: Our aim was to study the prevalence of diabetic microangiopathy and the importance of HbA1c and its variation, from diagnosis of diabetes and during certain periods: before/during/after puberty, for the development of retinopathy and nephropathy in an unselected population.
Methods: The prevalence and incidence of retinopathy and prevalence of nephropathy after 20–25 years of diabetes duration was analyzed in 437 patients with type 1 diabetes with onset before the age of 35 years during 1983–1987 in South East Sweden. Data on nephropathy were collected from medical records. Fundus photos were examined independently by two ophthalmologists. Long-term mean HbA1c from diagnosis of diabetes and during the whole follow-up was calculated.
Results: The prevalence of microalbuminuria and macro-albuminuria was 11% and 4% respectively. Long term mean HbA1c was 71 mmol/mol and 80 mmol/mol in these groups compared to 65 mmol/mol in patients with no signs of nephropathy (P < 0.001). The prevalence of lower grades of simplex retinopathy was 33%, more severe simplex retinopathy 41% and proliferative retinopathy 13%. Long term mean HbA1c was 63 mmol/mol, 69 mmol/mol and 76 mmol/mol in these

patients compared to 55 mmol/mol in patients without retinopathy ($P < 0.001$). The median time to first sign of retinopathy was shorter in patients with higher long term HbA1c($P < 0.001$),17.7 years in patients with long term HbA1c ≤56 mmol/mol 13.9 years for HbA1c 57–67 mmol/mol%, 12.1 years for HbA1c 68–77 mmol/mol and 11.4 years for HbA1c ≥78 mmol/mol respectively.

Conclusions: The prevalence of diabetic microangiopathy is lower in this population than previously described in other cohorts. There is a strong association between long-term mean HbA1c measured from diagnosis and development of microvascular diabetic complications suggesting that keeping HbA1c below 60 mmol/mol prevents severe retinopathy or nephropathy.

O/1/WED/06

The AGE methylglyoxal-derived hydroimidazolone and early atherosclerosis in children with type 1 diabetes

M. Heier[1,2,3], H.D. Margeirsdottir[2,4], P.A. Torjesen[2,5], I. Seljeflot[2,6], C. Brunborg[7], K.F. Hanssen[2,3,8] & K. Dahl-Jørgensen[1,2,3]

[1]*Oslo University Hospital, Department of Pediatrics, Oslo, Norway,* [2]*University of Oslo, Faculty of Medicine, Oslo, Norway,* [3]*Oslo Diabetes Research Centre, Oslo, Norway,* [4]*Akershus University Hospital, Department of Pediatrics, Lørenskog, Norway,* [5]*Oslo University Hospital, Hormone Laboratory, Oslo, Norway,* [6]*Oslo University Hospital, Center for Clinical Heart Research and Department of Cardiology, Oslo, Norway,* [7]*Oslo University Hospital, Unit of Biostatistics and Epidemiology, Oslo, Norway,* [8]*Oslo University Hospital, Department of Endocrinology, Oslo, Norway*

Advanced protein glycation is an important mechanism for the development of late diabetic complications and atherosclerosis. Hydroimidazolones are the most abundant advanced glycation end products (AGEs) in human plasma, and methylglyoxal-derived hydroimidazolone (MG-H1) is a major contributor. High sensitive C-reactive protein (HS-CRP) and other inflammatory factors have shown the ability to identify risk of atherosclerosis.

Objectives: To investigate the relationship between MG-H1 and early signs of inflammation in children with type 1 diabetes compared to healthy controls.

Methods: A total of 314 diabetic patients aged 8–18 years, were compared to 118 healthy controls of the same age and sex. MG-H1 and HS-CRP were measured by immunoassay.

Results: Mean age of the diabetic patients was 13.7 years, diabetes duration 5.5 years and HbA1c 8.4%. We found that MG-H1 was significantly increased in the diabetic group compared to controls, 155.3 (SD = 41.0) vs. 142.7 (SD = 35.1) U/ml, P = .002. MG-H1 levels correlated positively with HbA1c, $r_s = .186$ and P = .00016. Diabetic girls had significantly higher levels of MG-H1 than diabetic boys, 161.3 (SD 44.2) vs. 149.1 (SD 36.5), P = .009. This was not the case in the control group. MG-H1 also correlated positively with the duration of diabetes, r = .117, P = .041. There was a positive association between MG-H1 and HS-CRP, r = .181, P = .004, and the levels were significantly higher in the diabetic group compared to controls 1.0 vs. 0.62, P < .001. The diabetics also had significantly higher levels of the inflammation marker E-selectin than the controls, 27.0 (SD = 10.2) vs. 24.3 (SD = 8.7), P = .008.

Conclusions: Serum levels of methylglyoxal-derived hydroimidazolone are increased, and despite short duration of disease, our findings support a relationship between MG-H1 and low grade inflammation indicative of an early atherosclerotic process in diabetic children.

O/1/WED/07

Evidence of low grade inflammation in diabetic children and adolescents on intensive insulin treatment: a population based study

H.D. Margeirsdottir[1,2,3], M. Heier[2,3,4], J.R. Larsen[3], C. Brunborg[5], K. Dahl-Jørgensen[2,3,4] & I. Seljeflot[2,6]

[1]*Akershus University Hospital, Department of Paediatrics, Lørenskog, Norway,* [2]*University of Oslo, Faculty of Medicine, Oslo, Norway,* [3]*Oslo Diabetes Research Centre, Oslo, Norway,* [4]*Oslo University Hospital Ullevaal, Department of Paediatrics, Oslo, Norway,* [5]*Oslo University Hospital, Centre for Clinical Research Ullevaal, Oslo, Norway,* [6]*Oslo University Hospital Ullevaal, Center for Clinical Heart Research, Department of Cardiology, Oslo, Norway*

There is indicating evidence that diabetes is associated with proinflammatory state. Furthermore, some inflammatory markers measured in the blood have shown to be predictive of atherosclerosis and Cardiovascular disease (CVD).

Objective: To evaluate early signs of inflammation in children and adolescents with type-1 diabetes.

Methods: A total of 314 diabetic patients aged 8–18 years (40% of eligible subjects) participated in this population based study and were compared to 118 healthy controls. Fasting blood samples were taken and various inflammatory markers associated with atherosclerosis measured by ELISA method.

Results: (Mean [SD]): Mean age of the diabetic patients was 13.7 years, diabetes duration 5.5 years and HbA1c 8.4%. The majority (97%) were using intensive insulin treatment, 60% insulin pumps. The diabetic patients had a significantly higher levels of IL-18 than the controls (243 (91) vs. 232 (121) pg/ml; P = 0.01), as well as MCP-1 (340 (112) vs. 316 (95) pg/ml; P = 0.03) and CRP (2.05 (3.9) vs. 0.88 (2.3) mg/l; P < 0.001). They also had higher levels of IL-6 (1.6 (2.5) vs. 1.1 (0.7) pg/ml), although not statistically significant (P = 0.2) with a positive correlation between CRP and IL-6 ($r_{sp} = 0.35$, P < 0.001). Furthermore, the diabetes patients had elevated levels of MMP-9 compared to controls, although not significantly so (240 (158) vs. 200 (90) ng/ml; P = 0.08), whereas significantly higher levels of TMP-1 were found in the diabetic group (165 (27) vs. 158 (25) ng/ml; P = 0.008). There was no difference between the groups in the mean levels of TNFα. A positive correlation was found between HbA1c and CRP ($r_{sp} = 0.24$, P < 0.001), IL-6 ($r_{sp} = 0.11$, P = 0.04), IL-18 ($r_{sp} = 0.2$, P < 0.001) and TNFα ($r_{sp} = 0.12$, P = 0.035) in the diabetic group.

Conclusions: Despite short disease duration and intensive insulin treatment, a low grade inflammation seems to be present in this group of type 1 diabetic children and adolescents, with a positive correlation with HbA1c.

O/1/WED/08

Impaired growth during puberty in young people with type 1 diabetes and microalbuminuria

M.L. Marcovecchio[1], R.N. Dalton[2] & D.B. Dunger[1]

[1]*University of Cambridge, Department of Paediatrics, Cambridge, United Kingdom,* [2]*King's College London, Evelina Children's Hospital, WellChild Laboratory, London, United Kingdom*

Objective: In adults with type 1 diabetes (T1D) short stature has been associated with diabetic nephropathy. Our aim was to assess whether pubertal growth is impaired in young people with T1D who develop microalbuminuria (MA).

Methods: Repeated height measurements were available for 201 adolescents with T1D. Longitudinal data on albumin/creatinine ratios and HbA1c were also collected from the study participants. Height standard deviation scores (H-SDS) were

compared between subjects with (MA+; n = 66) and without MA (MA–; n = 135).

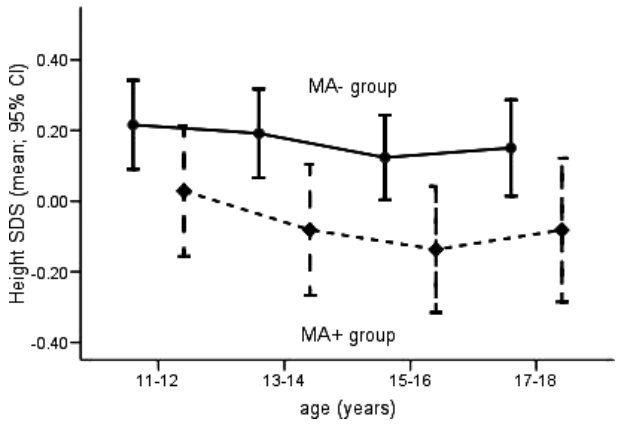


Figure 1

Results: H-SDS progressively declined during puberty, from 0.22 ± 0.97 to 0.07 ± 1.04, P < 0.001. This decline was significantly different between the MA+ and MA– groups (P = 0.04) (Figure 1).

H-SDS was lower in the MA+ group at the age of 15–16 years: –0.11 ± 1.02 vs. 0.22 ± 0.96, P = 0.02, and at the age of 17–18 years: –0.17 ± 1.06 vs. 0.19 ± 1.01, P = 0.02. Within the MA+ group, H-SDS after MA onset was significantly lower than before MA onset (–0.24 ± 0.96 vs. –0.03 ± 0.94, P = 0.001). Final height was inversely associated with MA (HR [95%CI]:0.968 [0.943–0.994] P = 0.01), although this association was no longer significant after adjusting for HbA1c, which was higher in the MA+ group (10.5 ± 1.7 vs. 9.8 ± 1.4%, P = 0.003).

Conclusions: In this cohort of young people with T1D, growth during puberty was impaired, particularly in subjects with MA. These findings could be due to common genetic/environmental factors involved in the pathogenesis of impaired growth and MA and/or to poor glycemic control.

Oral Session II: Education and Psychosocial Issues

O/2/WED/01

A comparative effectiveness trial of two internet programs for youth with type 1 diabetes (T1D)

R. Whittemore[1], S. Jeon[1], S.S. Jaser[1], K. Murphy[2], M.S. Faulkner[3], A. Delamater[4], M. Grey[1] & The TeenCope Study Group
[1]*Yale School of Nursing, New Haven, United States,* [2]*The Children's Hospital of Philadelphia, Philadelphia, United States,* [3]*University of Arizona, Tucson, United States,* [4]*University of Miami, Miami, United States*

Objectives: The purpose of this ongoing multisite clinical trial is to compare the effectiveness of TEENCOPE™ (internet coping skills training) with MANAGING DIABETES (internet education program) for youth with T1D on A1C, self-management, self-efficacy, stress, coping, quality of life, and family conflict. We report 3 month outcomes.
Methods: Teens with T1D (n = 320, 11–14 years) from 4 sites were randomly assigned to one of the programs & completed data via the internet. A1C was obtained from clinic records. Teens were 12.3 + 1.1 years old, diabetes duration 1.0 + 0.6 years, A1C 8.30 + 1.5%, and 59% on pump therapy. Fifty-five percent were female & 62% non-Hispanic White (20% Hispanic, 8% Black). Groups were comparable at baseline. Participation (78% of youth completed 4 of 5 sessions) & satisfaction were high. Data were analyzed with mixed models.
Results: Teens in both groups reported a significant increase in self-efficacy (P = .004), emotional QOL (P = .039), & decrease in family conflict (P = .057) over time. Controlling for baseline score, race, income, and therapy type, teens participating in MANAGING DIABETES reported greater improvements in self-management (P = .049), coping (P = .037), perceived stress (P = .005), and emotional QOL (P = .013) than those in TEENCOPE. Treatment effects were moderated by family income; teens from lower income – but not higher income – families who participated in MANAGING DIABETES showed greater improvement in self-management than those who participated in TEENCOPE (P = .032). There were no differences on other QOL measures (e.g., physical, social) or A1C.
Conclusions: Participation in both programs was excellent & led to improved psychosocial and family outcomes after 3 months in diverse youth with T1D. MANAGING DIABETES also contributed to improved self-management and other psychosocial outcomes. These results suggest the benefit of diabetes-specific coping and educational internet programs in young teens. Longer-term follow-up is indicated.

O/2/WED/02

Longitudinal study of psychiatric disorders and metabolic control in children and adolescents with type 1 diabetes mellitus

J.-J. Robert[1], M. Vera[2], C. Bertrand[2], M.-C. Mouren-Simeoni[3], A. Delamater[4] & G. Vila[5]
[1]*Hôpital Necker Enfants Malades, Université René Descartes Paris 5, Diabète de l'Enfant et de l'Adolescent, Paris, France,* [2]*Hôpital Necker Enfants Malades, Paris, France,* [3]*Hôpital Robert Debré, Paris, France,* [4]*University of Miami, Dept of Pediatrics, Miami, United States,* [5]*Hôpital Trousseau, Paris, France*

Objectives: To evaluate psychiatric disorders in a large sample of youth with type 1 diabetes, and determine the relationships to familial psychopathology, metabolic control and health complications.
Methods: All youth with type 1 diabetes followed in a Pediatric Diabetes unit (114 girls/120 boys, 13.4 ± 4.4 years) were assessed by structured psychiatric diagnostic interviews DISC-R and by self-questionnaires STAIC and CESD, and for their parents CBCL and CPRS. Parentś psychiatric problems were assessed by GHQ-28. Patients were followed at regular intervals over 5 years for clinical diagnoses of psychiatric disorders, metabolic control and health complications. Path analysis was utilized to model the relationships between psychopathology and metabolic control.
Results: At first assessment, 104 (55%) patients had at least one psychiatric disorder: 33% an anxiety disorder; 13% an affective disorder; and 12% a disruptive behavior disorder. Youth with a diagnosed psychiatric disorder had higher HBA1c (9.6 vs. 9.1%, P < .03). Affective disorders and disruptive behavior disorders, not anxiety disorders, were associated with higher HBA1c. HBA1c was higher with more child-reported anxiety and depression, and more parent-reported internalizing and externalizing problems. Lower socioeconomic status, higher mother reports of their own psychological symptoms were associated with higher HBA1c. During the 5 year follow-up, 42% of youth had at least one psychiatric disorder and higher longitudinal mean HBA1c (P < .002). Patients with higher HBA1c and a higher rate of psychiatric disorders had more microangiopathy (P < .02) and retinopathy (P < .01). Longitudinal path analyses showed that lower socio-economic status and parental psychological problems were associated with higher HBA1c and psychiatric problems in the child.
Conclusions: High rate of psychiatric disorders in youth with type 1 diabetes is associated with poor metabolic control and increased risk for health complications.

O/2/WED/03

Diabetes resilience: a prevention model of risk and protective factors

M.E. Hilliard[1], J. Weissberg-Benchell[2], M.A. Harris[3] & K.K. Hood[1]
[1]*Cincinnati Children's Hospital, Adherence Center, Division of Behavioral Medicine, Cincinnati, United States,* [2]*Children's Memorial Hospital, Chicago, United States,* [3]*Oregon Health & Science University, Portland, United States*

Objectives: Many youth with type 1 diabetes exhibit declines in diabetes management and control during adolescence. Data on risk factors for suboptimal management and control are available; however, there are few data on protective factors. Resilience theory states that protective factors lead to positive outcomes in the face of risk. Thus, our aim was to examine resilience in pediatric type 1 diabetes.
Methods: The sample consisted of 145 adolescents with type 1 diabetes (14 to 18-years old, M age = 16.5 ± 1.4 years, M diabetes duration = 7.2 ± 3.8 years, 52% female, 64% on CSII, 72% on private insurance). The independent variable (i.e., risk factor) was adolescent depressive symptoms (parent-report). The mediator was blood glucose monitoring (BGM) adherence, obtained through meter download. The dependent variable was glycemic control (A1c), collected at the study visit via DCA 2000+. The moderator (i.e., protective factor) was diabetes self-efficacy.
Results: BGM adherence mediated the link between depressive symptoms and A1c (b = –.37, P < .0001). The prediction of the mediating variable, BGM adherence, was moderated by the interaction of depressive symptoms and self-efficacy (b = –.01, P < .05). *Post hoc* probing showed that the impact of moderate

depressive symptoms on BGM adherence was attenuated in teens with higher diabetes self-efficacy. These teens engaged in more frequent BGM, which was linked with lower A1c.
Conclusions: Consistent with previous research, depressive symptoms are a risk factor for poor glycemic control, mediated by less frequent BGM. However, these data show that a protective factor, diabetes self-efficacy, buffers the risks associated with subclinically elevated depressive symptoms. Prevention efforts to reduce the negative impact of depression on diabetes management and control should involve promoting adolescents' self-efficacy. These data are one illustration of how diabetes resilience can impact diabetes management and control.

O/2/WED/04

A network delivered ``out of hours'' specialist telephone support service for young people and families with type 1 diabetes

N. Abdullah[1], B. Van Meijgaarden[2], B. Anand[3], S. Arun[4], C. Bound[2], N. Cackett[5], C. Pesterfield[6], V. Raman[7], R. Williams[8], K. Wilson[9], C. Acerini[8] & East of England Paediatric Diabetes Network
[1]*Cambridge University Hospitals Foundation Trust, Weston Centre, Cambridge, United Kingdom,* [2]*Basildon and Thurrock University Hospitals NHS Foundation Trust, Basildon, United Kingdom,* [3]*West Suffolk Hospital NHS Trust, Bury St Edmunds, United Kingdom,* [4]*Mid Essex Hospital, Chelmsford, United Kingdom,* [5]*Colchester Hospital University NHS Foundation Trust, Colchester, United Kingdom,* [6]*Cambridge University Hospitals Foundation Trust, Cambridge, United Kingdom,* [7]*James Paget University Hospitals NHS Foundation Trust, Great Yarmouth, United Kingdom,* [8]*University of Cambridge, Paediatrics, Cambridge, United Kingdom,* [9]*NHS Diabetes, East of England, United Kingdom*

Background: Guidelines for children with type 1 diabetes (TID) recommend 24 hour/7-day-a-week access to advice from specialist health-care professionals. However limited resources often precludes provision of this service outside normal working hours. Regional networks may enable the implementation of safe, high quality and cost-effective support to patients and families ''out of hours''.
Methods: Prospective 16 week pilot study involving 5 paediatric centres (n = 965 TID patients, 15% CSII) in the East of England. Out of hours (17.00 – 0900 hour & weekends) telephone advice for patients was delivered by 7 clinicians and 7 nurse specialists. Advice was given using standardised management algorithms. Calls were logged, and data collected on type / nature of query, advice given, hospital attendance and patient satisfaction.
Results: A total of 193 calls were received from 99 patients (n = 51M. n = 21 CSII). Median (range) age 9 (2–17) years. 50.5% of calls occurred between 17:00 – 21:00 hours (21–23:00 hours (14.6%), 23–07:00 hours (5.2%); 07 – 17:00 hours (29.7%)). Median duration of calls was 9 (range 1– 25) minutes. Reasons for contact shown in Table 1.

Nature of Call	% of calls
CSII queries	23
Hyperglycaemia	21
High Ketones	13
Hypoglycaemia	11
Vomiting	10
Insulin dose errors	6
other diabetes related issues	22

Four calls (2%) resulted in a subsequent emergency hospital attendance. 63 hospital attendances were avoided, with estimated saving of 35.7 in-patient bed days and cost savings of £23K. Mean (SD) satisfaction score (1 = poor, 10 = high) was 9.7 (0.7).
Conclusion: Safe and effective telephone advice can be delivered ''out of hours'' by sharing resources and experience across an established clinical diabetes network with significant cost savings and high patient satisfaction.

O/2/WED/05

Do or don't? CSII and multiple injection therapy have no negative impact on quality of life in younger children

C. de Beaufort[1], K. Lange[2], L. Castano[3], E. Kaprio[4], J. J. Robert[5], T. Danne[6], T. Urakami[7], P. Njolstad[8], H. Hoey[9], M. Phillip[10], E. Schoenle[11] & Hvidoere Study Group
[1]*Clinique Pediatrique de Luxemburg, DECCP, Luxembourg, Luxembourg,* [2]*Medizinische Psychologie, Medizinische Hochschule, Hannover, Germany,* [3]*University of Basque Country, Dept of Pediatrics Endocrinology & Diabetes Research Group, Barakaldo, Spain,* [4]*Dept of Paediatrics, Peijas Hospital, HUS, Finland,* [5]*Hopital Necker, Enfants Malades, Diabete de l'Enfant et de l'Adolescent, Paris, France,* [6]*Kinderkrankenhaus auf der Bult, Paediatrie, Hannover, Germany,* [7]*Nihon University, Dept of Paediatrics, Tokio, Japan,* [8]*Haukeland University Hospital, Dept of Paediatrics, Bergen, Norway,* [9]*Dept of Paediatrics, National Children's Hospital, Dublin, Ireland,* [10]*National Center of Childhood Diabetes, Schneiders Childrens Medical Center, Petah Tikvah, Israel,* [11]*University Hospital Zurich, Dept of Diabetes and Endocrinology, Zurich, Switzerland*

Objective: To compare quality of life of young children with t1dm, and their parents' well-being with intensified (IT:CSII + ICT) or conventional insulin (CT) therapy.
Methodology: In a cross sectional study, all children of 18 centres in North America Australia, Europe and Japan, age <11 years with a diabetes duration (DD) ≥1 year, and their parents, were invited to participate. Information on clinical characteristics, treatment, severe hypoglycaemia and diabetic ketoacidosis were collected. HbA1c was measured centrally by ^{R}Tosoh liquid chromatography (DCCT aligned normal range 4.4–6.3%). Quality of Life (QoL) was evaluated by kidscreen index (≥7 years); kidscreen-27 proxy (Physical well-being, Psychological well-being, Autonomy & parent relation, Social support & peers, School) for children and WHO-5 for parents.
Results: In total 1133 children participated: IT (n = 562, 47.4% ♀, age 8.1 ± 2.1 years, CT n = 570 ; 48%♀ ; age 7.9 ± 2.1 years). Diabetes duration in the IT was significantly longer (3.6 ± 2.9 vs. 3.1 ± 2.0 years) with a significantly lower HbA1c (7.9 ± 0.9 vs. 8.1 ± 1.1%) and less severe hypoglycaemic events (.02 vs. .05). Children with diabetes overall do not differ from norm data of healthy peers in any of the QoL dimensions. A significantly better QoL was reported in the IT group (<.02) on all subscales of kidscreen questionnaire, except psychological well being. Parent well-being did not differ between the two groups.
Conclusion: In this large international cross-sectional study, IT in young children with T1DM results in an improved metabolic outcome, less hypoglycaemia and in 4/5 dimensions better quality of life, suggesting that intensification of therapy can be started early onwards.

O/2/WED/06

A randomised trial of a psychosocial program to improve glycaemic control and psychosocial wellbeing in adolescents with type 1 diabetes

A. Serlachius[1,2], E. Frydenberg[2], E. Northam[3,4] & F. Cameron[1]
[1]*Murdoch Childrens Research Institute, Department of Endocrinology and Diabetes, Melbourne, Australia,* [2]*The University of Melbourne, Melbourne Graduate School of Education, Melbourne, Australia,* [3]*Murdoch Childrens Research Institute, The Australian Centre for Child Neuropsychology Studies, Melbourne, Australia,* [4]*The University of Melbourne, Department of Psychology, Melbourne, Australia*

Objectives: Adolescents with type 1 diabetes mellitus (T1DM) are considered a vulnerable group, as they are at increased risk for a deterioration in glycaemic control as well as for psychiatric disorders. Psychosocial interventions in T1DM have attempted to reduce these morbidities, but despite some modest success, it is still unclear which specific therapeutic approaches and intervention components are the most effective in improving glycaemic control and psychological wellbeing. In order to clarify these questions a randomised controlled trial (RCT) was conducted to evaluate a coping skills program based on cognitive behavioural theory in improving glycaemic control and psychosocial outcomes in T1DM.
Methods: One hundred and fifty six adolescents aged 13–16 years with T1DM were recruited from a paediatric hospital and randomised into the control group or the coping skills program. Glycaemic control and psychosocial outcomes were measured at baseline and 3-months after treatment, and the data analysed using independent samples *t*-tests and analysis of covariance.
Results: Per-protocol analyses demonstrated statistically significant improvements in productive coping skills (P = .022), diabetes-specific self-efficacy (P = .046), stress levels (P = .047), and quality of life (P = .030) in the treatment group compared to the control group at the 3 month follow-up. Although glycaemic control improved in the treatment group compared to the control group (effect size of 0.28), the difference was not statistically significant (P = .227).
Conclusions: The significant improvements seen in psychosocial outcomes testify to the efficacy of the coping skills program, and if offered as part of standard care this intervention may reduce mental health morbidity and improve quality of life in adolescents with T1DM.

O/2/WED/07

Prevalence of behaviour difficulties and their predictors in an international cohort of 1090 young children with type 1 diabetes

K. Lange[1], C. de Beaufort[2], L.K. Fisher[3], H. Hoey[4], M. Kocova[5], H. B. Mortensen[6], T. Danne[7], A. Neu[8], J. -J. Robert[9], E. Kaprio[10], L. Castano[11], E.J. Schönle[12], J. Aman[13], M. Phillip[14], M. Vanelli[15], T. Urakami[16], F. Cameron[17], P. R. Njolstad[18], H. Dorchy[19], T. G. Barrett[20], H.J. Aanstoot[21], F. Chiarelli[22], K.J. Robertson[23], P. Swift[24] & on behalf of the Hvidoere Study Group
[1]*Hannover Medical School, Medical Psychology, Hannover, Germany,* [2]*Clinique Pediatrique, Luxembourg, Luxembourg,* [3]*Children's Hospital, Los Angeles, United States,* [4]*National Children's Hospital, Dublin, Ireland,* [5]*University Pediatric Clinic, Skopje, Macedonia, the Former Yugoslav Republic,* [6]*Herlev University Hospital, Copenhagen, Denmark,* [7]*Kinderkrankenhaus auf der Bult, Hannover, Germany,* [8]*Universität Tübingen, Klinik für Kinder- und Jugendmedizin, Tübingen, Germany,* [9]*Hopital Necker . Enfants Malades, Paris, Dominica,* [10]*Peijas Hospital, Department of Pediatrics, Peijas, Finland,* [11]*University of Basque Country, Barakalo, Spain,* [12]*University Childreńs Hospital, Zürich, Switzerland,* [13]*Örebro University Hospital, Örebro, United States,* [14]*Schneider Children's Medical Center of Israel, Petah Tikva, Israel,* [15]*University of Parma, Parma, Italy,* [16]*Nihon University School of Medicine, Tokyo, Japan,* [17]*Royal Children's Hospital, Parkville, Australia,* [18]*Haukeland University Hospital, Bergen, Norway,* [19]*Hôpital Universitaire des Enfants Reine Fabiola, Bruxelles, Belgium,* [20]*University of Birmingham, Birmingham, United Kingdom,* [21]*Diabeter (National Center of Diabetes in Children and Young Adults), Rotterdam, Netherlands,* [22]*Clinica Pediatrica, Chieti, Italy,* [23]*Royal Hospital for Sick Children, Glasgow, United Kingdom,* [24]*Children's Hospital Leicester Royal Infirmary, Leicester, United Kingdom*

Objective: To assess the prevalence of behaviour difficulties in children with T1DM and its association with type of insulin regimen and socio demographic factors.
Methods: Demographic and clinical data (centrally analysed HbA1c) were collected in 1133 children <11 years (47.7% girls; mean age 8.0 ± 2.1 years; mean diabetes duration 3.8 ± 2.1 years) from 18 centres in Europe, Japan, North America and Australia. 1090 parents completed the Strength and Difficulties Questionnaire (SDQ-parents) and the WHO-5 (well-being).
Results: Boys had more behaviour difficulties than girls (SDQ index) (9.9 ± 5.3 vs. 8.6 ± 5.1; P < 0.001) and less prosocial behaviour (6.1 ± 1.5 vs. 6.5 ± 1.4; P < 0.001). For 7.8% of all children SDQ index revealed borderline scores (bs), for 9.4% abnormal high scores indicating substantial clinically problems (as). There were significant centre differences (SDQ index) (F = 4.86; P < 0.001). Subscales of SDQ: emotional problems 10.9% (bs), 16.5% (as); behaviour problems 15.6% (bs), 18.1% (as); hyperactivity 5.3% (bs), 8.5% (as), problems with others 9.3% (bs), 9.7% (as) of the sample. Children with CSII or multiple injection therapy had significantly less difficulties (SDQ index and all subscales) than children with 2–3 daily injections (CT) (bs: 6.4 vs. 8.1%; as: 9.4 vs. 10.8%). After adjusting for centre differences these differences remain stable. Behaviour difficulties were associated with HbA1c (r = 0.074; P = 0.016) and with parents' well-being (r = –0.25; P < 0.001). Other factors associated with more behaviour difficulties were parents living apart, low family affluence, father's unemployment and severe life events.
Conclusion: More than 17% of these young children with T1DM had borderline or abnormal high and clinically significant emotional and behaviour problems. More flexible types of intensified insulin regimen, as CSII or MDI, were associated with less emotional and behaviour difficulties in these children and better well-being of their carers.

O/2/WED/08

Numeracy in adolescents with type 1 diabetes – development of an innovative gaming intervention

E. Bassilious[1,2], A. Dubrowski[2,3] & F.H. Mahmud[1]

[1]*Hospital for Sick Children, Endocrinology, Toronto, Canada,* [2]*Wilson Centre for Research in Education, Toronto, Canada,* [3]*SickKids Learning Institute, Toronto, Canada*

Objectives: Patients with Type 1 diabetes (T1D) engage in multiple diabetes related calculations every day. Numeracy, the ability to understand and apply numbers to daily life, directly affects clinical outcomes. Adolescents prefer to learn via interactive methods, such as gaming, which support active and experiential learning. In this study we develop an interactive video game to improve diabeted related numeracy (DN) in adolescents with T1D.

Methods: Through focus groups with diabetes team members at our institution we determined five essential DN topics: blood glucose (BG) interpretation; carbohydrate counting; insulin dose calculation for meals; calculation of correction insulin; BG and exercise. Input from adolescents added features to enhance interactivity and stimulation. Using this data, in collaboration with experts in technology development and education research, we created a game addressing DN.

Results: We successfully developed an innovative video game that addresses DN and employs various educational strategies to enhance learning and transfer of knowledge and skill to diabetes self-management. The player has tools analogous to diabetes skills to achieve goals analogous to BG management. In addition diabetes specific questions are presented at different intervals. Each player therefore *implicitly* and *explicitly* learns how to manage BG levels. Immediate and on-going feedback is provided in order to reinforce knowledge acquisition.

We piloted the game in a group of adolescents with T1D for feasibility, interactivity, and ability to address DN. The adolescents felt challenged, remained engaged, and indicated interest in playing the game outside of a structured environment.

Conclusion: Video games should be explored for enhancing diabetes education. The development of a game must be based on input from experts in the field of diabetes, education, and technology and most importantly on the learning needs and desires of the target population.

Oral Session III: Genetics and Immunology

O/3/WED/01

Is the honeymoon phase of type 1 diabetes a phase of immune tolerance?

H. H. Aly[1,2], D. Homann[2] & P. Gottlieb[2]
[1]*Ain Shams University, Cairo, Egypt,* [2]*Barbara Davis Center, University of Colorado at Denver, Aurora, United States*

Background and objective: The Honeymoon Phase (HMP) of Type 1 diabetes (T1D) is a period of improved glycemic control attributed to improved beta cell function following initiation of insulin. We hypothesized that HMP may represent a period of ''adaptive immune tolerance (AIT)'' following persistence of antigens.
Methods: To test AIT in-vitro, CFSE stained sorted CD4+CD45RO+ T cells were cultured in two fractions: one with HLA-matched islet-specific peptides (3–6 peptides) for 7 days and another cultured with no antigen for 7 days (to allow for recovery of responses aborted in presence of antigen persistence) then same peptides were added on day 7 and culture continued for additional 7 days. Proliferative responses were detected by flow cytometry at day 7 (D7) and day 14 (D14). The assay was carried out on fifteen T1D children and adolescents at 1 month after diagnosis, then regularly every 2 months until HMP exit. HMP was defined according to the ISPAD 2009 guidelines.
Results: Ten subjects passed into HMP (HMP+) and 5 did not (HMP–). So far, 9/10 have exited HMP. Sixty percent HMP- subjects showed D7 responses but none had D14 responses to more than one peptide during the first 6 months after diagnosis. Significantly more HMP+ subjects had D7 responses at HMP exit (44.4%) than at either 1 month after diagnosis (10%) or during HMP (0%) ($P < 0.01$). Significantly more HMP+ subjects had D14 responses to more than one peptide at 1 month (40%) or during HMP (60%) than at HMP exit (0%) ($P < 0.01$). The differences in D7 and D14 responses between HMP- and HMP+ subjects during HMP were also highly significant ($P < 0.01$).
Conclusion: The assay in this newly developed way could unmask responses undetected in the standard 7-day assay. The HMP of T1D may represent a phase of in-vivo tolerance that can be unmasked in-vitro after a period of T cell rest in the absence of antigen. Exploring the mechanism of this tolerance may help in developing new therapeutic options for T1D.

O/3/WED/02

Humoral rejection in xenogeneic IBMIR: plasma causes membrane damage, mitochondrial dysfunction, and cell death in pig pancreatic islets

M. Marigliano[1,2], D.J. van der Windt[1,3], J. He[1], T.V. Votyakova[1], D.K. Cooper[4], M. Trucco[1] & R. Bottino[1]
[1]*Children's Hospital of Pittsburgh, University of Pittsburgh, Pediatrics, Pittsburgh, United States,* [2]*Regional Center for Diabetes in Children and Adolescents, Ancona, Italy,* [3]*Department of Surgery, Erasmus University Medical Center Rotterdam, Rotterdam, Netherlands,* [4]*Thomas E Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, United States*

Objectives: We have previously demonstrated that in vitro exposure of pig islets to fresh human blood causes greater damage to pig islet cells than to human islet cells, in terms of complement activation and C-peptide leakage. In the present experiments, we investigated the effect of exposing pig islets to human plasma, to test whether the blood humoral component could induce the instant blood-mediated inflammatory reaction (IBMIR).
Methods: A total of 2500 porcine IEQ with a purity of 60–80% were resuspended in 1.5ml of culture medium (CMRL) in petri dishes. 500 μl of recalcified human plasma was added. The experiment was performed in an incubator-shaker at 37 °C and 100 rpm. After 60 minutes of incubation, islet cell death was assessed by FACS analysis using propidium iodide (PI) after islet cells were dissociated. Islets were fixed in 2% paraformaldehyde, and frozen for immunofluorescent staining. Mitochondrial performance was assessed by measuring oxygen consumption.
Results: IgM and C5b-9 deposition was seen on plasma-exposed islets. As a measure of cell membrane damage, pig C-peptide concentrations after exposure to human plasma were comparable to those after exposure to whole blood (1386 ± 199 vs. 1378 ± 103 ng/ml, $p>0.05$). An increase in the proportion of PI^+-cells from 5.3 ± 1.4 before, to 43.0 ± 12.6% after exposure to plasma was observed. Heat-inactivation of plasma significantly reduced IgM and C5b-9 deposition, C-peptide release to 445 ± 45 ng/ml ($P < 0.05$), and PI^+-cells to 14.9 ± 7.7%. Pig islets exposed to xenogeneic plasma had elevated basal mitochondrial respiration when compared to autologous, indicating proton leakage through the mitochondrial membrane. The maximal respiratory activity of islet mitochondria was decreased twofold, as impaired mitochondrial function.
Conclusions: Human plasma causes IgM binding, complement activation, membrane damage, mitochondrial dysfunction, and cell death in pig pancreatic islets, suggesting humoral rejection as a mechanism of IBMIR.

O/3/WED/03

Cytokines and chemokines induce β-cell destruction following enterovirus infection

A. Al-Shabeeb[1,2], S. Nair[1,3], W.D. Rawlinson[3] & M.E. Craig[1,2,4]
[1]*Prince of Wales Hospital, Virology Research Laboratory, Sydney, Australia,* [2]*University of New South Wales, School of Women's and Children's Health, Sydney, Australia,* [3]*University of New South Wales, School of Biotechnology and Biomolecular Sciences, Sydney, Australia,* [4]*The Children's Hospital at Westmead, Institute of Endocrinology and Diabetes, Sydney, Australia*

Objectives: Type I diabetes (T1D) results from immune mediated destruction of pancreatic β cells. Increasing evidence implicates enterovirus (EV) infection in the initiation of β cell destruction, as well as progression to T1D. We have previously shown that infection with Coxsackie virus B (CVB) increases cytokine and chemokine mRNA levels. In this study we measured cytokine and chemokine protein production by β cells.
Methods: The human insulinoma cell line INS-1 was infected with EV genotypes that have a recognised associated with T1D (CVB 1-6, EV71, ECHO viruses 4, 6, 9, 11 and 18). Protein levels of 23 cytokines and chemokines in cultured supernatants of the infected INS-1 cells were determined using Millipore multiplex suspension array technology. Increases in cytokine/chemokine levels were measured over time and across different EVs. R statistical analysis software was used for cluster analyses (to measure correlation between cytokines), for creating heat maps, principle component analysis and partial least squares analysis.
Results: Following EV infection, increases were detected in the levels of IL-1α ($P < 0.01$), IL-1β ($P < 0.01$), IL-2 ($P < 0.01$), IL-4

(P = 0.012), MIP-1a (P = 0.01), VEGF (P < 0.01), TNF-α, (P = 0.002), IL18 (P = 0.001), IFNγ (P = 0.001), Eotaxin (P < 0.01), IL-10 (P < 0.01), IL-13 (P < 0.01), with some evidence for a rise in CCL-2 (P = 0.08) and GCSF (P = 0.08) compared with the no virus control. Peak levels were detected on day 3–4 post-infection, which preceded cell death (day 6–7). In contrast, Leptin and GRO-CK showed no change.

Conclusions: EV infection induces proinflammatory cytokine and chemokine secretion by insulin producing cells, with subsequent β-cell death. The measurement of cytokines and chemokines using protein array suspension technology provides the opportunity to examine the relationship between multiple cytokines in EV infected INS-1 cells and human islets, and to distinguish those that may be targeted for therapeutic interventions.

O/3/WED/04

Residual insulin secretion in patients with recently-diagnosed type 1 diabetes mellitus after GAD65 antigen-specific therapy

J. Ludvigsson[1], R. Casas[1], J. Palmer[2] & European Diamyd Phase III Trial Investigators

[1]*Linköping University, Div of Pediatrics, Dept of Clin Exp Medicine, Linköping, Sweden,* [2]*Washington University, Seattle, United States*

Objectives: To assess the ability of alum-formulated GAD65 (GAD-alum) to preserve beta cell function in recent onset type 1 diabetes (T1D).

Methods: A total of 334 T1D patients between 10 and 20 years of age with fasting C-peptide levels >0.1 nmol/l (0.3 ng/ml) and pos GADA were recruited, from 63 sites in 9 countries, <3 months of T1D diagnosis for a multi-centre, randomized, double-blind, placebo controlled Phase III clinical study. They were randomly assigned to one of three treatment arms. An sc injection of 20 microg of GAD-alum on days 1, 30, 90 and 270. B. sc GAD-alum on days 1 and 30 then an injection of placebo on day 90 and day 270. C. sc placebo on days 1, 30, 90, and 270. Mixed meal tolerance test (MMTT) was performed on day 1 (baseline) and 3, 9, and 15 months after study entry. The primary outcome was change in serum C-peptide after MMTT between the baseline visit and the 15 month visit. Secondary outcomes included HbA1c, mean daily insulin dose, fasting C-peptide. Safety outcomes included neurologic assessments, injection site reactions, and rate of all hypoglycaemia/severe hypoglycaemia.

Results: Stimulated C-peptide had declined in all treatment arms by the 15 month visit. There were no statistically significant differences between subjects who received GAD-alum or placebo, although a positive trend was seen. The treatment was well tolerated with adverse events rates of similar intensity and frequency between the three treatment arms. Subgroup analyses suggest beneficial effects in certain subgroups, which supports the concept.

Conclusions: Treatment with GAD-alum within 3 months of T1D diagnosis failed to reach the primary endpoint but subgroup analyses suggest beneficial effects in certain subgroups of patients.

(Clinicaltrials.gov identifier: NCT00723411).

O/3/WED/05

Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and the risk of type 1 diabetes in the offspring

I.M. Sørensen[1], G. Joner[1,2], P.A. Jenum[3], A. Eskild[4,5], P.A. Torjesen[6] & L.C. Stene[7]

[1]*Oslo University Hospital Ullevål, Dept. of Pediatrics, Oslo, Norway,* [2]*University of Oslo, Institute of Health and Society, Oslo, Norway,* [3]*Vestre Viken Hospital Trust, Dept. of Medical Microbiology, Bærum, Norway,* [4]*Akershus University Hospital, Dept. of Obstetrics and Gynaecology, Oslo, Norway,* [5]*University of Oslo, Institute of Clinical Medicine, Oslo, Norway,* [6]*Oslo University Hospital Aker, Hormone Laboratory, Oslo, Norway,* [7]*Norwegian Institute of Public Health, Oslo, Norway*

Background/aim: On account of previous studies that indicated reduced risk of type 1 diabetes following intake of Vitamin D supplements during pregnancy and early childhood, we investigated whether increased maternal serum concentrations of 25-hydroxy-vitamin D (25-OH D) during pregnancy were associated with reduced risk of childhood onset type 1 diabetes.

Methods: In a prospective cohort of 29,072 pregnant women who gave birth in Norway during 1992–94, we analysed serum samples from 109 pregnant women delivering a child who developed type 1 diabetes before 15 years of age, and 219 randomly selected control women without type 1 diabetes children. The sera were collected at a median gestational age of 37 weeks. Cases were identified by linking the cohorts of women and their offspring to The Norwegian Childhood Diabetes Registry. The serum levels of 25-OH D were analysed by radio-immunoassay.

Results: The mean serum levels of 25-OH D were 65.8 nmol/l and 73.1 nmol/l in cases and controls respectively, P = 0.02. Serum 25-OH D levels showed an expected seasonal pattern with a peak in summer. 25-OH D levels were divided into quartiles derived from values in the control group (1 ≤ 54, 2.>54 and ≤69, 3.>69 and ≤89, 4.>89 nmol/l). When comparing the positive and negative outcome of the 4th vs. 1st quartile of maternal 25-OH D in late pregnancy, odds ratio (OR) was 0.44 (95% CI 0.22–0.88, P = 0.02), and the dose response relationship was significant according to the test for trend (P = 0.02). Correction for seasonal levels of 25-OH D in summer vs. winter did not change the above observations.

Conclusion: In this first study of its kind, maternal serum concentrations corresponding to the upper quartile of 25-OH D during late pregnancy were associated to a decreased risk of type 1 diabetes development in the offspring.

O/3/WED/06

High prevalence of different species of enteroviruses (EV) in peripheral blood leukocytes (PBL) of children at the clinical onset of type 1 diabetes

A. Toniolo[1], G. Maccari[2], O. Diaz-Horta[2], G. Bianchi[2], G. Federico[3], A. Salvatoni[2] & A. Baj[2]

[1]*University of Insubria Medical School & Ospedale di Circolo, Experimental Medicine, Laboratory of Microbiology, Varese, Italy,* [2]*University of Insubria Medical School, Experimental Medicine, Varese, Italy,* [3]*University of Pisa Medical School, Pediatrics and Gynecology, Pisa, Italy*

Objectives: EV have long been suspected to trigger T1D. To test this hypothesis, EV infectivity and genome were searched for in PBL of pediatric patients on the day of clinical diagnosis.

Methods: A total of 112 children diagnosed with diabetes at two Pediatric Endocrinology Centers of Northern and Central Italy (median age 9.5 years; 2–16 years) were studied. EV-susceptible

cell lines (RD, HeLa, AV3, CaCo) were immediately co-cultured with the patients' PBLs. Primers covering the 5'UTR, VP4, and 3D genome regions of 100 EV types were used in highly sensitive RT-PCR assays run both on plasma and tissue culture medium from cell lines exposed to patients' PBLs. Expression of viral proteins was evaluated in ''infected'' cell cultures with mAbs directed to the capsid protein VP1. Routine methods were used to measure levels of blood glucose, HbA1c, C-peptide (time 0 and 6 minutes after glucagon stimulation), diabetes related auto-Abs (GAD65, IA2, ZnT8, IAA), and – one year after diagnosis – the insulin requirement (IU/Kg/day).

Results: EV infectivity and genome fragments were found in PBLs of 89/112 (79%) children, versus only 2/69 (2.8%) matched non-diabetic controls. EV of the B species were predominant (58% of positives). Viruses of the A, C, and D species were also detected. Tests on infected cell lines confirmed the intracellular production of viral capsid proteins and of the MCP1 chemokine. As compared to EV-negative children, EV-positive patients had significantly higher levels of HbA1c at diagnosis, significantly reduced levels of glucagon-stimulated C-peptide, and – 1 year after diagnosis – greater HbA1c levels. Insulin requirement and titers of diabetes-related auto-Abs were not significantly different between the two groups.

Conclusions: The presence of EV in blood is a frequent and significant biomarker of early stage T1D and may also be linked to a more difficult control of glucose homeostasis.

We thank: CARIPLO Foundation (IT), VIDIS Group (UK), Gianni Valcavi, Attorney.

O/3/WED/07

Enterovirus IgM in early pregnancy may predict islet autoantibody seroconversion

S. Resic Lindehammer[1], M.O. Oikarinen[2], A. Nix[3], H. Honkonen[4], K.F. Lynch[1], I. Hansson[1], K. Marsal[5], M. Pallansch[3], S. Oberste[3], H.H. Hyöty[2], Å. Lernmark[1] & Diabetes Prediction in Skåne Study Group

[1]*Clinical Sciences, Diabetes and Celiac Disease, Malmoe, Sweden,* [2]*University of Tampere, Department of Virology, Tampere, Finland,* [3]*Centers for Disease Control and Prevention, Division of Viral Diseases, Atlanta, United States,* [4]*University of Tampere, Tampere, Finland,* [5]*Clinical Sciences, Department of Obstetrics and Gynecology, Lund, Sweden*

Objectives: Gestational enterovirus (EV) infections have been associated with HLA-DR as well as with type 1 diabetes in the offspring. We analyzed EV exposure in relation to type 1 diabetes HLA-DQ risk genotypes and to islet auto antibodies in mothers studied both in early pregnancy and at delivery.

Methods: Non-diabetic mothers (n = 365) who had islet auto antibodies against glutamic acid decarboxylase (GADA), islet antigen-2 (IA-2A), or insulin (IAA), alone or in combination in early pregnancy and at delivery were compared to islet autoantibody negative mothers (n = 1457) matched for age and sampling date. Mothers were genotyped for HLA-DQ and analyzed for both EV-RNA by PCR and EV-IgM in capture ELISA.

Results: EV-IgM, but not EV-RNA was detected during early pregnancy in 12% (44/365) of islet autoantibody positive mothers, compared to 11% (156/1457) of the controls (P = n.s.). In early pregnancy, mothers with HLA-DQ 2/2 or 2/X genotypes showed, in adjusted logistic regression, an increased risk for islet auto antibodies (OR 1.85, 95% CI 1.34–2.54; P = 0.001). EV-IgM was not associated with HLA-DQ in early pregnancy. However, after adjusting for parity, maternal age, year of birth and season of early pregnancy, early pregnancy EV-IgM combined with DQ2/2 or 2/X increased the risk for the mother to be positive for islet auto antibodies at delivery (OR 3.10, 95% CI 1.35–7.15; $P = 0.008$).

Conclusions: Gestational EV infections have been associated with risk HLA-DR as well as with type 1 diabetes in the child. We analyzed EV-RNA and EV-IgM in relation to type 1 diabetes HLA-DQ risk genotypes and to islet auto antibodies in non-diabetic mothers studied both in early pregnancy and at delivery. EV-IgM in early pregnancy increased the risk for islet auto antibodies at delivery in non-diabetic mothers who carry HLA-DQ 2/2 or 2/X type 1 diabetes risk genotypes.

O/3/WED/08

Persistence of autoimmunity after clinical diagnosis of type 1 diabetes: demonstration of Islet-autoreactive CD8 T cells in insulitic lesions from recent onset and long-term type 1 diabetes patients

M.G. von Herrath, K. Coppieters & A. Wiberg

La Jolla Institute for Allergy & Immunology, Type 1 Diabetes Center - LIAI, La Jolla CA, United States

Major Histocompatibility Class (MHC) class I antigens present intracellular peptides to CD8 T cells and render the expressing cell susceptible to killing. Islet cells from recently diagnosed type 1 diabetes patients are known to exhibit upregulated expression of MHC class I for yet unclarified reasons. This study reports on a systematic survey of MHC class I expression patterns and potentially causal pathways in samples obtained via the network for Pancreatic Organ Donors (nPOD). Freshly frozen pancreas samples were obtained from 39 longstanding type 1 diabetes patients, 14 non-diabetic control individuals, 5 non-diabetic, islet autoantibody positive individuals, 6 type 2 diabetes patients, 1 patient with gestational diabetes and 1 undefined case of diabetes. Sections were stained for insulin, MHC class I and CD8 by immunofluorescence. Consecutive sections from samples with pronounced MHC class I hyperexpression on islets were subjected to PCR analysis and immunofluorescence for enterovirus species and type I interferon signature genes. MHC class I hyperexpression on islets was found in four cases and was specific to type 1 diabetes. Upregulation may persist for as long as 8 years after clinical onset and was observed independent of insulin sufficiency and CD8+ infiltration. Despite modulation of type I interferon signature genes, none of the samples showed evidence of chronic enteroviral infection. Persistent MHC class I upregulation on pancreatic islets is a type 1 diabetes-specific phenomenon that is unlikely to be a consequence of chronic enteroviral infection, but could maybe be due to epigenetic changes elicited after a viral hit-and-run event.

Oral Session IV: Epidemiology

O/4/FRI/01

Classification of childhood diabetes in the Norwegian childhood diabetes registry

G. Joner[1], T. Skrivarhaug[1], L.C. Stene[2], J.V. Sagen[3], D.E. Undlien[4], H.E. Akselsen[4], P.R. Njølstad[5] & Norwegian Childhood Diabetes Study Group

[1]*Oslo University Hospital Ulleval, Dept of Pediatrics, Oslo, Norway,* [2]*Norwegian Institute of Public Health, Dept of Epidemiology, Oslo, Norway,* [3]*Haukeland University Hospital, Hormone Laboratory, Bergen, Norway,* [4]*Oslo University Hospital Ullevaal, Dept of Medical Genetics, Oslo, Norway,* [5]*Uinversity of Bergen, Dept of Pediatrics, Bergen, Norway*

Diabetes in childhood is classified into Type 1, Type 2 and other types. Alarming increase of T2D in children has been reported. Molecular genetic research has revealed etiological causes of several subtypes of monogenic diabetes incl. neonatal diabetes and MODY.

Objectives: To describe the epidemiology of diabetes subtypes <15 years in a country with increasing prevalence of obesity, high incidence of childhood-onset diabetes and organized screening on monogenic forms.

Methods: Norway has a National Childhood Diabetes Registry with a biobank and case completeness of 92%. In 2002–2008 hospital records and biological samples were collected from all new cases allowing genotyping, testing of auto-ab and non-stimulated c-peptide. HLA genotypes were categorized as high,intermediate or low risk. Relevant genes were screened in selected cases when monogenic diabetes was suspected on basis of clinical criteria.

Results: During the period 2002–2008, 1608 new cases <15 years were reported, and we performed HLA-typing and auto-ab analysis in 1216 cases. Nine cases of monogenic diabetes were found. Of the ten cases diagnosed before 1 year of age, 2 were confirmed monogenic. (Kir 6.2). Of the remaining 1207 cases, 1107 (91.7%) could be classified as Type 1A. 80 antibody-negative cases (6.7%) were classified as Type 1B based on HLA-genotype and low-c-peptide (< 0.4 nmol/l), confirmed by a record of insulin treatment from diagnosis. Of the remaining 20 cases, 9 (0.7%) were classified as T2D because they were on diet and/or oral agents and had BMI>25. Eleven cases (0.9%) were not classified. The proportion of children with DKA (ph< 7,30) at onset was remarkably low; 18.9% in Type 1A and 13,6% in Type 1B and none among the Type 2 children.

Conclusion: Type 1 diabetes is still the dominating type in children and adolescents in this nationwide study. Type 2 and monogenic forms currently constitute less than a percentage-point each of childhood onset diabetes in Norway.

O/4/FRI/02

Population based incidence of type 1 diabetes in New South Wales Australia 1990-2010 – have we reached a plateau?

J.A. Kraan[1,2,3], K.D. Elliott[2], F. Claessen[1,2,3], M. Lloyd[1], H.J. Woodhead[4,5], P.A. Crock[6], M.J. Jack[2,7], N.J. Howard[1] & M.E. Craig[1,2,5]

[1]*The Children's Hospital at Westmead, Institute of Endocrinology and Diabetes, Sydney, Australia,* [2]*University of Sydney, Sydney, Australia,* [3]*Erasmus University, Rotterdam, Netherlands,* [4]*Sydney Children's Hospital, Sydney, Australia,* [5]*University of New South Wales, School of Women's and Children's Health, Sydney, Australia,* [6]*John Hunter Children's Hospital, Newcaste, Australia,* [7]*Royal North Shore Hospital, Sydney, Australia*

Objectives: The incidence of type 1 diabetes (T1D) in Australia is among the top 10 countries globally. Increases in T1D incidence were observed in many countries during the 1990s and into the new millennium, although data are limited from 2005 onwards. We examined trends in T1D incidence in NSW (population ~7 million) over the last two decades (1990–2010).

Methods: Prospective population based childhood diabetes incidence register, established in 1990. Primary ascertainment was from the Australasian Paediatric Endocrine Group NSW Diabetes Register, with secondary ascertainment from the National Diabetes Supply Scheme and the National Diabetes Register. Age standardised incidence, by the direct method, was determined using population data from the Australian Bureau of Statistics. Poisson regression was used to examine the effect of age-group, gender and time on T1D incidence.

Results: Mean annual T1D incidence in children aged <15 years increased significantly from 18.8 per 100,000 person years (95% CI 18.1 to 19.6) over 1990–1999 to 22.8 per 100 000 (95% CI 22.0 to 23.6) over 2000–2010, incidence rate ratio (IRR) 1.21 (95% CI 1.15 to 1.28, $P < 0.001$). However, during 2000–2010, there was evidence for a plateau with incidence remaining steady from 2000–2004 (22.5 per 100,000) to 2005–2010 (23.0 per 100,000), IRR 1.02, $P = 0.52$. Incidence was higher in girls during the first decade (19.8 vs. 17.9 per 100,000, $P = 0.01$), but not from 2000 onwards (22.4 vs. 23.2, $P = 0.3$). The age-specific incidence rates per 100,000 per year were 13.2, 20.8, and 27.1 at ages 0–4 years, 5–9 years and 10–14 years, respectively for the total period. Between the first and second decades, incidence increased significantly across all age groups, with a greater rise in the younger age groups (IRR 1.24, 1.28 and 1.14 at ages 0–4, 5–9 and 10–14 years respectively).

Conclusion: While the incidence of T1D has increased in NSW since 1990, there is some evidence for a plateau in the last decade.

O/4/FRI/03

HbA1c at diagnosis and follow up in young patients with type 1 diabetes. Variation regarding month, gender and age

K. Akesson[1], L. Hanberger[2] & U. Samuelsson[2]

[1]*Pediatric Clinic, Länssjukhuset Ryhov, Jonkoping, Sweden,* [2]*Linköping University, Department of Clinical and Experimental Medicine, Div of Pediatrics, Linkoping, Sweden*

Objectives: To analyze the monthly variation of diabetes and HbA1c at diagnosis as well as the relationship between HbA1c at diagnosis and during clinical follow-up.

Method: Data from 4430 boys and 3590 girls registered in the Swedish pediatric diabetes quality registry, SWEDIABKIDS, were analyzed regarding month of diagnosis (n = 8020) and HbA1c at diagnosis (n = 7688). HbA1c (n = 76874) during year 2008–2010 were followed.
Results: We found a variation in month of diagnosis ($P < 0.001$) where 47% of the patients diagnosed during spring-summer (March - August), most obvious in the youngest age group, <5 years of age (42% diagnosed during spring-summer).
The mean HbA1c at diagnosis varied with the highest value in May (96 mmol/mol) and the lowest in October (89 mmol/mol) ($P < 0.000$). This variation was most obvious in the youngest age group. No monthly variation was seen during the clinical follow-up.
Age at diagnosis varied with lowest mean age in October and highest in January (8.9 ± 4.5 and 10.3 ± 4.2 resp. ($P < 0.000$)). HbA1c at diagnosis was higher in girls than in boys (94 and 90 mmol/mol resp., P = <0.001). At follow-up (year 2010) this gender difference was most obvious in children >10 years of age in year 2010, $P < 0.01$. Among the children (n = 1148) with a year mean-HbA1c < 57 mmol/mol in 2005 only 6% had >78 mmol/mol in 2010. Among those with year mean HbA1c >78 mmol/mol (n = 183) in 2005 51% still had such a high HbA1c in 2010. Only in 7% HbA1c had decreased to < 57 mmol/mol.
Conclusions: Most of the children with poor metabolic control during a certain period still have high HbA1c several years later. Even though we do not know whether the level is mainly due to severity of the disease or behavioral patterns, new ways to treat and support these children is needed. The gender difference in HbA1c levels seen already at onset could be due to physiological gender differences but also to psychosocial reasons. HbA1c have a monthly variation at diagnosis but not thereafter.

O/4/FRI/04

The clinical and economic burden of type 1 diabetes in children, adolescents and adults

S. Greene[1], S. Goring[2], L. Cochrane[3], P. Donnan[3], A. Bell[3], D. Heather[3], S. Lane[2], A. Levy[2] & G. Leese[4]
[1]*University of Dundee, Child Health, Dundee, United Kingdom,* [2]*Oxford Outcomes, Vancouver, Canada,* [3]*University of Dundee, Health Informatics, Dundee, United Kingdom,* [4]*University of Dundee, Medicine, Dundee, United Kingdom*

Aims: Type 1 diabetes (T1D) imposes a substantial burden on health care. We measured uniquely the direct costs across a population from childhood (C; 8 to 12 years.), through adolescence (Ad; 13 to 18 years.) to mid-adulthood (A; 19 to 35 years).
Methods: A retrospective population cohort study (2000–2008) for subjects treated with insulin in Tayside, Scotland, UK. We estimated the mean annual direct medical cost of diabetes resource utilisation – clinic visits, eye/foot screening, hospitalisations, laboratory tests, insulin and glucose testing strips. Descriptive statistics were calculated annually and stratified by age.
Results: We identified a median of 527 subjects per year: mean period prevalence/1,000 person year: 2.5(C); 3.8(Ad); 3.9(A); mean incidence/100,000 person year: 49.6(C); 44.5(Ad); 28.0(A); 87–95% had at least an annual clinic visit, least among adults; 79% (A) had an annual eye and foot screening visit; fewer than 5% C used these services; length of hospital admission (mean ± SD days) C = 6.7(2.2), Ad = 19.0(8.6), A = 25.6(16.5); hospitalisation for ketoacidosis was 5.5–9.3%/annum, greatest among adolescents; 52–76% of subjects had annual micro-albuminuria tests, 38–42% thyroid tests; 85 to 95% of subjects had at least one HbA_{1c} test/year; only 11% C, 10% Ad, and 32% A achieved target levels. The median annual direct medical cost (2009; GBP/person) was: C £2747 Ad £6,655; A £4023 with the largest component cost for hospitalisation. Costs per annum for glucose testing strips increased significantly: C 250 to 500; Ad 180 to 355; A 180 to 224.
Conclusions: In our cohort over the last decade a more intensive approach to T1D management was adopted, reflected in the rising use of glucose strips. Despite this, admissions remain a major concern and glycaemic control is poor in the majority of these subjects, particularly adolescents. Regardless of these current costs, newer technologies must be considered to improve the health of young people with T1D.

O/4/FRI/05

Role of a diabetic family history in beta-cell autoimmunity in children with HLA-associated disease risk

H. Siljander[1,2], R. -T. Salonsaari[2], A. Hekkala[3], S. Simell[4], R. Veijola[3], J. Ilonen[5,6], O. Simell[4] & M. Knip[1,2]
[1]*Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland,* [2]*Tampere University Hospital, Department of Pediatrics, Tampere, Finland,* [3]*University of Oulu, Department of Pediatrics, Oulu, Finland,* [4]*University of Turku, Department of Pediatrics, Turku, Finland,* [5]*University of Turku, Immunogenetics Department, Turku, Finland,* [6]*University of Kuopio, Department of Clinical Microbiology, Kuopio, Finland*

Objectives: To assess the role of a positive family history for type 1 diabetes (T1D) in the appearance and progression of beta-cell autoimmunity in children recruited from the general population based on HLA-associated disease susceptibility.
Methods: Children carrying HLA-conferred disease susceptibility with (n = 177, 2.4%) and without (n = 7233) a positive family history for T1D were recruited from the general population, and were observed for beta-cell autoimmunity and progression to T1D. ICA were analyzed as the first step of autoantibody screening. If a child seroconverted to ICA-positivity or presented with T1D, all samples from that child were analyzed in addition for IAA, GADA, and IA-2A.
Results: Children with a positive family history seroconverted to autoantibody positivity at an earlier age, developed advanced autoimmunity more frequently, and had higher autoantibody levels than children without affected family members. However, T1D was diagnosed at the similar age in both groups, and in children with advanced autoimmunity, autoantibody levels were of the same magnitude regardless of family history. The highest disease risk was associated with the combination of paternal T1D (Figure 1) and the high-risk HLA genotype (DQB1*02/*0302).
Conclusions: A positive family history for T1D accelerates the initiation of the pre-clinical disease process, but after beta-cell autoimmunity is established, the family background plays a minor role in terms of disease progression. The association between paternal T1D and the high-risk HLA genotype may at least partly contribute to the higher rate of T1D seen among offspring of affected fathers.
A: $P < 0.001$ for 0 vs. 1, $P = 0.03$ for 0 vs. 3, and $P = 0.002$ for 1 vs. 2.
B: $P < 0.001$ for 0 vs. 1 and
C: $P = 0.03$ for 1 vs. 3. Figure 1

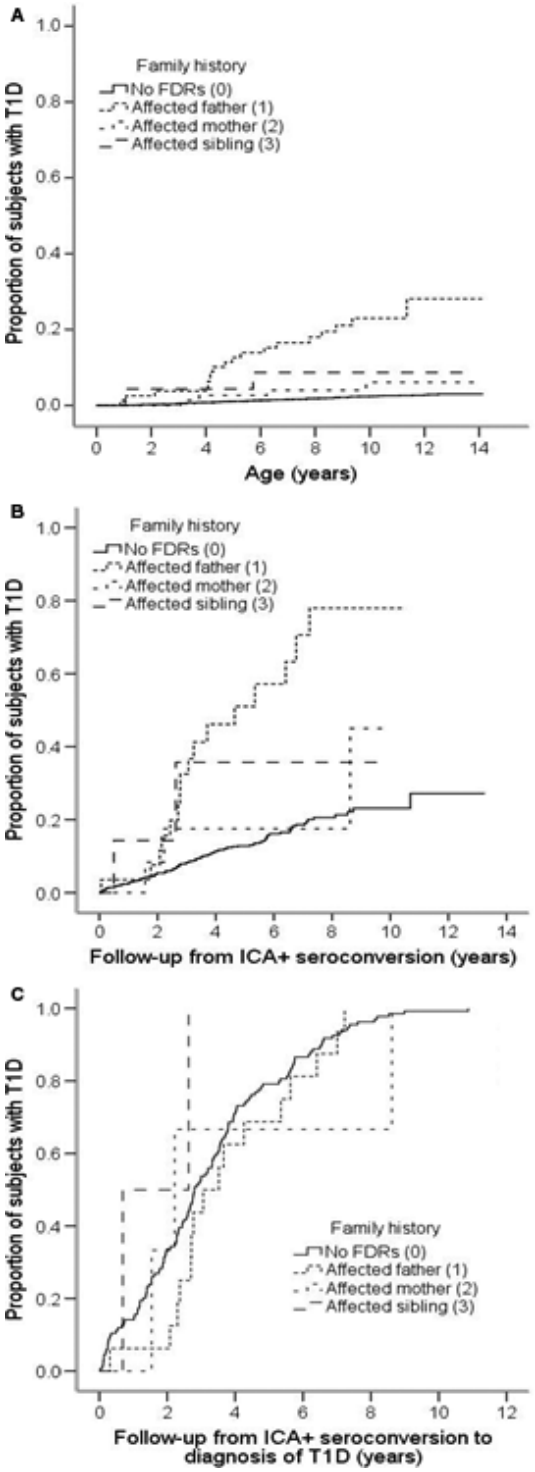


Figure 1 Progression of beta-cell autoimmunity in children with and without family history of type 1 diabetes (T1D), recruited from the general population based on HLA-conferred disease susceptibility.

O/4/FRI/06

Racial disparities in insulin pump therapy and hemoglobin A1c (HbA1c) among children with type 1 diabetes (T1D) enrolled in the T1D exchange clinic registry

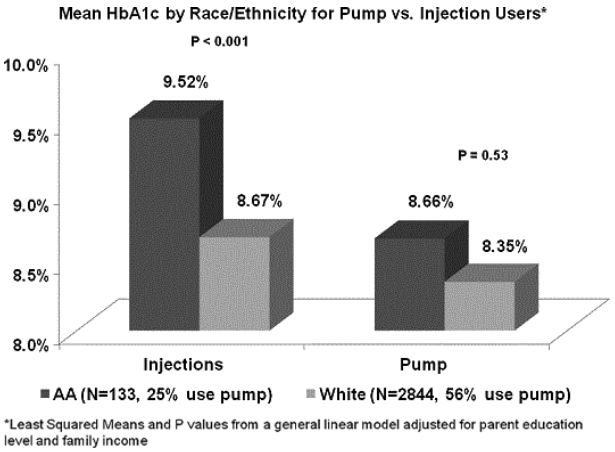
T. Lipman[1], S. Willi[1] & K.M. Miller[2], for the T1D Exchange Clinic Network

[1]*Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, United States,* [2]*Jaeb Center for Health Research, Tampa, United States*

Objectives: The purpose of this study was to compare insulin pump therapy and HbA1c in African American (AA) and white children with T1D.

Methods: The analysis included 2980 AA and white children (age <18 years, T1D for ≥1 year, 48% female, mean [range] age 11.7 [1–17] years, T1D duration 5.2 [1, 17] year) enrolled in the multicenter (60 site) T1D Exchange Clinic Registry who had available data for socioeconomic status (SES) (parental education and income). Prevalence rate ratios (PRR) between AA and white children were obtained for insulin method and poor glycemic control (HbA1c >9.0%), controlling for SES. The association between insulin method and HbA1c was also assessed.

Results: Among 2844 white children and 133 AA children, 56% and 25% were being treated with insulin pumps, respectively. After controlling for SES, AA children were 43% less likely to use a pump than white children (PRR = 0.57; 95%CI = 0.42–0.76; P < 0.001) and 69% more likely to have an HbA1c > 9.0% compared with white children (PRR = 1.69, CI = 1.39–2.06; P < 0.001). Insulin pump use was associated with lower HbA1c in both white and AA children. However, the difference between HbA1c for white vs. AA children was significant in the injection, but not the pump users (figure).



[Mean HbA1c by Race/Ethnicity for Pump vs. Inj User]

Conclusions: The marked racial disparity in insulin pump use among children with T1D may help to explain higher HbA1C levels in AA children. Possible causes, including provider factors, that contribute to these treatment disparities must be explored.

O/4/FRI/07

Trends in diabetes prevalence and incidence in children and youth with diabetes in Quebec, Canada 2000–2008: a population-based study

M. Nakhla[1], L. Rochette[2], E. Rahme[3] & I. Larocque[2]
[1]*Montreal Children's Hospital, McGill University, Division of Endocrinology, Department of Pediatrics, Montreal, Canada,* [2]*Institut National de Santé Publique du Québec, Quebec, Canada,* [3]*McGill University, Department of Epidemiology, Biostatistics and Occupational Health, Montreal, Canada*

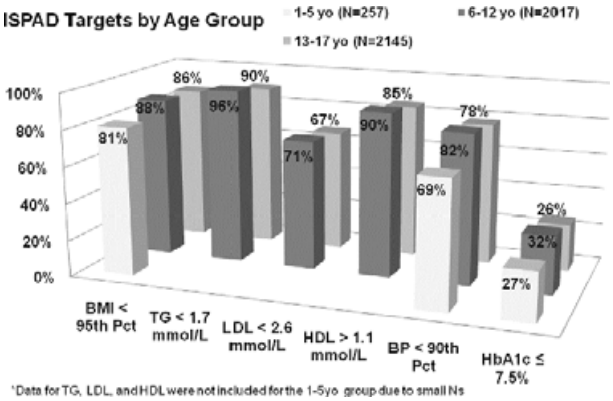
Objectives: To describe temporal trends in diabetes incidence and prevalence over time in individuals under 20 years of age, living in Quebec, Canada.
Methods: Using population-based administrative data, including a provincial diabetes database, we examined temporal trends in diabetes incidence and prevalence from 2000 to 2008, in individuals under 20 years of age. We used Poisson regression analysis to test for changes in diabetes incidence over time. We used the Carriere–Roos method to compare standardized rates between groups.
Results: Overall age/sex-standardized prevalence per 100,000 increased from 187.2 (95% confidence intervals (CI) 180.7–193.9) in 2000 to 250.9 (95% CI 243.2–258.7) in 2008, representing an overall increase of 34.0% and an annual increase of 4.0%. The greatest rise in prevalence occurred in males, particularly in those aged 5–9 years (54.2%) compared with a 37.5% increase in females ($P < 0.0001$). Furthermore, the number of children with diabetes increased by 31.2%, from 3117 to 4103, whereas the overall population under 20 years of age decreased by 4.0%. Overall age/sex-standardized incidence remained relatively stable over time and was 31.8 per 100,000 (95% CI 29.1–34.7) in 2008. In 2000, the incidence was highest in 10 to 14-year-old youth, a trend that persisted to 2008 (38.1 per 100,000, 95% CI 32.59–44.28). Despite relatively stable rates in overall incidence over time, the greatest rate of change in incidence was observed in the 1 to 4-year-old age group, increasing by 3.0% per year since 2000; these results did not reach statistical significance likely due to small sample size in this group.
Conclusions: The prevalence of diabetes in Quebec has increased substantially in children and youth over the past 8 years. We did not observe an increase in overall incidence rates; however an increased trend in incidence in the 1 to 4-year-old group was seen.

O/4/FRI/08

Most youth with type 1 diabetes (T1D) do not meet ISPAD clinical goals for HbA1c: the T1D exchange clinic registry

J.R. Wood[1], D. M. Maahs[2], K.M. Miller[3] & The T1D Exchange Clinic Network
[1]*Children's Hospital of Los Angeles, Keck School of Medicine at USC, Los Angeles, United States,* [2]*Barbara Davis Center for Childhood Diabetes, Aurora, United States,* [3]*Jaeb Center for Health Research, Tampa, United States*

Objectives: To describe hemoglobin A1c (A1c), blood pressure (BP), lipids, and body mass index (BMI) according to ISPAD targets in youth with T1D participating in the T1D Exchange Clinic Registry.
Methods: The Registry began enrollment in September 2010 and includes ~60 adult and pediatric centers in the U.S. The most recent A1c, BP, high density lipoprotein (HDL), fasting low density lipoprotein (LDL), triglycerides (TG) and BMI were used to evaluate the proportion of participants (<18 years of age, T1D for >1 year) meeting ISPAD targets overall and by age group. The analysis included 4419 participants (mean age 11.9 years, 48% female, 82% non-Hispanic white, 52% on insulin pumps, mean T1D duration 5.3 years). A subset of participants had data for BP (n = 4140), HDL (n = 2720), fasting LDL (n = 929) and TG (n = 894), and BMI (n = 4362). BP and BMI data were converted to percentiles based on U.S. standards for age, gender, and height.
Results: Mean A1c was 8.4% and only 28% of participants met the ISPAD target for A1c <7.5%. In contrast, 79% met BP <90%tile targets, 87% for HDL >1.1 mmol/L, 69% for fasting LDL < 2.6 mmol/L, 92% for fasting TG < 1.7 mmol/L, and 87% for BMI <95%tile. The proportions of ISPAD targets met by age group are shown in the figure.



Conclusions: Most participants met the ISPAD targets for BP, lipids, and BMI; however, <1/3 met the A1c target of ≤7.5%. Achieving optimal A1c remains a significant challenge for the majority of children with T1D in this registry.
[ISPAD Targets by Age Group]

Oral Session V: Pumps and Sensors

O/5/FRI/01

Prolonged use of continuous glucose monitoring (CGM) improved HbA1c in poorly-controlled adults and adolescents with type 1 diabetes (T1D): a 1-year randomized multicenter study

C. Vignon-Savoye[1], N. Tubiana-Rufi[1], V. Sulmont[2], A.-S. Musial-Salmon[2], S. Guilmin-Crépon[1], F. Kaguelidou[1], A. Clergeot[3], L. Dufaitre[4] & J.-P. Riveline[5]

[1]*Robert Debré Hospital, Endocrinology-Diabetology and Clinical Investigation Center, Paris, France,* [2]*American Memorial Hospital, CHU, Pediatric Endocrinology, Reims, France,* [3]*CHU, Endocrinology, Besançon, France,* [4]*University Hospital Sainte Marguerite, Nutrition-Endocrinology-Métabolic Disorders, Marseille, France,* [5]*Centre Hospitalier Sud-Francilien, Diabetology, Corbeil-Essonnes, France*

Introduction: Benefits on glycemic control of Real-Time CGM have been shown in T1D patients in 3 to 6 months-studies. The aim of the study is to assess the metabolic effects of two strategies of 1-year use of CGM in poorly-controlled T1D.

Materials and methods: A 1-year, randomized multicenter trial was conducted in T1D adults and children (age 8 to 60 years, A1c level ≥8%, under multiple daily insulin injections (MDI) or pump therapies). Two modes of using CGM (FreeStyle Navigator™) were assessed: G1: patient-led (advised to use the sensors continuously), G2: physician-driven where sensors were prescribed gradually according to the results achieved. These two strategies were compared to a Self Blood Glucose Monitoring practice (G3: control). The primary outcome was the change in A1c level at 1 year vs. baseline.

Results: A total of 178 patients completed the study: age: 36 ± 14 years, duration of T1D: 17 ± 10 years, A1c: 8.9 ± 0.9% at inclusion. Among them, 24 adolescents participated: age: 16 [13; 18.9] years ± 1.7, duration of T1D: 7 [2; 13] years (±3), 11 using pump, A1c: 9.1[8–11.6]% ± 0.9%. In the whole population at 1 year, A1c was significantly improved in both CGM groups vs. control group (G1 vs. G3: –0.52%, P = 0.0006, G2 vs. G3: –0.47%, P = 0.0008, G1 + G2 vs. G3: –0.50%, P < 0.0001). Frequency of hypoglycemia did not rise in G1 and G2 vs. G3. Glycemic variability (SD of mean glycemia) was significantly reduced in G1 and G2 vs. G3 (P = 0.018). The total number of sensors used over 1 year was significantly lower of 34% in G2 vs. G1 (P = 0.001). Improvement in A1c was higher in patients on pump (G1 + G2 vs. G3: –0.7%, P < 0.0001) than on MDI (G1 + G2 vs. G3: –0.23%, P = 0.10).

Conclusion: A long-term use of CGM resulted in a sustained improvement in glycemic control in poorly-controlled T1D adults and adolescents using intensive treatments. A CGM prescription by the physician achieved a same metabolic improvement and a better efficiency in term of sensors consumption, than a patient-led strategy.

O/5/FRI/02

Follow-up of patients with sensor-augmented pump therapy during the first year of diabetes – pediatric onset study

O. Kordonouri[1], R. Hartmann[1], E. Pankowska[2], B. Rami[3], T. Kapellen[4], R. Coutant[5], K. Lange[6] & T. Danne[1]

[1]*Kinderkrankenhaus auf der Bult, Diabeteszentrum für Kinder und Jugendliche, Hannover, Germany,* [2]*Medical University of Warsaw, Department of Paediatric Diabetology and Birth Defects, Warsaw, Poland,* [3]*Medical University of Vienna, Department of Paediatrics, Vienna, Austria,* [4]*Universitätsklinik und Poliklinik für Kinder und Jugendliche, Leipzig, Germany,* [5]*Centre Hospitalier Universitaire, Département de Pédiatrie, Angers, France,* [6]*Medizinische Hochschule Hannover, Abt. f. Medizinische Psychologie, Hannover, Germany*

Objectives: In the multicentric randomized Pediatric Onset Study, children and adolescents with sensor-augmented pump therapy and frequent use of sensors during the first year of type 1 diabetes had significantly lower HbA1c values at 12 months than those with less frequent or without sensor use. Aim of the follow-up study was to evaluate the metabolic control and beta-cell function 1 year after the end of the interventional study.

Methods: A total of 131 of 154 patients (85.1%) were re-examined 24 months after diabetes onset (age 8.9 ± 4.3 years). 62 patients belonged to the primary group applying the Paradigm Real-Time System (Medtronic MiniMed Inc) and 69 patients belonged to the control group with conventional pump therapy (CSII) and self-monitoring blood glucose. Age and gender distribution were not significantly different between groups. HbA1c and fasting C-peptide values were measured centrally.

Results: At follow-up, 52.4% of patients used the sensor-augmented pump system, 46.0% conventional CSII, and 1.6% multiple daily injections. HbA1c was 7.6 ± 1.3% in the primary and 7.7 ± 1.2% in the control group (P = .493). Frequent sensor use during the first year of diabetes was not significantly associated with lower HbA1c values at 24 months as compared with irregular or even no sensor use (7.4 ± 1.0% vs. 7.7 ± 1.3%, P = .236). Although daily insulin requirement (0.75 ± 0.23 U/kg), partial remission rate (12.4%) and fasting C-peptide (0.11 ± 0.14 nmol/l) were not clearly different between the primary and control group, patients with initially frequent sensor use had significantly less C-peptide loss within 24 months than controls (C-peptide reduction 0.02 ± 0.18 vs. 0.07 ± 0.11 nmol/l, P = .046). Severe adverse events (2 DKA, 1 SH) occured in controls only.

Conclusions: Sensor-augmented pump therapy from onset of type 1 diabetes may lead to better long-term glycemic control and help to preserve endogenous beta-cell function if patients comply with frequent use of continuous glucose monitoring.

O/5/FRI/03

The SWITCH study: continuous glucose monitoring in type 1 diabetes

T. Battelino[1], I. Conget[2], B. Olsen[3], I. Schütz-Fuhrmann[4], E. Hommel[5], R. Hoogma[6], U. Schierloh[7], N. Sulli[8], J. Bolinder[9] & SWITCH Study Group
[1]*UMC-University Children's Hospital, Dept. of Pediatric Endocrinology, Diabetes and Metabolism, Ljubljana, Slovenia,* [2]*University Clinical Hospital, Barcelona, Spain,* [3]*Herlev University Hospital, Glostrup, Denmark,* [4]*Landsteiner Institut, Hietzing Hospital, Vienna, Austria,* [5]*Steno Diabetes Center, Gentofte, Denmark,* [6]*Groene Hart Hospital, Gouda, Netherlands,* [7]*Clinique Pediatrique de Luxemburg, Luxembourg, Luxembourg,* [8]*Sapienza University, Rome, Italy,* [9]*Karolinska Institutet, Stockholm, Sweden*

Objectives: The SWITCH study establishes if adding personal continuous glucose monitoring (CGM) to existing, capable, insulin-pump users enables better metabolic control.
Methods*:* This 17 month multicenter, randomized, controlled, cross-over study included a run-in period and two 6-month sequences, separated by a 4 month wash-out period. 72 children and 81 adults (aged 6–70 years) with HbA1c between 7.5% and 9.5% using pump therapy alone were randomized to CGM Sensor On or Sensor Off arms for 6 months, then crossed-over. The primary outcome was the end of period difference in HbA1c levels between Sensor On and Sensor Off arms in the intent to treat population, with a power of 90% to detect a mean difference of 0.3% in the primary endpoint assuming a standard deviation of 1.0%.
Results: The mean difference in HbA1c was –0.43% in favour of Sensor On arm (95% confidence interval [CI], -0.32 to -0.55; $P < 0.001$), with –0.46% (95% CI, -0.26 to -0.66; $P < 0.001$) in children ($n = 72$) and –0.41% (95% CI, -0.28 to -0.53; $P < 0.001$) difference in adults ($n = 81$). Stopping sensor use (On/Off sequence) resulted in HbA1c reverting to base-line levels. Mean sensor use was 79.73% (median 84.34%); in children, mean sensor usage was 73.12% (median = 78.41%) compared to adults mean = 85.63%, (median = 89.42%). No difference in severe hypoglycemic episodes was observed. Significantly less time was spent with sensor glucose <70 mg/dl during the Sensor On vs. Sensor Off (19 vs. 31 minutes/day; $P = 0.009$). SMBG significantly decreased during Sensor On (median 4.9 vs. 5.5 compared to Sensor Off; $P < 0.001$). Children using CGM missed significantly less school days compared to Sensor Off (#days/100 pt years; ON vs. OFF; 51.9 vs. 183 $P = 0.0043$).
Conclusions: Continuous glucose monitoring was associated with a significant decrease in glycated hemoglobin and a concomitant decrease in time spent in hypoglycemia in children and adults with type 1 diabetes sub-optimally controlled with insulin-pump therapy.

O/5/FRI/04

A randomized controlled trial (RCT) to assess the efficacy and safety of real-time continuous glucose monitoring (CGM) in the management of type 1 diabetes (T1D) in young children

N. Mauras[1], R. Beck[2], D. Xing[2], K. Ruedy[2], B. Buckingham[3], M. Tansey[4], N. White[5], S.A.W. Weinzimer[6], W. Tamborlane[6], C. Kollman[2] & for the Diabetes Research in Children Network DirecNet
[1]*Nemours Children's Clinic, Jacksonville, United States,* [2]*Jaeb Center for Health Research, Tampa, United States,* [3]*Stanford University, Palo Alto, United States,* [4]*University of Iowa, Iowa City, United States,* [5]*Washington University in St. Louis, Department of Pediatrics, St. Louis, United States,* [6]*Yale University, New Haven, United States*

Objective: CGM improves glycemic control in adults with T1D, but benefit has been shown to be less in children ≥8 years old. We designed an RCT to assess CGM benefit in young children (4 to 9 years) with T1D.
Methods: Following a 6-week run-in phase, 146 youth with T1D (mean age: 7.5 ± 1.7 years, 64% on pumps, median diabetes duration 3.5 years) were assigned randomly to CGM ($n = 74$) or usual care ($n = 72$) for 26 weeks. The primary analysis was a comparison of the proportion in each group with a ≥0.5% reduction in HbA1c from baseline to 26 weeks without severe hypoglycemia.
Results: The primary outcome was achieved by 18% in the CGM group and 30% in the Control group (odds ratio 0.48, 95% confidence interval 0.19 to 1.21, $P = 0.12$). Other outcomes are listed in Table 1.
At 26 weeks, 42% of the CGM group averaged ≥6 days/week of CGM wear. There was no correlation between CGM wear and change in HbA1c ($r = –0.13$, $P = 0.29$). Severe hypoglycemia rates were similarly low between groups. CGM use was well tolerated and parental satisfaction with CGM, measured on the CGM Satisfaction Scale, was high.

	CGM	Control	P value
HbA1c Outcomes	N=65	N=64	
baseline *mean ± SD*	7.9% ± 0.8%	7.9% ± 0.8%	-
26 weeks *mean ± SD*	7.8% ± 0.8%	7.8% ± 0.8%	0.82
HbA1c drop ≥0.5% *N(%)*	12 (18%)	20 (31%)	0.08
CGM Glucose Values *% of values baseline/26w*			
71 to 180 mg/dl	46%/48%	47%/48%	0.96
>200 mg/dl	44%/41%	39%/42%	>0.99
≤60 mg/dl	1.0%/0.4%	0.6%/0.6%	0.16
Severe Hypoglycemic Events			
# Events	3	6	
# (%) of subjects with at least 1 event	3 (4%)	5 (7%)	0.49
Incidence rate (per 100 person-years)	8.7	17.7	0.81
Quality of Life Questionnaires *baseline/26w*			
Hypoglycemia Fear Survey [a]	41/38	43/39	0.50
Blood Glucose Monitoring System Rating Questionnaire			
Past Month [b]	2.5/2.7	2.3/2.4	0.006
Change over past 6 months [c]	2.0/2.3	2.0/2.0	<0.001
Problem Areas in Diabetes [d]	50/44	55/48	0.60

a-scale 0-100 with higher score denoting more fear; b-scale 1-4 with higher score denoting fewer problems; c-scale 1-3 with higher score denoting improvement; d-scale 0-100 with higher score denoting worse condition.

Conclusions: CGM in 4 to 9 year olds did not improve glycemic control despite a high degree of parental satisfaction with CGM. We speculate this may be due in part to inconsistent incorporation of CGM data into day-to-day management and by parental unremitting fear of hypoglycemia. Full integration of CGM with insulin delivery systems remains an essential goal for young children with T1D.
Funding: This research was supported by the following NIH/NICHD HD41890-10; HD41906-10; HD41908-10; HD41915; HD41918; HD56526.Abbott Diabetes Care (Alameda, CA) provided the FreeStyle Navigator CGMS and the FreeStyle blood glucose Meter and test strips. Medtronic Minimed (Northridge, CA) provided the both CGMS and sensors at a discounted price.

O/5/FRI/05

Effectiveness of the low glucose suspend feature of the medtronic paradigm Veo insulin pump in children and adolescents

F.R. Kaufman, P. Agrawal, S. Askari, B. Kannard & J.B. Welsh
Medtronic, Inc., Northridge, United States

Objectives: Sensor-augmented insulin pumps may be programmed to suspend insulin delivery in response to hypoglycemia. The MiniMed Paradigm Veo System (Medtronic MiniMed, Inc.) has low glucose suspend (LGS) functionality and was first released in 2009. Data from children and adolescents who used the system were analyzed to assess the effectiveness of LGS.

Methods: Data from 1100 subjects aged <15 years totalling 37,042 patient-days were extracted from the CareLink database; the LGS feature was on for 75% of these days.
Results: A total of 28,489 LGS events occurred with 42% occurring between noon and 8:00 pm. The median duration of LGS events was 8 minutes, 47% lasted for <5 minutes, and 12% lasted for >115 minutes. Among the episodes lasting for >115 minutes, the mean sensor glucose (SG) was 57.7 ± 12.2 mg/dl at LGS activation (time 0), rose to 109.62 ± 56.5 mg/dl by the end of the LGS episode (120 minutes, when insulin delivery was automatically resumed) and was 153.9 ± 70.9 mg/dl at 240 minutes, by which time other interventions may have taken place. LGS usage significantly reduced the percentage of SG readings <80 mg/dl (P = 0.027) as well as the percentage of SG readings >300 mg/dl (P = 0.032) (Table).

SG (mg/dl)	% of SG Values, LGS Off	% of SG Values, LGS On	P-Value
<60	3.49	2.49	0.246
<70	6.55	5.02	0.060
<80	10.91	8.83	0.027
>180	34.62	36.57	0.025
>240	14.40	14.54	0.070
>300	4.96	4.76	0.032

[LGS effect on hypo- and hyperglycemia]

Conclusions: In subjects <15 years old, use of the LGS feature appears to improve glycemic control. This first commercial device that allows pre-specified SG levels to stop insulin delivery is an important milestone in the path toward an artificial pancreas.

O/5/FRI/06

Failure to achieve target glycaemic control on continuous subcutaneous insulin infusion (CSII) – is passive pumping to blame?

M. White, O. Neylon, M. O'Connell & F. J. Cameron
Royal Children's Hospital, Department of Endocrinology & Diabetes, Melbourne, Australia

Introduction/objective: Our institutional experience shows that HbA1c of CSII patients at 12–18 months post-initiation is stable to 4–5 years. The aim of this study is to explore CSII adherence and its association with glycaemic control at 12–18 months post-initiation of CSII.
Methods: Patients were analysed according to adherence, defined as ''adherent'' (HbA1c ≤7.5%), ''non-adherent'' (<4 blood glucose levels (BGL) ± <6 bolus wizard events (BWE) per day, HbA1c >7.5%) or ''passive adherence'' (BGL >4 ± BWE >6, HbA1c >7.5%). Fourteen-day data were obtained (Medtronic Carelink®) from patients with T1DM 12–18 months post-initiation of CSII. HbA1c was documented pre-CSII and at the time of the data. Patient CSII behaviours (frequency of BGL, bolus & carbohydrate patterns, basal rate percentage and insulin doses) were recorded.
Results: Data was analysed for 60 youth (male = 31) commenced on Medtronic CSII devices from April 2008–10. Mean (±SD) age was 11 ± 3.7 years, duration of diabetes 3.6 ± 2.8 years at CSII initiation and pre-CSII HbA1c 8 ± 0.8%. At 12–18 months post-CSII, 31/60 were ''adherent'' (BGL 6 ± 2.3/day, BWE 9 ± 3/day, HbA1c 6.9 ± 0.5%), and 10/60 were fully ''non-adherent'' (n = 10, BGL 3.9 ± 1.2/day, BWE 5 ± 0.9/day, HbA1c 8.5 ± 0.7%). Comparing the ''passive adherence'' (n = 19, BGL 6.0 ± 1.2/day, BWE 8.5 ± 1.8/day, HbA1c8.2 ± 0.4%) and ''adherent'' groups, the only differences were a higher baseline HbA1c (8.4 ± 0.7% vs. 7.6 ± 0.7%, P < 0.001) and a smaller decrease from baseline HbA1c (0.2 ± 0.8% vs. 0.7 ± 0.6%, P = 0.01).
Conclusion: Baseline HbA1c is predictive of glycaemic control at 12–18 months post-CSII. Despite intensive CSII treatment, a subgroup of patients do not achieve HbA1c ≤7.5% at 12–18 months post-CSII initiation. While frank non-adherence is associated with HbA1c >7.5%, measureable CSII behaviours alone do not discriminate in all patients. A passive attitude towards CSII, characterised by a lack of perception of targets may be causative.

O/5/FRI/07

Race and socioeconomic status are independent predictors of youth receiving insulin pump therapy in the first year of type 1 diabetes (T1D) treatment

M. H. Lin[1,2], J. R. Wood[1,2], B. M. Kaminski[3] & Pediatric Diabetes Consortium
[1]*Children's Hospital of Los Angeles, Los Angeles, United States,* [2]*Keck School of Medicine at USC, Los Angeles, United States,* [3]*Jaeb Center for Health Research, Tampa, United States*

Objectives: To describe the clinical characteristics and predictors of youth participating in the Pediatric Diabetes Consortium (PDC) who were started on insulin pump therapy within the first year of T1D diagnosis.
Methods: The PDC began enrolment in July 2009 and includes 7 centers throughout the U.S. with longitudinal data collected from time of diabetes diagnosis by review of medical records. The analysis included 427 youth (mean age at T1D diagnosis 9.3 years, 51% female, 66% white) with T1D duration ≥1 year receiving care at one of the PDC centers. Logistic regression was used to determine factors associated with insulin pump use within the first year of diagnosis.
Results: Of 427 youth, 29% (n = 125) were placed on insulin pump therapy within the first year of T1D diagnosis, although this varied by center (range 18–60%). Median T1D duration at pump start was 8.5 months (IQR 6.0 months to 11.4 months). Mean age at pump start was 9.4 years (range 1.1 to 18.5 years). Youth started on pump therapy were more likely than those not started on pump to be white (87 vs. 59%, P < 0.001), privately insured (90 vs. 60%, P < 0.001), living with both parents (90 vs. 66%, P < 0.001), with a household income >$100,000 (67 vs. 29%, P < 0.001), and college educated caregivers (83 vs. 67%, P = 0.002). In a multivariate model, each of these factors remained significant except having a college educated caregiver. Initiation of pump therapy was associated with a greater number of blood glucose meter measurements per day (P < 0.001).
Conclusion: Initiation of insulin pump therapy in youth within the first year of T1D diagnosis is common. Race and socioeconomic factors play a significant role in whether youth with T1D are placed on insulin pump therapy within the first year of diagnosis.

O/5/FRI/08

INTERPRET, an international report on routine practice of sensor-augmented pump therapy: results from the 6 months interim analysis of the pediatric population

A. Scaramuzza[1], K. Nørgaard[2], N. Bratina[3], P. Jarosz-Chobot[4], R. Verkauskiene[5], E. Örtqvist[6], B. Florys[7], O. Carrette[8], J. Castañeda[9], O. Cohen[10] & INTERPRET Study Group

[1]*Luigi Sacco Hospital, Milano, Italy,* [2]*Hvidovre Hospital, Hvidovre, Denmark,* [3]*UMC-University Children's Hospital, Ljubljana, Slovenia,* [4]*Specjalistyczna Praktyka Lekarska, Gliwice, Poland,* [5]*Lithuanian University of Health Sciences, Medical Academy, Endocrinology Clinic, Kaunas, Lithuania,* [6]*Astrid Lindgrens Children's Hospital, Stockholm, Sweden,* [7]*Medical University of Biălystok, IInd Department of Pediatrics, Bialystok, Poland,* [8]*Medtronic International Trading SàrL, Tolochenaz, Switzerland,* [9]*Medtronic Bakken Research Center, Maastricht, Netherlands,* [10]*Chaim Sheba Medical Center, Tel Hashomer, Israel*

Objective: INTERPRET (NCT00790088) is the first international prospective observational study providing data from real life practice of sensor-augmented pump (SAP) therapy in Type 1 Diabetes Mellitus patients.

Methods: Patients treated with insulin pump therapy for more than 6 months were enrolled at the time of starting SAP under usual care, with a sensor usage recommendation of at least 10% of the time. The clinical outcomes were assessed every 3 months during 1 year. A sub-group analysis of the pediatric population was performed on the 6 months follow-up data.

Results: A total of 263 T1DM patients including 84 children and adolescents (0–18 years) were eligible for analyses. The pediatric group was subdivided into three subgroups: young children: 0–7 years (n = 28), children: 8–12 years (n = 21), and adolescents: 13–17 years (n = 35). The HbA1c reduction at 6 months was higher in the young children (0.37%) than in the children and adolescents (0.10% and 0.13% respectively) (young children vs. children and adolescents, P-value = 0.1412). Similarly, the sensor usage was higher in the young children (40%); than in the other two groups (34% and 25%) (young children vs. children and adolescent, P-value = 0.1126). Although we did not have enough data to show significant correlations in the pediatric population alone, in a multivariate analysis performed on the overall population, we have shown that improvement in HbA1c after 6 months of treatment was associated with high HbA1c levels at baseline ($P < 0.0001$), more frequent sensor use ($P = 0.021$) and age group ($P = 0.016$). Additional analyses on the glycemic variability and hypo/hyperglycemia occurrence will be presented.

Conclusion: This real life practice observational study complements previous investigations showing the relation between baseline HbA1c, age, compliance with sensor use and clinical improvement. Additional predictive factors for long-term benefit of SAP remain to be interpreted from the 1 year follow-up data.

Oral Session VI: Obesity/Puberty/New Agents/MODY

O/6/FRI/01

Greater reduction in arterial elasticity occurs in adolescents with insulin resistance and obesity than in type 1 diabetes

P.Z. Benitez-Aguirre[1,2], M. Ho[1,2], M.E. Craig[1,2,3], A.J. Jenkins[4], P. Mitchell[5,6], S. De[1,2], C.T. Cowell[1,2], L.A. Baur[1,2], S.P. Garnett[1,2] & K.C. Donaghue[1,2]

[1]*The Children's Hospital at Westmead, Institute of Endocrinology and Diabetes, Westmead, Sydney, Australia,* [2]*University of Sydney, Discipline of Paediatrics and Child Health, Sydney, Australia,* [3]*University of New South Wales, School of Women's and Children's Health, Sydney, Australia,* [4]*The University of Melbourne, Department of Medicine, St Vincent's Hospital, Melbourne, Australia,* [5]*University of Sydney, Faculty of Medicine, Sydney, Australia,* [6]*Centre for Vision Research, Westmead Millennium Institute, Sydney, Australia*

Objectives: Reduced arterial elasticity (AE) in adults is associated with cardiovascular events but AE has not been examined in obese adolescents with clinical insulin resistance (IR) or type 1 diabetes (T1D). This study compared AE in 3 adolescents cohorts aged 11–18 years: obese with IR, T1D and healthy non-obese controls.

Methods: The IR cohort (n = 36; 12 male) were participants from an ongoing RCT, the T1D cohort (n = 175; 83 male) were outpatients from a tertiary hospital in Sydney, Australia (mean HbA1c 8.7 ± 1.6% and diabetes duration 6.6 ± 3.4 years) and 96 (56 male) non-obese controls were recruited from a convenience sample of school children. BMI z-scores for the cohorts were: IR 2.33 ± 0.33, T1D 0.68 ± 0.77 and controls –0.20 ± 0.94 ($P < 0.001$). AE was measured using radial tonometry pulse wave analysis (Pulse Wave CR-200 system, Hypertension Diagnostics Inc.). ANCOVA was used to detect differences between groups.

Results: Small AE indices (SAE) raw values were highest in the IR cohort and lowest in the T1D cohort (mean ± SEM: IR 10.8 ± 0.5, T1D 8.9 ± 0.2 and Control 9.1 ± 0.3 ml/mmHg × 100, $P = 0.003$). There were no significant differences in large AE indices (LAE). SAE and LAE were positively associated with weight, height and age in all groups.

After adjusting for weight, age and gender, SAE in the IR cohort was significantly lower than both T1D cohort and controls (3.0 ± 1.3, 8.8 ± 0.2 and 9.5 ± 0.4 ml/mmHg × 100, $P < 0.001$).

Conclusion: Obese adolescents with clinical IR had lower arterial elasticity than those with T1D or control subjects, which may contribute to an increased risk of pre-mature cardiovascular disease.

O/6/FRI/02

BMI in children with autoimmune type 1 diabetes

M.J. Redondo[1], B.M. Kaminski[2], J. Block[3], B. Buckingham[3], E. Cengiz[4], M. Haller[5], M. Haymond[1], J. Lee[6], D. Schatz[5], J. Silverstein[5], W. Tamborlane[4], J. Wood[7], G. Klingensmith[8,9] & Pediatric Diabetes Consortium

[1]*Baylor College of Medicine, Houston, United States,* [2]*Jaeb Center for Health Research, Tampa, United States,* [3]*Stanford University Medical Center, Stanford, United States,* [4]*Yale School of Medicine, New Haven, United States,* [5]*University of Florida, Gainesville, United States,* [6]*University of Michigan, Ann Arbor, United States,* [7]*Children's Hospital of Los Angeles, Los Angeles, United States,* [8]*Barbara Davis Center for Childhood Diabetes, Aurora, United States,* [9]*University of Colorado, Denver, Aurora, United States*

Objectives: We hypothesized that obese or overweight children have different characteristics than lean children at diagnosis of autoimmune type 1 diabetes.

Methods: The 7 centers that comprise the Pediatric Diabetes Consortium collected data on children (2– <19 years) with newly diagnosed type 1 diabetes (T1D). We analyzed data from 657 children with BMI measured within 8 weeks (median 4 days) of diagnosis of autoimmune T1D who expressed at least one anti-islet autoantibody. Clinical characteristics were compared between overweight or obese (BMI ≥ 85th percentile) and lean (BMI < 85th percentile) children using logistic regression. Beta-cell function was assessed in 34% patients and considered ''preserved'' for values >0.2 and >0.6 ng/ml, respectively, for fasting and random C-peptide.

Results: Of the 657 children, 167 (25%) were obese or overweight. In multivariate analysis obese/overweight children were associated with non-White race, lower HbA1c, and presentation with DKA (Table). The percentages of multiple antibodies and preserved beta cell function were higher among obese/overweight children, but the difference was not statistically significant. There was no detectable association with age or gender.

Table. Clinical characteristics of children with newly diagnosed autoimmune T1D

	Overweight or obese N=167 N (%)	Lean N=490 N (%)	Multivariate P-value
Age *mean ± SD yrs*	9.5 ± 3.8	9.6 ± 3.8	NS *
2-<5 years	24 (14%)	68 (14%)	
5-<12 years	97 (58%)	293 (60%)	
12-<19 years	46 (28%)	129 (26%)	
Female	81 (49%)	256 (52%)	NS *
Race/Ethnicity			0.003
White (non-Hispanic)	84 (51%)	303 (63%)	
Hispanic	52 (31%)	108 (23%)	
Af-Am	23 (14%)	31 (6%)	
Other	7 (4%)	37 (8%)	
HbA1c *mean ± SD*	10.9 ± 2.4	11.4 ± 2.3	0.004
DKA at onset	65 (39%)	153 (32%)	0.01
Beta Function Preserved	45 (68%)	87 (55%)	NS *
Number of positive anti-islet antibodies			NS *
1	25 (20%)	83 (23%)	
2	50 (39%)	149 (42%)	
3	52 (41%)	125 (35%)	

* Factor omitted from multivariate regression model because not significant (p > 0.10).

Conclusions: Obese and overweight children presented with lower HbA1c and DKA at diagnosis of autoimmune T1D. Whether these findings reflect pathogenic differences remains to be investigated.

O/6/FRI/03

Increased Body Mass Index (BMI) is associated with higher hemoglobin A1c (A1c) among 6–12 year olds but is not associated with total daily insulin dose per kg (TDI) in type 1 diabetes (T1D) participants enrolled in T1D Exchange Clinic Registry

A. Criego[1], K. Bethin[2] & K.M. Miller[3], for the T1D Exchange Clinic Network

[1]*Park Nicollet/International Diabetes Center, Minneapolis, United States,* [2]*University of Buffalo/Women & Children's Hospital of Buffalo, Buffalo, United States,* [3]*Jaeb Center for Health Research, Tampa, United States*

Objectives: This analysis sought to evaluate the effect of BMI on TDI requirements and A1c in children and young adults with type 1 diabetes (T1D).

Methods: The T1D Exchange Clinic Registry is a multicenter registry that includes over 60 U.S. centers. This analysis included 4427 participants (>1 year T1D duration, mean duration 5.8 years, 2–24 years old, mean age 12.9 years, 48% female, 82% non-Hispanic white, 49% on insulin pumps,) with available data for TDI and BMI. Participant reported TDI in pediatric (<18) and young adult (18–24) participants were used for analysis. BMI was standardized on age and gender, and grouped into normal and overweight/obese categories.

Results: Table 1 shows the mean TDI and A1c for each BMI category overall and by age group. In the 6–12 year olds, mean A1c for the overweight/obese group was greater (8.3%P = 0.006) compared with the normal weight group (8.1%); however a significant difference was not observed in the other age groups. A significant difference in TDI between BMI categories was not observed. Insulin resistance (TDI ≥ 1.5) was associated with higher mean A1c (8.9% vs. 8.4%; P < 0.001).

Table 1. Total Daily Insulin Dose per Kg and Hemoglobin A1c According to Body Mass Index Category* for Child and Young Adult Participants in the T1D Exchange Clinic Registry[a]

	Overall N =4427	Age 2-5 yrs old N=224	Age 6-12 yrs old N=1734	Age 13-17 yrs old N=1834	Age 18-24 yrs old N=635
Total Daily Insulin Dose per Kg					
Normal weight (N=3019)	0.84 ± 0.46	0.66 ± 0.32	0.77 ± 0.43	0.93 ± 0.49	0.88 ± 0.45
Overweight/Obese (N=1408)	0.85 ± 0.49	0.58 ± 0.27	0.81 ± 0.47	0.91 ± 0.53	0.81 ± 0.42
Hemoglobin A1c					
Normal weight (N=3019)	8.4% ± 1.6	8.3% ± 1.2	8.1% ± 1.2	8.6% ± 1.7	8.8% ± 1.9
Overweight/Obese (N=1408)	8.5% ± 1.4	8.4% ± 1.3	8.3% ± 1.2	8.7% ± 1.5	8.6% ± 1.7

*Overweight/Obese is defined as BMI ≥ 85th percentile for age < 18 and a BMI ≥ 25 for age18-24
[a] Mean ± standard deviation are reported

Conclusions: Although overweight and obesity have been associated with insulin resistance, there is no evidence of differences in TDI related to excessive weight in this population. A1c was higher in those with higher BMI and TDI > 1.5 which may indicate the need for additional therapy in this patient group.

O/6/FRI/04

Interaction of high-fat feeding, exercise and oxidative stress in the pediatric pre-diabetic state

P. Galassetti

UC Irvine, Irvine, United States

The pre-diabetic state in children, often characterized by the simultaneous presence of components of the metabolic syndrome (obesity, hyperlipidemia), is often associated with oxidative stress (OS) and inflammation, now identified as pathogenetic mechanisms increasing long-term cardiovascular (CV) risk. Excessive dietary lipid and exercise have been shown to separately exert opposite effects on long-term CV risk, i.e., respectively to worsen and reduce it. Very little is known, however, on the simultaneous effect of high-fat feeding and exercise, especially in obese children, a vulnerable, understudied and alarmingly growing population.

We therefore measured F_2-Isoprostanes (F_2-IP), reflecting systemic lipid peroxidation, in 15 healthy (NW, 12 ± 1 years, 8F, BMI% 53 ± 7), and 19 obese (OW, 12 ± 1 years, 13F, BMI% 97 ± 0.4) children, who ingested a high-fat meal 45-minutes before exercise (ten 2-min cycling bouts @ 80% VO_2max, with 1-minute rest intervals). Samples: baseline, 45-minutes after fat feeding, end- and 30-minutes post-exercise.

In OW, F_2-IP (pg/ml) were consistently greater than NW; baseline (68 ± 7 vs. 50 ± 2, $P < 0.05$), 45-minutes after fat ingestion (71 ± 7 vs. 47 ± 3, $P < 0.01$), end-exercise (56 ± 5 vs. 42 ± 2, $P < 0.05$); 30-min post (53 ± 4 vs. 41 ± 3, $P < 0.05$). Importantly, while exercise had little effect on F_2-IP in NW, in OW F_2-IP decreased significantly at end-exercise (–15 ± 4 vs. –5 ± 2, $P < 0.05$ vs. NW).

Our data indicate that despite a consistently elevated oxidative status (increase F_2-IP at baseline, after feeding and end-exercise) when compared to healthy controls, obese children may be more responsive to interventions aimed at reducing oxidative stress. These results stress the vital necessity to identify and implement, in obese children, optimal preventive and therapeutic strategies, including customized exercise regimens aimed towards specific pathogenetic mechanisms of long-term cardiovascular complications.

O/6/FRI/05

Urinary C-peptide creatinine ratio is a non-invasive measure of endogenous insulin secretion to identify MODY from Type 1 in paediatric diabetes

R. E. Besser[1], M.H. Shepherd[1], B.M. Shields[1], T.J. McDonald[1,2], S.E. Hammersley[1], B.A. Knight[1], S. Ellard[3], A.T. Hattersley[1]

[1]*Peninsula Medical School, Peninsula NIHR Clinical Research Facility, Exeter, United Kingdom,* [2]*Royal Devon & Exeter NHS Foundation Trust, Department of Clinical Biochemistry, Exeter, United Kingdom,* [3]*Royal Devon & Exeter NHS Foundation Trust, Department of Molecular Genetics, Exeter, United Kingdom*

Objectives: Children with Maturity Onset Diabetes of the Young (MODY) are frequently misdiagnosed as Type 1 diabetes (T1D), and inappropriately treated with insulin. Urinary C-peptide creatinine ratio (UCPCR), a stable measure of endogenous insulin secretion, offers the potential to be a non-invasive outpatient tool to differentiate MODY from T1D. This has never been studied in children or in patients close to diagnosis.

We aimed to:

(1) Determine the reproducibility of post-prandial UCPCR, and

(2) Assess whether post-prandial UCPCR can discriminate MODY from T1D in children with diabetes.

Methods: We measured 2 hour post-prandial UCPCR in 156 patients <18 years with clinically defined T1D (n = 114) or genetically confirmed MODY (n = 42; HNF1A/4A n = 16, GCK n = 26). Urine samples were collected at home as they were stable for 3 days at room temperature in boric acid preservative and posted for analysis. The coefficient of variation (CV) was assessed by taking 2 further samples in 42 patients.

Results: The CV of UCPCR was 29%. UCPCR was similar for HNF1A/4A MODY and GCK MODY (median (interquartile range): 3.4(2.8–4.6) v 3.2(1.8–4.5) nmol/mmol, P = 0.5) so were subsequently analysed together. UCPCR was lower in T1D than MODY (0.06(<0.02–0.5) v 0.3(1.9–4.5) nmol/mmol; P < 0.0001). Receiver Operating Characteristic Curves showed excellent discrimination (area under curve 0.95) and identified a cut-off UCPCR ≥0.7 nmol/mmol for discriminating MODY from T1D

with 100% sensitivity and 79% specificity. 24/114 T1D patients had UCPCR ≥0.7 nmol/mmmol, and all 24 patients were within 5 years of diagnosis. 16 T1D patients with UCPCR ≥0.7 nmol/mmol had antibody testing and 15/16 had positive GAD and/or IA2 antibodies.

Conclusions: In children with diabetes, a single post-meal UCPCR which is stable for 3 days at room temperature, gives excellent discrimination of T1D from MODY. Patients should only be selected for MODY testing if the UCPCR is ≥0.7 nmol/mmol.

O/6/FRI/06

High levels of serum perfluorinated compounds in children and adolescents with endocrine autoimmune disease

L. Iughetti[1], B. Predieri[1], C. Guerranti[2], P. Bruzzi[1], S. F. Madeo[1], V.D. Patianna[1], C. Catellani[1], E.L. Fanello[2], G. Perra[2] & S.E. Focardi[2]
[1]*University of Modena and Reggio Emilia, Pediatrics, Modena, Italy,* [2]*University of Siena, Environmental Sciences ``G.Sarfatti'', Siena, Italy*

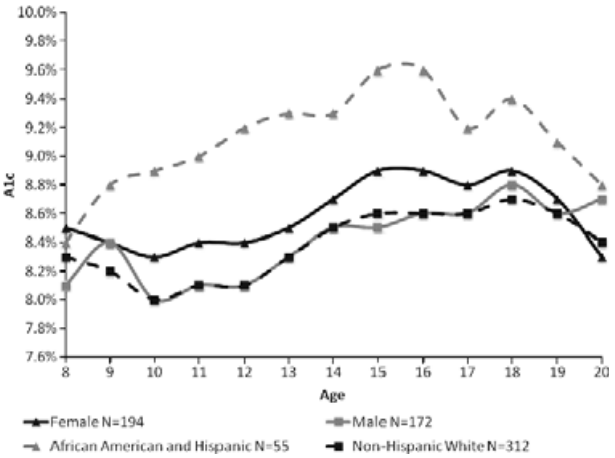
Background: Impairments of endocrine system may be associated with exposure to certain chemical compounds. Much attention has recently focused on interference with thyroid function in relation to exposure to endocrine disruptors chemicals among which perfluorinated compounds (PFCs) are considered a priority research issue. Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are widely diffused since used in the productions of polymers, additives, adhesives, cosmetics, insecticides and many other uses. PFCs are characterized by a high potential to bioaccumulate, by binding proteins, aspect that allows transmission of contamination through food chains and retention in the body, once assumed.
Objective: Aim of this study is to assess PFCs concentrations in children and adolescents with type 1 diabetes (T1DM) compared to healthy controls.
Methods: Forty-four children and adolescents were recruited and subdivided in the following groups: (1) twenty-five subjects (6.11 ± 3.33 years.) with T1DM and (2) nineteen healthy controls matched for age and gender. Blood samples to assay PFCs were collected and stored few days after T1DM was diagnosed. PFOS and PFOA have been extracted following an ion-pairing extraction procedure and determined by HPLC-ESI-MS. Non-parametric statistical analysis was performed.
Results: PFOS concentrations resulted significantly higher in T1DM patients respect to controls (1.53 ± 1.50 vs. 0.55 ± 0.15 ng/ml, respectively; P = 0.0001, Mann–Whitney *U*-test). No difference was found in PFOA levels (0.53 ± 0.09 vs. 0.50 ± 0.06 ng/ml, respectively; P = 0.148, Mann–Whitney *U*-test).
Conclusions: Our data suggests that higher serum levels of PFOS may be considered as a biomarker of exposure and susceptibility to develop TIDM. Further studies are necessary to better understand the role of this and other chemical compound as triggers of autoimmune endocrine diseases during childhood.

O/6/FRI/07

The natural history of hemoglobin A1c (HbA1c) from pre-to-post-adolescence among type 1 diabetes (T1D) participants enrolled in the T1D exchange clinic registry

M.A. Clements[1], J. Lee[2] & K.M. Miller[3], for the T1D Exchange Clinic Network
[1]*Children's Mercy Hospitals & Clinics, Pediatrics, Kansas City, United States,* [2]*University of Michigan, Division of Pediatric Endocrinology, Child Health Evaluation and Research Unit, Ann Arbor, United States,* [3]*Jaeb Center for Health Research, Tampa, United States*

Objectives: Average HbA1c levels of individuals with T1D influence the longitudinal risk for diabetic complications. Few studies have examined the HbA1c trends of adolescents. The authors hypothesized that race/ethnicity and gender influence HbA1c trends during the adolescent years.
Methods: The T1D Exchange Clinic Registry began enrollment in 9/2010 and now includes approximately 60 U.S. centers, with over 8000 child and adult participants. Available HbA1c lab results for the past 10 years were collected at enrolment. The analysis included 367 participants who were between the ages of 17 and 22, were diagnosed with diabetes before the age of 8 and had at least 8 years of available HbA1c test results (53% female, 85% non-Hispanic white, 60% using a pump, mean age at diagnosis 4.8 years, mean T1D duration 13.8 years). The annual average HbA1c values of participants from ages 8 to 20 were used in this analysis.
Results: As seen in the figure, while HbA1c levels were similar according to race and gender at age 8, through the teenage years, HbA1c levels increased more in minorities than in non-Hispanic Whites.



[HbA1c across adolescence]

Conclusions: Among children with T1D, HbA1c appears to increase more in minority race/ethnicity groups during adolescent years and may also be influenced by gender. The identification of additional clinical or socioeconomic risk factors for the adolescent rise in HbA1c may help clinicians to target specific interventions to high risk groups.

O/6/FRI/08

The pharmacokinetic properties of insulin degludec in children and adolescents compared with adults with type 1 diabetes after single-dose administration

T. Danne[1], T. Biester[1], S. Blaesig[1], K. Remus[1], B. Aschemeier[1], O. Kordonouri[1], C. Granhall[2], F. Søndergaard[3], A. M. Ocampo Francisco[2] & H. Haahr[2]
[1]*Kinderkrankenhaus auf der Bult, Hannover, Germany,* [2]*Novo Nordisk A/S, Søborg, Denmark,* [3]*Novo Nordisk A/S, Aalborg, Denmark*

Objectives: Insulin degludec (IDeg) is an ultra-long-acting basal insulin that forms soluble multi-hexamers upon injection. The slow and sustained release of IDeg monomers into circulation from a s.c. depot results in a duration of action of >42 hours in adults. The primary objective of this study was to investigate the pharmacokinetic (PK) properties of IDeg in children and adolescents as compared with adults.

Methodology: This was a randomised, single-centre, double-blind, two-period cross-over, single-dose trial with IDeg and insulin glargine. 12 children (6–11 years), 13 adolescents (12–17 years) and 12 adults (18–65 years) received IDeg (0.4 U/kg s.c.) and were included in the PK evaluation. Serum IDeg was assessed for 72 hours after injection.
Results: The mean ± SD of age / diabetes duration in children, adolescents, and adults groups were 10.3 ± 1.1/5.1 ± 2.4, 14.3 ± 1.6 / 5.9 ± 4.1, and 25.6 ± 11.9 / 13.8 ± 8.3 years, respectively. Mean HbA_{1c} was comparable (7.7 ± 0.8, 7.7 ± 0.5, and 7.6 ± 1.0%). IDeg was detected after 72 hours (end of observation) for all subjects. Total exposure tended to be higher in children than adults (AUCIDeg, 0–∞, SD: estimated ratio (children/adults) 1.48 [95% CI: 0.98; 2.24]), and was statistically higher in adolescents than adults (1.33 [95% CI: 1.08; 1.64]). No statistically significant differences in maximum IDeg concentrations were found between age groups: (children/adults) 1.20 [95% CI: 0.90; 1.60]; (adolescents/adults) 1.23 [95% CI: 1.00; 1.51]. Median time to maximum concentration was within the same range across age groups (11–15 hours). No safety issues were identified.
Conclusions: The ultra-long pharmacokinetic properties of IDeg in adults are preserved in children/adolescents; serum IDeg concentrations persist beyond 72 hours after a single fixed dose. Extent of exposure tends to be greater in children/adolescents than in adults; but as with other insulin products, IDeg should always be titrated according to individual needs.

Oral Session VII: Complications; Psychosocial Issues

O/7/SAT/01

Risk factors for diabetic retinopathy – long-term observation in 8784 patients with type 1 diabetes

O. Kordonouri[1], H.-P. Hammes[2], W. Kerner[3], S. Hofer[4], K. Raile[5], R.W. Holl[6] & DPV-Wiss Study Group

[1]*Kinderkrankenhaus auf der Bult, Diabeteszentrum für Kinder und Jugendliche, Hannover, Germany,* [2]*University of Heidelberg, 5th Medical Department, Medical Faculty Mannheim, Mannheim, Germany,* [3]*Heart and Diabetes Center Mecklenburg-Vorpommern, Department of Diabetes and Diseases of Metabolism, Karlsburg, Germany,* [4]*Medical University of Innsbruck, Department of Pediatrics, Innsbruck, Austria,* [5]*Charité Children's Hospital, Department of Pediatric Endocrinology and Diabetes, Berlin, Germany,* [6]*Unversity of Ulm, Department of Epidemiology, Ulm, Germany*

Objective: Aim of this study was to evaluate the impact of established and suspected risk factors for diabetic retinopathy on the basis of a nationwide prospective survey in a large cohort of patients with type 1 diabetes (T1D).

Methods: Data from 8784 of 18,891 patients with childhood, adolescent, or adult onset of T1D from the German/Austrian Diabetes Documentation System Survey were analyzed. Inclusion criteria were: T1D onset below 40 years, recent age between 18 and 60 years, and at least one retinal examination based on the guidelines of the German Diabetes Association. Retinopathy grading, treatment regimens, and risk factors were recorded prospectively and tested as covariates by Kaplan–Meier and logistic regression analysis.

Results: Any diabetic retinopathy was present in 27.4% and advanced retinopathy (severe non-proliferative or proliferative) in 8.0% of the cohort. After 40 years of T1D, the cumulative proportion of patients with any retinopathy and advanced retinopathy was 84.1% and 50.2%, respectively. In multiple regression analysis, risk factors for any retinopathy were diabetes duration (odds ratio, OR 1.167 per year), HbA1c >7.0% (OR 2.225), smoking (OR 1.295) and male gender (OR 1.187, $P < 0.0001$ each). Young age at onset (5 vs. 15 years at T1D onset) was protective (OR 0.410, $P < 0.0001$). No glycemic threshold was detected for retinopathy protection. Risk factors for advanced retinopathy were duration (OR 1.124 /year, $P < 0.0001$), male gender (OR 1.323, $P = 0.0020$), HbA1c >7.0% (OR 1.499, $P < 0.0001$), triglycerides >150mg/dl (OR 1.398, $P = 0.0013$) and blood pressure > 140/90 mmHg (OR 1.911, $P < 0.0001$).

Conclusions: Longstanding type T1D is associated with a high proportion of diabetic retinopathy. Glycemic control has been confirmed to be the most important risk factor for this late complication. Regarding the importance of several risk and protective factors, multi-factorial concepts for morbidity protection have to be improved in the future.

O/7/SAT/02

Detection of hypertension and pre-hypertension in children and adolescents with type 1 diabetes: is there room for improvement?

C. Zuijdwijk[1], J. Feber[2] & M. Nakhla[3]

[1]*Children's Hospital of Eastern Ontario, Department of Pediatrics, Division of Endocrinology and Metabolism, Ottawa, Canada,* [2]*Children's Hospital of Eastern Ontario, Department of Pediatrics, Division of Nephrology, Ottawa, Canada,* [3]*The Montreal Children's Hospital, Department of Endocrinology and Metabolism, Montreal, Canada*

The identification and management of hypertension (HTN) in pediatric patients with types 1 diabetes (T1D) is vital in preventing the development of long-term HTN- related complications. However, studies in both the general pediatric and T1D populations have shown that the diagnosis of HTN is often unrecognized. Pediatric blood pressure (BP) standards are based on gender, age and height and are presented in complex tables (Standard BP Tables), which have been hypothesized to be potential barriers to the diagnosis of pediatric HTN. To address this problem, a simplified table of BP values (Simple BP Table) has been proposed as an effective screening tool for HTN.

Objectives: (1) To determine the prevalence of unrecognized HTN and pre-HTN in children and adolescents with T1D based on the Standard BP Tables, and

(2) To determine the sensitivity and specificity of the Simple BP Table in identifying HTN and abnormal BP (HTN/pre-HTN).

Methods: We conducted a retrospective chart review. Data collection included baseline characteristics, BP measurements, and documentation of whether pre-HTN or HTN was recognized. Patients were categorized as normal, pre-hypertensive, or hypertensive using the Standard and Simple BP Tables.

Results: Seventeen of 72 children (23.6%) had abnormal BP, of which 8 (11.1%) were hypertensive and 9 (12.5%) were pre-hypertensive. Of these 17 patients, 13 (76.4%) had an unrecognized diagnosis. The Simple BP Table had a sensitivity of 100% in identifying HTN and abnormal BP, and specificities of 76.6% and 89.1% for the identification of HTN and abnormal BP respectively.

Conclusion: The diagnoses of HTN and pre-HTN are often missed in pediatric T1D patients. The Simple BP Table is a useful screening tool, which may allow for earlier detection and treatment of HTN. Our study is the first to validate the use of the Simple BP Table in the pediatric T1D population.

O/7/SAT/03

The feasibility of corneal confocal microscopy in pediatrics: a pilot study

E.A. Sellers[1], I. Clark[2], R. Malik[3], M. Tavakoli[3], J. McGavock[1] & H.J. Dean[1]

[1]*University of Manitoba, Pediatrics and Child Health, Winnipeg, Canada,* [2]*University of Manitoba, Ophthalmology, Winnipeg, Canada,* [3]*University of Manchester, Manchester, United Kingdom*

Objectives: Diabetic neuropathy is a major cause of morbidity, but is difficult to detect early. Techniques such as electrophysiology are uncomfortable. Quantitative sensory testing is not reproducible. Nerve or skin biopsy is invasive. Corneal confocal microscopy (CCM) is a non-invasive technique which has been used in adults with diabetes to demonstrate a significant early reduction in corneal nerve fiber density (NFD), length (NFL) and branching (NBD) with an increase in

tortuosity (NFT). These abnormalities are comparable with skin biopsy and are related to increasing severity of neuropathy. The objective of this pilot study was to determine the acceptability and feasibility of CCM in a pediatric population.
Methods: Children aged 10–18 with type 1or 2 diabetes and children without diabetes were recruited. Participants underwent CCM and a brief questionnaire to assess tolerability and time for examination. Descriptive statistics and ANOVA for differences between the groups were used to analyze the data.
Results: 18 children participated (6 in each group). No child reported that the exam was uncomfortable, 1 found it difficult to sit still. All stated that they would have it performed again. 1 child had a minor vaso-vagal episode. Mean duration of the exam was 5.4 minutes (range 4–7.75). There was no significant difference between those with type 1 or 2 diabetes or controls in NFD (23.6 ± 3.3 vs. 24.5 ± 2.8 vs. 21.9 ± 2.5), NBD (38.5 ± 11.9 vs. 48.8 ± 15.4 vs. 39.4 ± 12.6), NFL (16.9 ± 1.8 vs. 19.4 ± 2.9 vs. 16.4 ± 3.8) and NFT (15.4 ± 2.5 vs. 14.6 ± 2.3 vs. 15.6 ± 3.1).
Conclusions: This pilot demonstrates that CCM can be used in children to quantify corneal nerve morphology. No significant change was seen between children with type 1 or type 2 diabetes compared to controls, although those with type 2 diabetes had evidence of early nerve repair. Further studies aimed at validation of this technique for detection of diabetic neuropathy in pediatrics are needed.

O/7/SAT/04

Impact of informing children and parents of high risk of developing type 1 diabetes (T1D)

U. Swartling, R. Casas, L. Akerman & J. Ludvigsson
Division of Paediatrics, Dep. Clinical and Experimental Medicine, Linkoping, Sweden

Objectives: Informing children that they have increased risk for T1D raises many ethical and psychological issues. However, little is known of the effect it has on parents and children.
Methods: From the ABIS study (All Babies In South-east Sweden), 45 children were identified as T1D high-risk individuals. During the study 22 developed T1D, the remaining 23 were parallel asked to participate in a follow-up study with shorter intervals (6 months). Children and parents completed extensive questionnaires every 6 months. We used established psychological measurements (STAI; indicator of worry/anxiety).), and included questions regarding concern, preventive measures, and risk understanding.
Results: Children and parents are in general positive to high-risk information and the clinical follow-up to identify early symptoms. STAI-levels (0–18 months) were within normal range (≤41) among both children and parents. From 0–6 months, ¼ report parental preventive behavior (50% at 12 months) and also personal changes in behavior (52%; sweets, exercise).
At 6 months, 35% of the children report feeling worried. In addition, ¼ believe their parents are concerned, 85% are positive towards research on high-risk prevention strategies, and state positive to participate in preventive trials. Data indicate difficulties in communicating risk-information: 50% of the children do not believe they have an increased risk. Even though repeated information, many parents also assess their childs risk as normal.
Conclusions: Ethical and psychological follow-up is important when children are screened for risk status. More knowledge is needed in order to inform children/families of risk status in a way that minimizes negative consequences. Better strategies to communicate risk-status should be developed.

O/7/SAT/05

Seeking harmony: parents' and adolescents' experience living with sensor-augmented pump therapy

C. Richardson[1], M. Lawson[1], J. Rashotte[2], F. Fothergill-Bourbonnais[3], K. Tousignant[3], M. Nakhla[1] & P. Olivier[1]
[1]*Children's Hospital of Eastern Ontario, Endocrinology and Metabolism, Ottawa, Canada,* [2]*Children's Hospital of Eastern Ontario, Nursing Research, Ottawa, Canada,* [3]*University of Ottawa, Ottawa, Canada*

Objective: Relatively little is known about how parents and adolescents perceive and manage sensor-augmented pump therapy [SAPT] in daily life. To address this gap, parents' and adolescents' experiences with and perceptions of living with SAPT were explored.
Methods: Study design comprised interpretive phenomenological interviews with a purposive convenience sample of seven parent/adolescent dyads recruited through one Canadian pediatric diabetes program. The adolescents were 12 to 17 years of age with type 1 diabetes, who had experience (current or past) living with SAPT. Semi-structured interviews were audiotaped, transcribed verbatim, and subjected to an analysis guided by van Manen's (1997) phenomenological processes.
Results: Analysis revealed that SAPT changed the way parents and adolescents attempted to optimize control of daily blood sugars. Seeking harmony reflected the parents' and adolescents' daily struggle to harmonize seemingly opposing choices that were brought to the fore with the introduction of SAPT while also struggling to live with both wellness and chronic illness. Two themes within seeking harmony emerged: confronting responsibility and seeking normality. For example, within confronting responsibility, parents searched for a balance between parental control with the use of SAPT and youth control and in the end found shared control. Similarly, in seeking normality, adolescents struggled to just live (with diabetes) with the use of SAPT rather than fleeing from diabetes or living for diabetes.
Conclusion: These findings enhance our understanding of the parents' and adolescents' personal experiences of living with SAPT. For example, healthcare professionals can facilitate parental and adolescent decision-making as to the optimal timing of SAPT introduction. It is important to explore parental expectations for SAPT and the degree to which they have fostered child involvement in and responsibility for diabetes management.

O/7/SAT/06

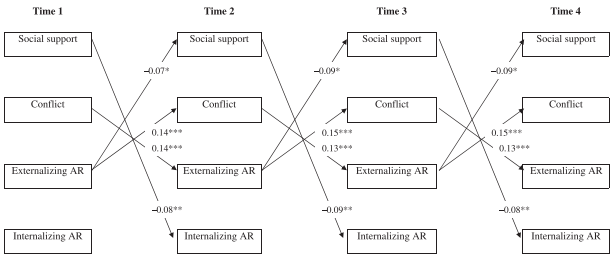
Adolescents with type 1 diabetes and their parents: developmental pathways to health and well-being

E. Goethals[1], K. Luyckx[2], L. Missotten[2], K. Casteels[1] & I. Seiffge-Krenke[3]
[1]*University Hospital Leuven, Department of Pediatrics, Leuven, Belgium,* [2]*Catholic University Leuven, Department of Psychology, Leuven, Belgium,* [3]*University of Mainz, Mainz, Germany*

Objectives: Little is known about how relationship quality with parents in adolescents with type 1 diabetes relates to internalizing and externalizing symptoms, treatment adherence, and glycemic control over time. Such research is crucial given the hypothesized influence of parent-adolescent relationships on such processes.
Methods: For this multi-source longitudinal study, adolescent patients and parents were recruited in 17 German hospitals and specialized clinics offering outpatient care. Healthy controls and parents were recruited in high schools.A total of 228 adolescents(109 with diabetes; M_{age} = 13.9 years; SD = 1.28;

52% girls),218 mothers and 169 fathers participated. Adolescent perceptions of relationships with parents (social support and conflict) were measured using the Network of Relationships Inventory. Adolescent internalizing and externalizing symptoms were measured using the Youth Self-Report and the parent's form of the Child Behavior Check List. Treatment adherence and glycemic control were assessed by physicians. There were 4 measure times.

Results: Cross-lagged findings on psychological symptoms were similar for adolescents with diabetes and healthy controls. Using adolescent reports, social support negatively predicted internalizing symptoms, whereas conflict positively predicted externalizing symptoms. Externalizing symptoms, in turn, negatively predicted social support and positively predicted conflict. Similarly, using both parent reports, conflict and externalizing symptoms were reciprocally related over time. Further,in the diabetic sample, conflict was related to poorer adherence which, in turn, was related to poorer glycemic control over time.



Conclusions: This study generated important information on how relationships with parents and psychological and physical health reinforce one another over time in adolescents with type 1 diabetes. These findings could inform family-based interventions for improving psychosocial and illness-related functioning in this population.

O/7/SAT/07

Streamlined screening for mood disorders in children with type 1 diabetes using centile-based glycated hemoglobin threshold

A. Butwicka[1,2], W. Fendler[3], A. Zalepa[4], A. Szadkowska[3], A. Gmitrowicz[1] & W. Mlynarski[3]

[1]*Medical University of Lodz, Department of Adolescent Psychiatry, Lodz, Poland,* [2]*Medical University of Warsaw, Department of Child Psychiatry, Warsaw, Poland,* [3]*Medical University of Lodz, Department of Pediatrics, Oncology, Hematology and Diabetology, Lodz, Poland,* [4]*Warsaw School of Social Science and Humanities, Warsaw, Poland*

Objectives: To compare the diagnostic accuracy of glycated hemoglobin level (HbA1c) and psychometric measures in detecting mood disorders among children with type 1 diabetes (T1DM).

Methods: 163 consecutively hospitalized subjects aged 8–18 years with T1DM lasting longer than 6 months were enrolled to the study. HbA1c of each patient was calculated as a mean of 4 results from the preceding year. A centile grid of HbA1c for the center was obtained on the basis of all 677 patients treated during that period with T1DM lasting longer than 1 year. Efficacy of HbA1c level as a screening tool for mood disorders was compared with three standardized measures administered to children with T1DM: the self-rated and parent-rated Children Depression Inventory (CDI) and clinician rated Childreńs Depression Rating Scale (CDRS). Semi-structured clinical interview (KSADS-PL) performed by a child psychiatrist was used as reference standard. The optimal screening threshold score for evaluated tools were identified using ROC (Reciever operating characteristic) curve analysis.

Results: The optimal screening threshold score for HbA1c was the 93rd percentile in the study center which translated to 8.7%. A HbA1c level above cut-off point had a sensitivity of 86% and specificity of 79% for detecting children who met DSM-IV criteria for mood disorders. HbA1c level had an area under the curve of 0.84 (95% confidence interval: 0.77–0.89), which was similar to AUC for CDI self-report (0.83; 95%CI 0.76–0.88) or CDI parent-report (0.78; 95%CI 0.71–0.85) and higher than CDRS (0.73; 95%CI 0.66–0.80). Threshold score for those tests was as following: CDI self-report – above 51, CDI parent-report – above 66 and CDRS – above 42 points.

Conclusions: Centile of HbA1c level shows good sensitivity and specificity for detecting mood disorders. Therefore HbA1c shows promise as a first step for screening individuals with T1D prior to psychiatric consultation.

O/7/SAT/08

The influence of process, structure and policy on HbA1c levels in treatment of children and adolescents with type 1 diabetes

L. Hanberger[1], U. Samuelsson[1], C. Berterö[2] & J. Ludvigsson[1]

[1]*Linköping University, Dept of Clinical and Experimental Medicine, Div of Pediatrics, Linköping, Sweden,* [2]*Linköping University, Dept of Medical and Health Sciences, Division of Nursing Sciences, Linköping, Sweden*

Objectives: We aimed to identify factors for improvements of mean HbA1c at centres treating children and adolescents with diabetes.

Methods: Through data from the Swedish paediatric diabetes quality registry, SWEDIABKIDS, five centres with the lowest mean HbA1c (Low group), five with the highest (High group), and five with the largest decrease in centre mean HbA1c (Decrease group) were identified. The diabetes team members completed a questionnaire, response rate 85%, (109/128) and reported team structure, process and policy. Open-ended questions regarding messages to patients about important diabetes matters were analysed with summative content analysis.

Results: Compared to the High group, the Low and Decrease groups showed shorter professional experience and lower proportion of special diabetes-educated team members, and higher compliance with guidelines. Trends for higher mean insulin dose, larger centre size and larger team size were found. The content analysis indicated that the Low and Decrease groups gave a clear message and had lower HbA1c target value. The team members in these groups were engaged, had a positive attitude and a perception of a well-functioning team. The High group gave a vague message, needed more frames and had a perception of lack of cooperation in the team.

Conclusions: The team memberś approach seems to affect metabolic control in children and adolescents. The team members need to be aware of their approach and how it affects patients and parents, and also of the importance of the possibility of using resources and competence within the team.