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ORAL SESSIONS

New Approaches in Chronic Complications

O/1/WED/01

Assessment of tissue glycation by measurement of plantar fascia thickness in children and adolescents with type 1 diabetes

M.A.K. Salem[1], S.M. Farid[1], I.M. Rassem[2] & M.A.H. Ahmed[3]
[1]*Paediatrics, Ain Shams University, Cairo, Egypt,* [2]*Radiology, Ain Shams University, Cairo, Egypt,* [3]*Ain Shams University, Cairo, Egypt*

Background: Chronic diabetic complications may cause morbidity and disability, so early identification of these complications are of great importance.
Objectives: This study aimed to investigate the relation between thickness of planter fascia as a measure of tissue glycation with different demographic and disease characteristics in patients type 1DM.
Design: This study was conducted on 50 children and adolescents with type 1DM. Patients were divided into two groups according to the duration of diabetes: group (I): comprised patients with disease duration less than or equal to 5 years and group (II) comprised patients with disease duration more than 5 years. The control group consisted of 20 healthy children and adolescents matched in age, gender and BMI to the study group. A written consent was taken from the parents of both patients and controls. Patients were subjected to full history taking; general examination for detection of complication including autonomic and peripheral neuropathy, limited joint mobility and retinopathy. HbA1c measurements and ultrasound for plantar fascia aponeurosis were also done.
Results: Patients with type 1 DM had significantly thicker PFT compared to controls ($P < 0.01$), although both were well matched regarding age, sex and BMI percentile. Patients in group II had poorer metabolic control as evidenced by higher HbA1c% and more frequent diabetic ketoacidosis attacks compared to group I ($P < 0.05$). They also showed more frequent chronic complications with thicker plantar fascia thickness than group I ($P < 0.05$). PFT was significantly positively correlated with disease duration, BMI percentile, frequency of DKA, and mean HbA1c. HbA1c and PFT were the most sensitive predictors for diabetic complication.
Conclusions: Assessment of PFT using ultrasound is a non invasive measure of early damage of collagen and accumulation of AGEs in plantar aponeurosis that can be related to the development of complication in patients with type 1 DM.

O/1/WED/02

Ocular surface disorders in children and adolescents with type 1 diabetes mellitus

M.A. Salem[1], A.A.-F. El-Shazly[2], A.A. Abdelmaksoud[1], A.S. Shalash[3] & E. Abdelmohsen[1]
[1]*Pediatrics, Ain Shams University, Cairo, Egypt,* [2]*Ophthalmology, Ain Shams University, Cairo, Egypt,* [3]*Neuropsychiatry,Ain Shams University, Cairo, Egypt*

Diabetes mellitus (DM) and its clinical association with dry eye and ocular surface disorders are becoming a frequent and complicated problem in Ophthalmology.

Aim of this study: To assess the prevalence and risk factors of ocular surface disorders in patients with type 1 DM and their relation to disease duration and metabolic control.
Patients & methods: Forty patients with type 1 DM and twenty age and sex matched controls were included. Data collected regarding; age sex, disease duration, history of diabetic complications and any symptoms suggestive of eye affection. Mean HbA1c over one year were estimated. Microalbuminuria and nerve conduction velocity were done. Detailed ophthalmological assessment included, schirmer-1, rose bengal staining, fluorescein staining, tear break up time (BUT), impression cytology tests and fundus examination. Patients were subdivided into two groups: group I; with disease duration less than 5 years and group II; with disease duration more than 5 years.
Results: All tear film tests except for rose bengal test were significantly affected in patients more than the controls ($P < 0.001$) with significant affection of group II of patients ($P < 0.001$). Abnormalities in schirmer-1, rose bengal staining, fluorescein staining and impression cytology tests were not significantly related to age, sex, metabolic control parameters or chronic diabetic complications ($P > 0.05$). BUT test abnormalities were significantly related to age [94.4% of test abnormalities in patients older than 10 years] ($P = 0.047$), neuropathy [63.2% of affected eyes in patients with delayed NCV] ($P = 0.008$) and nephropathy [87.5% of eye affection in patients with nephropathy] ($P = 0.011$). No significant relation between BUT test results and sex, HbA1c or retinopathy ($P > 0.05$).
Conclusion: Patients with type 1 DM are prone for ocular surface disorders especially those with longer disease duration.

O/1/WED/03

Risk factors for sensitive and motor polyneuropathy in type 1 diabetes

A. Tilmanne[1], C. Mélot[1], P. Deltenre[2] & H. Dorchy[3]
[1]*Université Libre de Bruxelles, Brussels, Belgium,* [2]*Brugmann University Hospital, Brussels, Belgium,* [3]*Children's University Hospital Queen Fabiola, Brussels, Belgium*

Introduction: Sensitive and motor polyneuropathy are among the major complications of diabetes. The study of their risk factors has the dual goal of understanding and preventing those complications.
Methods: A total of 135 type 1 diabetic patients regularly followed at the diabetology clinic of the Childreńs University Hospital Queen Fabiola, who were between 17 and 30 years old from 2004 to 2009, were included for this retrospective work of 6 years. The mean duration of diabetes was 10.5 years. Multiple potential risk factors have been taken into account: HbA1c, total cholesterol, HDL cholesterol, triglycerides, height, smoking, blood pressure, age, subclinical retinopathy and subclinical nephropathy. The following parameters of nervous conduction were studied: velocity, amplitude and distal latency of the peroneal nerve; tibial nerve F wave latency; sural nerve velocity and amplitude; radial nerve velocity and amplitude.

Multivariable correlations between nervous conduction measures and potential risk factors have been looked for.
Results: Significant correlations were found between mean HbA1c and three electrophysiological parameters (conduction velocities of peroneal and sural nerves; tibial nerve F wave latency). Most of other studied risk factors were non significant, except height. Regarding peroneal nerve conduction velocity, from a threshold of HbA1c of 7.75%, an increase of 1% decreased the mean velocity by 0.89 m/s. About sural nerve, the HbA1c threshold was 9.56% and the mean velocity decreased by 1.70 m/s for each additional percentage of HbA1c. Concerning tibial nerve F wave latency, the HbA1c threshold was 9.58% and the mean latency deterioration was +0.8 ms for each additional percentage.
Conclusions: According to HbA1c threshold, the fastest deterioration appears in the peroneal nerve. Tibial nerve F wave latency is rarely studied in the literature but it gives as much information as peroneal and sural velocities.

O/1/WED/04

Reduction of endothelial progenitor cells and poor glycemic control are predictors for microvascular and macrovascular aberrations in type 1 diabetic (T1D) children within three years

M.J. Fritsch[1], K. Nagl[2], T. Hoertenhuber[2], E. Schober[1], O. Schlager[2], M.E. Gschwandtner[2], A. Willfort-Ehringer[2], C. Margeta[2], R. Koppensteiner[2], G. Schernthaner[3], B. Rami[1] & G.-H. Schernthaner[2]
[1]*Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria,* [2]*Department of Medicine II, Division of Angiology, Medical University of Vienna, Vienna, Austria,* [3]*Department of Medicine I, Rudolfstiftung, Vienna, Austria*

Objectives: Risk of cardiovascular death is high in young patients with T1D compared with controls. Endothelial Progenitor Cells (EPC) estimate vascular damage and predict cardiovascular events. We have demonstrated that worsening of glycemic control resulted in indirect proportional changes in EPC in T1DM-children within 1 year. We asked whether a 3-year follow-up could already reveal vascular impairment.
Methods: We present data of 74 T1D children, 51.4% female; Age: 12.7 ± 0.3 years; Body Mass Index: 20.8 ± 0.4 kg/m^2; HbA1c: 7.0–9.1 rel.%; diabetes duration 4.8 ± 0.4 years (all at inclusion). Study visits: inclusion, 1 and 3 years. EPC (flow cytometry) were measured at all visits. Macrovascular damage was assessed by Carotid Intima Media Thickness (IMT). Microvascular damage was investigated by Laser Doppler perfusion Flowmetry (LDPF). Results are given in mean ± SD or median (25;75 percentile).
Results: EPC at inclusion: 3410/106WBC (2515;4237), EPC at 1 year: 3334/106WBC (2929;3898). LDPF after 3 years: time to absolute peak 9.5 s (6.0;21.3), time to baseline: 80.5 s (63.0;108.3), Total Time (LDPF-TT): 95.5 s (78.0;118.3), Perfusion at absolute peak 1.435 au (1.020;2.050), Perfusion at baseline: 0.390 au (0.258;0.598), Difference of perfusion at peak and baseline: 1.055 au (0.610;1.513). IMT after 3 years: 0.285 mm (0.258;0.350). EPC at baseline and 1 year were predictive for LDPF-TT ($R = -0.259$; $P = 0.042$) and IMT ($R = -0.344$; $P = 0.003$). Cross-sectional associations with LDPF-TT: HbA1c ($R = 0.255$; $P = 0.045$) and mean-blood-glucose ($R = 0.331$; $P = 00.013$); with IMT: systolic blood pressure ($R = 0.248$; $P = 0.035$) and duration of diabetes ($R = 0.0255$; $P = 0.028$).
Conclusions: We show an association of EPC with disturbed micro- and macrovascular function in children with T1D after a short observation period. It is most likely that glucose fluctuation (HbA1c) lead from depression of EPC to micro- and macrovascular changes (LDPF and IMT) and finally to premature cardiovascular disease.

O/1/WED/05

Evidence for early stage atherosclerosis and low grade inflammation in diabetic children on intensive insulin treatment: a population based study

H.D. Margeirsdottir[1,2,3], K.H. Stensaeth[4], I. Seljeflot[2,5], H. Arnesen[2,5], J.R. Larssen[3], C. Brunborg[6], S.J. Kummernes[1] & K. Dahl-Jørgensen[1,2,3]
[1]*Pediatric Department, Oslo University Hospital, Ullevaal, Oslo, Norway,* [2]*Faculty of Medicine, University of Oslo, Oslo, Norway,* [3]*Oslo Diabetes Research Centre, Oslo, Norway,* [4]*Radiology Department, Oslo University Hospital, Ullevaal, Oslo, Norway,* [5]*Center for Clinical Heart Research and Department of Cardiology, Oslo University Hospital, Ullevaal, Oslo, Norway,* [6]*Centre for Clinical Research, Oslo University Hospital, Ullevaal, Oslo, Norway*

Objective: To evaluate early stages of atherosclerosis and low grade inflammation in childhood diabetes compared to age- and sex matched healthy control subjects.
Research design and methods: All children and adolescents with type 1 diabetes, aged 8–18 years in Health Region South-East in Norway were invited to participate in the study (n = 800). 40% (n = 314) agreed to participate and were compared to 118 age-matched healthy controls. Carotid artery Intima Media Thickness (cIMT) and elasticity was measured using standardized methods. High sensitive C-reactive protein (hs-CRP) was measured by ELISA method.
Results: Mean age of the diabetic patients was 13.7 years, diabetes duration 5.5 years and HbA1c 8.4%. 97% were using intensive insulin treatment, 60% insulin pumps. Diabetic patients had more frequently elevated cIMT than healthy controls: 19.5% were above 90th centile of healthy controls and 13.1% above 95th centile (both $P < 0.01$). Mean cIMT was higher in diabetic boys (n = 155) compared to healthy control boys (0.46 mm /SD 0.06 mm vs. 0.44 mm/SD 0.05 mm, $P = 0.04$) but not significantly so in girls. There was no significant difference between the groups regarding carotid distensibility, compliance and wall stress. None of the subjects had atherosclerotic plaque formation. The Diabetic patients had significantly higher hs-CRP than the controls (2.01 vs 0.88 mg/L; $P < 0.001$), this was true for both sexes. No association was found between hc-CRP and cIMT. A positive correlation was found between hs-CRP and HbA1c in the diabetic group ($r_{sp} = 0.25$, $P < 0.001$), but not in the control group.
Conclusions: Despite short disease duration and intensive insulin treatment, early stage atherosclerosis and low grade inflammation seems to be present in this group of type 1 diabetic children and adolescents.

O/1/WED/06

Impaired 24-hour blood pressure variation in adolescents and adult normoalbuminuric type 1 diabetes patients

G. Deja[1], L. Machnica[1], P. Jarosz-Chobot[1], L. Czupryniak[2], M. Pawlowski[2], E. Szymanska-Garbacz[2], M. Saryusz-Wolska[2] & J. Loba[2]
[1]*Medical University of Silesia, Katowice, Poland,* [2]*Medical University of Lodz, Lodz, Poland*

The absence of >10% blood pressure (BP) drop at night (''non-dipping'' phenomenon) is being recognized as a significant risk factor of vascular complications of diabetes. Little is known about the role of endothelium function in these processes. The aim of the study was to assess BP rhythm in adolescent and adult subjects with T1DM.
Methods: The study comprised two groups of normoalbuminuric T1DM patients: Group A-52 adolescents (mean age 14.1 ± 3.0 years, diabetes duration 5.1 ± 2.2 years, HbA1c 7.2 ± 1.0%), Group B-62 adults (mean age

34.1 ± 7.2 years, diabetes duration 4.8 ± 2.5 years, HbA1c 7.2 ± 1.1%) and a group of healthy controls (Group C; mean age 23.1 ± 4.4 years). All subjects had 24-hour blood pressure monitoring performed (SpaceLabs). Fasting plasma of sVCAM, sICAM, sE-selectin, adiponectin, IL-6, and TNF-α concentration were measured.

Results: 25 (48%) subjects from Group A and 9 (15%) from Group B were ''non-dippers''; no ''non-dippers'' were found in Group C. There were no significant differences in vascular and inflammatory parameters between ''dippers'' and ''non-dippers'' in all groups. However, mean 24-hour systolic (SBP) and diastolic blood pressure (DBP) was significantly lower in Group A than in Group B and C: 118 ± 10 and 66 ± 5; 126 ± 11 and 73 ± 6, and 128 ± 12 and 73 ± 6 mmHg ($P < 0.01$). In particular, SBP at night was significantly lower in ''non-dippers'' than in ''dippers'' from Group A: 105 ± 8 and 113 ± 10 mmHg ($P < 0.01$), while DBP was similar: 57 ± 3 and 60 ± 7 mmHg, respectively. There was a significant positive correlation between 24-hour SBP and BMI in Group A and B ($r = 0.41$ and $r = 0.32$).

Conclusions: In adolescent or adult patients with T1DM non-dipping phenomenon is not associated with endothelial dysfunction or increased subclinical inflammation. In addition, unusually high prevalence of non-dipping in adolescent subjects with T1DM suggests that establishing this diagnosis with traditional criteria might not be at all appropriate in this population.

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O/1/WED/07

Longitudinal study of the endothelial function in children and adolescents affected by type 1 diabetes mellitus

L. Iughetti[1], R. Rossi[2], B. Predieri[1], A. Nuzzo[2], P. Bruzzi[1], A. Salvini[1], V. Patianna[1], G. Delle Donne[2] & M. G. Modena[2]
[1]*Pediatrics, University of Modena, Modena, Italy,* [2]*Cardiology, University of Modena, Modena, Italy*

Introduction: Cardiovascular diseases are the main cause of mortality and morbidity in patients affected by Type 1 Diabetes. The endothelial dysfunction, a precocious stage of the atherosclerotic process, can be analyzed through the brachial flow-mediated dilatation and through the evaluation, of the arterial stiffness.

Objective: The aim of this study is to evaluate the presence of subclinical cardiovascular alterations and their development in pediatric patients with T1DM.

Methods: A total of 42 patients with T1DM (18 females, 11.5 ± 3.6 years) entered this study. In all patients we analyzed the auxological, laboratory and clinical data (CT, HDL, LDL, TG, Glycemia, HbA1c, blood pressure (SBP-DBP). The evaluation of the endothelial function was obtained through the flow mediated dilation method (FMD), while stiffness was measured using pulse wave analysis (PWA). The measurements were repeated after 2 years and were compared with 30 healthy children and adolescents.

Results: At baseline FMD values were significantly reduced in children with T1DM (4.32 ± 8.36%; vs. 9.78 ± 6.1, $P = 0.003$) and the lipid values result normal with a significant improvement during the study ($P < 0.05$). After 2 years while FMD significantly impaired, HbA1c and lipid values remained unchanged. The regression model allowed to identify CT ($\beta = 0.683$, $P = 0.025$) and LDL ($\beta = -0.676$, $P = 0.025$) as FMD predictive factors. The PWA analysis showed in females a slight decrease in myocardial perfusion.

Conclusions: This study confirms that in children with T1DM the endothelial function can be already altered. The Pulse Wave Analysis results helpful to precociously individuate pathological alterations of the arterial elasticity and stratification of the cardiovascular risk.

O/1/WED/08

Changes in forearm vascular resistance (FVR) caused by hyperglycemia-induced vasodilation in adolescents with type 1 diabetes

A. Dye[1] & R. Hoffman[1]
[1]*Pediatrics, Nationwide Children's Hospital/Ohio State University, Columbus, United States*

Objectives: Endothelial dysfunction is an early indicator of vascular disease in type 1 diabetes. Endothelial dysfunction is present in adolescents with type 1 diabetes. However, previous studies have assessed endothelial function in subjects with type 1 diabetes at variable glucose values. The primary objective of this study was to determine the effect of acute changes in plasma glucose on endothelial function in adolescents with type 1 diabetes.

Methods: Forearm blood flow (FBF) was measured using strain gauge venous occlusion plethysmography in
(1) the fasted state (153 ± 44 mg/dL SE),
(2) euglycemic state (87 ± 8 mg/dL SE); using 40 mU/m2/min insulin infusion), and
(3) hyperglycemic state (224 ± 5 mg/dL SE,) for each subject.
FBF was measured before and after 5 minutes of upper arm arterial occlusion. Forearm Vascular Resistance (FVR) was calculated by dividing mean arterial pressure (MAP) by FBF. Endothelial-mediated vasodilation (EMVD) was determined as the change in FVR from pre to post-occlusion.

Results: Repeated measures ANOVA demonstrated a significant decline in pre-occlusion FVR from the fasting state to the euglycemic state ($P = 0.049$) and a further decline with hyperglycemia ($P = 0.027$). Post-occlusion FVR was not statistically different between the three states. Thus, there was a significant decrease in EMVD during euglycemia compared to fasting ($P = 0.047$) and during hyperglycemia ($P = 0.032$) compared to euglycemia.

Conclusions: We propose that the fall in forearm vascular resistance induced by hyperglycemia is due to increased blood volume (secondary to hyperosmolarity) and subsequent increase in shear stress which mediates vasodilation. The hyperglycemic vasodilation decreases the reserve capacity for additional endothelial mediated vasodilation to other stimuli.

Novel Findings in Pediatric Diabetes Management

O/2/WED/01

Recombinant igf-1 treatment induced-retinopathy in a youth with severe insulin resistance syndrome

E. Bismuth[1], M. Autié[2], N. Tubiana-Rufi[1], P. Massin[2] & J.-C. Carel[1]
[1]*Pediatric Endocrinology and Diabetes, Hopital Robert Debré, Paris, France,* [2]*Ophtalmology, Hopital Lariboisiere, Paris, France*

Objective: Experimental and clinical data suggest that IGF-1 may play a role in the development or progression of diabetic retinopathy. Recombinant IGF-1 is used in patients with severe insulin resistance. We report here a case of severe retinopathy during IGF-1 therapy.
Methods: An 18 year old girl with severe insulin resistance syndrome (IR) due to a compound heterozygous defect in the insulin receptor. Glycemic control was poor (mean HbA1c, 11%). No diabetes-related complications were detected pre-IGF-1 treatment. IGF-1 therapy was started at 0.1 mg/kg/j, increased after 4 weeks to 0.2 mg/kg/j.
Results: After an 8-week IGF-1 treatment, metabolic control markedly improved with a 1.6% drop in HbA1c (12.3–10.7%), near normalization of glycemic values, and a 50% decrease of fasting insulin levels. Plasma IGF-1 levels increased by 60% but remained in the normal range for age and gender. Regular retinographic examination revealed the appearance of bilateral proliferative retinopathy with pre-papillar neovascularisation and absence of peripheral ischemia. IGF-1 treatment was discontinued and follow-up retinal exam showed a partial regression of the lesions.
Conclusions: The rapid appearance and the papillar predominance of the lesions suggest a direct effect of IGF-1 therapy on the development of this severe complication. We can hypothesize that a rapid raise of free IGF-1 levels due to treatment induced more dramatic changes than what is usually observed during the classic normoglycemia re-entry phenomenon where upregulation of IGF-1 occurs gradually and is associated with a rise of the carrying protein IGFBP3. This observation highlights the risk of rapid retinal impairment when IGF-1 treatment is used in a patient with severe IR syndrome. Although therapeutic options are few and IGF-1 treatment is metabolically efficient in these rare and severe conditions, the risk/benefit balance should be carefully considered.

O/2/WED/02

Urinary c-peptide creatinine ratio is a possible novel non invasive alternative to the inpatient mixed meal tolerance test in children with type 1 diabetes

R.E.J. Besser[1], A.T. Hattersley[1], T. McDonald[1,2] & J. Ludvigsson[3]
[1]*Peninsula NIHR Clinical Research Facility, Peninsula Medical School, University of Exeter, Exeter, United Kingdom,* [2]*Department of Clinical Biochemistry, Royal Devon & Exeter Hospital NHS Foundation Trust, Exeter, United Kingdom,* [3]*Division of Pediatrics, Faculty of Health Sciences, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden*

Introduction: Stimulated serum C-peptide (sCP) during a mixed meal tolerance test (MMTT) is the gold standard measure of endogenous insulin secretion in children with Type 1 diabetes (T1D). However practical issues limit its routine use in clinical practice. Urinary C-peptide creatinine ratio (UCPCR) is stable in boric acid for 3 days at room temperature, offering a non invasive alternative measure of endogenous insulin secretion.
Objectives: To determine: (1) Can UCPCR replace serum in the MMTT?
(2) Is a home postprandial UCPCR an alternative to the MMTT?
Methods: We performed a MMTT (BOOST 6 ml/kg max 360 ml) on 21 T1D patients <18 years (age of diagnosis median (IQR) 10.5 (9.5–12.6) years, diabetes duration 2.6 (0.6–5.0) years) and measured sCP at 90 minutes and UCPCR at 120 minutes. Postprandial UCPCR was collected at home 120 minutes after supper the night before the MMTT, having voided prior to eating, with the usual evening insulin. Relevant UCPCR cutoffs were determined using the DCCT defined stimulated sCP cut off of 0.2 nmol/l.
Results: (1) 120 minutes UCPCR in the MMTT was well correlated with 90 minutes sCP in the MMTT ($r = 0.83$ (95%CI: 0.61,0.93), $P < 0.0001$.
(2) Home postprandial UCPCR was also well correlated with 90 minutes sCP in the MMTT ($r = 0.85$ (95% CI: 0.60,0.95), $P < 0.0001$).
(3) 120 minutes UCPCR during the MMTT correctly classified 20/20(100%) patients with significant endogenous insulin secretion (MMTT stimulated sCP > 0.2 nmol/l, equivalent to MMTT stimulated UCPCR > 0.6 nmol/mmol). Home postprandial UCPCR correctly classified 14/15(93%) patients (stimulated sCP > 0.2 nmol/l, UCPCR > 0.4 nmol/mmol). In both alternatives the best correlation was seen in patients with low C-peptide values.
Conclusions: Our data suggests that 120 minutes UCPCR during a MMTT may in routine clinical practice be an alternative to an invasive MMTT. Furthermore, a home post meal UCPCR may be an alternative to the 120 minutes UCPCR over MMTT, avoiding the need for inpatient investigation.

O/2/WED/03

Clinical and hormonal profile in adolescent girls with type 1 diabetes mellitus and polycystic ovary syndrome or polycystic ovary morphology

G. Deja[1], A. Zachurzok-Buczynska[1], A. Gawlik[1] & E. Malecka-Tendera[1]
[1]*Pediatric Endocrinology and Diabetes, Silesian University of Medicine, Katowice, Poland*

The aim of our study was to determine the clinical and hormonal profile of well controlled (HbA1c = 7.25 ± 0.65%) diabetic girls with PCOS and PCOM and compare it to non-diabetic controls.
Methods: We studied 36 diabetic girls (mean age 15.9 ± 0.8 years; mean gynecological age 33.0 ± 10.7 months) treated with multiple insulin injections (53%) or insulin pump (47%). PCOS was diagnosed in five (14%) girls and PCOM was found on ultrasound in 12 (33%). Nineteen (53%) girls without signs or symptoms of PCOS or PCOM served as T1DM control group (T1DM-CG) and 13 healthy, regularly menstruating girls served as control group (H-CG). In all girls basal and triptorelin-stimulated levels of hormones were measured.
Results: In PCOM group the occurrence of menstrual irregularities (oligomenorrhea, secondary amenorrhea) was significantly higher than in T1DM-CG (42.0% vs. 10.5%, $P = 0.04$). There was no difference in ovarian volume between the studied groups. In PCOS group FSH level (3.0 ± 1.5 mIU/ml) was significantly lower, LH/FSH ratio (1.8 ± 0.3) and basal 17OHP level (1.8 ± 1.2 ng/ml) significantly higher than in PCOM group (4.9 ± 1.2 mIU/ml, $P = 0.01$; 0.6 ± 0.4, $P = 0.02$, 1.0 ± 0.4 ng/ml $P = 0.04$, respectively), T1DM-CG

(4.6 ± 1.4 mIU/ml, P = 0.03; 0.5 ± 0.4, P = 0.003, 1.1 ± 0.4 ng/ml, P = 0.02, respectively) and in H-CG (5.0 ± 1.5 mIU/ml, P = 0.02; 0.9 ± 0.2, P = 0.04, 1.0 ± 0.5 ng/ml, P = 0.05, respectively). Significantly higher stimulated 17OHP levels was found in PCOS group than in CG (3.1 ± 1.3 ng/ml vs. 2.0 ± 0.7 ng/ml, P = 0.04). There was no difference between diabetic girls with PCOM and T1DM-CG and H-CG with respect to gonadotropins, androgens, estradiol, progesteron and SHBG level. It is concluded that hormonal profile in diabetic girls with PCOM is not different from those with T1DM and normal ovarian morphology as well as from healthy girls. As menstrual irregularities occur more often in diabetic girls with PCOM, longitudinal follow-up studies are needed to show whether PCOM is heralding PCOS in these patients.

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O/2/WED/04

Type 2 diabetes and MODY prevalence in a Belgian diabetic cohort

T. Mouraux[1] & H. Dorchy[2]

[1]*University Children's Hospital Queen Fabiola, Diabetology, Brussels, Belgium,* [2]*University Children's Hospital Queen Fabiola, Brussels, Belgium*

Objectives: To analyse in a cohort of diabetic patients the prevalence of type 2 diabetes (T2D) and Maturity Onset Diabetes of the Young (MODY).

Methods: In Belgium, about 2600 patients <18 year old are registered by the social security, about 1800 are followed in one of the 13 pediatric diabetic centers certified by the social security, about 800 diabetic children by diabetologists for adults. Our center follows 483 patients. At onset, with the Belgian Diabetes Registry, markers of the immune destruction were analyzed (islet cells auto-antibodies, and auto-antibodies to insulin, to glutamic acid decarboxylase, and to the tyrosine phosphatases) as well as the genetic marker of type 1 diabetes (HLA DQ). In case of negativity and with a strong family history, we search for the MODY types.

Results: Before 2000, no patient with T2D was identified; after 2007, only eight patients (1.65%) have been diagnosed T2D, the youngest patient is 9 year 7 months (m) of age and the oldest was 16 year of age (mean age at diagnosis was 13 year 8 months). All patients were diagnosed further with a check-up for obesity. There was no clinical complaint except for two patients. All patients except one had severe obesity. Acanthosis nigricans was observed in six patients. A family history of T2D existed in six patients. HbA1c normalized in six patients with diet and metformine. At diagnosis, insulin was used in two patients and stopped after a few months. In one patient, insulin was added to the treatment because of a bad metabolic control. The diagnosis of MODY was observed in eight patients (1.65%) (type 1: 1; type 2: 2; type 3: 4; type 5: 1). The delay for genetic diagnosis ranged from the onset to 7 years after the onset. At diagnosis, five patients received insulin which was stopped for three of them after genetic diagnosis.

Conclusion: In regard of the prevalence of T2D in children namely noted in the USA, the Belgian prevalence of T2D is growing slowly. The prevalence of MODY is similar to that of T2D.

O/2/WED/05

Relationship between Insulin Reserve and Weight Gain in Children with T1aDM

I. Libman[1], M. Cedillo[1], V. Arena[2], M. Pietropaolo[3], D. Ize-Ludlow[4] & D. Becker[1]

[1]*Children's Hospital of Pittsburgh of UPMC, Pittsburgh, United States,* [2]*University of Pittsburgh, Pittsburgh, United States,* [3]*University of Michigan, Ann Arbor, United States,* [4]*University of Illinois at Chicago, Chicago, United States*

Objectives: We have reported an increase in overweight (BMI percentile ≥ 85th) after onset of T1DM in children. It is unknown whether it is associated with changes in insulin reserve.

Methods: Children <19 years, diagnosed with T1aDM from January 1st 2004 to December 31st 2006 were included (n = 163). Autoantibodies (ICA, insulin, GAD and IA2) were measured. Post-meal c-peptide (CP) levels were assessed at onset and follow-up visits (FU) 1, 2, 3 and 4 (2.5 ± 1.2, 7.2 ± 3.3, 14.4 ± 4.2 and 19.9 ± 3.1 months after onset respectively).

Results: About 95% were Caucasian, 44% female, mean age at onset 9.4 ± 3.8 years, mean BMI percentile 50.3 ± 33.5 increased to 72.9 ± 20.5 at FU1. At onset 21% were overweight, at FU1 35%. There was a positive correlation between onset BMI percentile and CP (r = 0.325, P < 0.001). About 6% of the children had CP > 1.5 ng/ml. This increased to 51% at FU1, 38% at FU2, 21% at FU3 and 10% at FU4. Change in BMI percentile from baseline to FU1 was unrelated to changes in CP from baseline to FU1, FU2, FU3 and FU4 in the total group and in children <10 years. In children ≥10 years who were not overweight at onset (n = 53) but became overweight at FU1, larger increases in CP between onset and FU2, FU3 and FU4 were seen compared to those who did not become overweight (median [interquartile range] FU2 2.5 [0.6–4.4] vs. 0.8 [−0.02–1.7], FU3, 2.5 [−0.1–4.3] vs. 0.3 [−0.3–1.0], FU4 0.6 [−0.4–3.5] vs. −0.01 [−0.4–0.6] respectively P < 0.05), remaining significant when controlling for race, gender, HbA1c at onset and at FU1. In children who became overweight at FU1 vs. those who did not, HbA1c was higher at onset (14.0 ± 2.1 vs. 12.5 ± 2.4%) but lower at FU1 (6.8 ± 0.9 vs. 7.1 ± 0.9%).

Conclusions: These data suggest that older children with T1aDM who become overweight after diagnosis have greater insulin reserve, suppressed at onset by glucotoxicity and respond to therapy with increased CP secretion, which may contribute to improved control. CP levels, especially at 2–3 months after onset, may be high despite the presence of autoimmunity.

O/2/WED/06

Effect of GAD-ALUM treatment in type 1 diabetic children: 4 years follow-up

J. Ludvigsson[1], M. Hjorth[1], M. Chéramy[1], S. Axelsson[1], M. Pihl[1] & R. Casas[1]

[1]*Division of Pediatrics, Department of Clinical Experimental Medicine, Linköping, Sweden*

In a phase II trial, we have shown that injection of alum-formulated GAD_{65} (GAD-alum) may contribute to the preservation of residual insulin secretion in children and adolescents with recent-onset Type 1 diabetes. The treatment also induced a GAD_{65}-specific immune response.

Aim: To assess if the effect on beta cell function and the GAD_{65}-specific immune response persisted still 4 years after treatment.

Material and design: Fifty nine of the 70 type 1 diabetic patients who participated in our previous trial, (at inclusion 2005 10–18 years old) accepted to participate in a 4 years follow-up. They had received a primary injection of 20 μg recombinant human GAD-alum (n = 29) or placebo (n = 30), and a booster

dose 4 weeks later. Serum C-peptide was analyzed to evaluate beta cell function. GADA was measured, and safety was assessed by clinical history and physical examination.
Results: Fasting serum C-peptide levels tended to be higher in children who treated with GAD-alum compared to placebo (P = 0.059). In those treated <6 months after diagnosis, fasting C-peptide was higher by month 48 in the GAD-alum group (n = 10) than in the placebo group (n = 12) (P = 0.036). In the patients treated with GAD-alum, GADA levels remained higher (P = 0.034). No treatment-related adverse events occurred during the 4 years follow-up.
In conclusion, the preservation of fasting c-peptide and immunomodulatory effect of GAD-alum, previously seen after 30 months, was maintained still after 4 years, without any adverse events.

O/2/WED/07

Younger age at diabetes diagnosis increases risk of coeliac disease

A. Pham[1], K.C. Donaghue[1,2], A. Chan[1] & M.E. Craig[1,2]
[1]*The Children's Hospital at Westmead, Institute of Endocrinology and Diabetes, Sydney, Australia,* [2]*The University of Sydney, Sydney, Australia*

Objectives: To determine the prevalence of biopsy-confirmed coeliac disease (CD) in a large diabetes clinic population and to assess whether younger onset of childhood diabetes confers greater risk of CD than older onset diabetes.
Research design and methods: Retrospective cohort study of 4,541 young people (aged ≤18 years) with Type 1 Diabetes Mellitus (T1DM) attending The Children's Hospital at Westmead (CHW) from 1990 to 2009. Results and seroconversion of CD screening tests (anti-gliadin IgA/IgG, anti-endomysial IgA and/or tissue transglutaminase IgA antibodies) and small bowel biopsy reports were analysed. Patients were stratified by age group at diabetes diagnosis (< 5 years, 5–9.9 and ≥10 years) for analysis.
Results: There were 185 patients diagnosed with CD over the 20 years; prevalence increased from 1% in 1990 to 4.9% in 2009 (P < 0.001). CD was diagnosed within 1 year in 33%, 48% in 2 years, 78% within 5 years, and 94% in 10 years. The prevalence was highest in the <5 age group (6.8%), (see table 1, P < 0.001) of whom 43% seroconverted at a mean duration of 4.7 years.
Conclusion: The prevalence of CD in children and adolescents with T1DM has significantly increased over the past 19 years. This may reflect newer assays for detection of CD. Children with younger age of diabetes onset are at greater risk of CD, but were diagnosed after longer diabetes duration and were more likely to seroconvert.

Table 1. Characteristics of patient group

	T1DM diagnosis (years)	CD diagnosis (years)	Time between diagnoses (years)	Prevalence	Mean number of tests prior to CD diagnosis	Patients who seroconverted
Total group (n = 185)	6.7 ± 3.9	9.7 ± 3.8	2.1 ± 3.0	4.1%	3.8	32
Age group at diabetes diagnosis						
<5 years (n = 80)	2.6 ± 1.3	6.3 ± 3.4	3.3* (0–14.3)	6.8%**	2.2 ± 1.2	22/51
5 to < 10 years (n = 61)	7.7 ± 1.3	10.0 ± 2.6	2.1 (0–10)	3.8%	2.2 ± 1.5	8/32
>10 years (n = 44)	11.6 ± 1.5	13.2 ± 1.6	0.72* (0–3.8)	2.5%**	1.7 ± 0.9	2/32
			* P < 0.001	**P < 0.001		

O/2/WED/08

Effect of physical exercise on bone density and remodeling in egyptian type 1 diabetic osteopenic adolescents

S.A. Elhabashy[1], O.M. Said[1], M.H. Agaiby[1], A.A. Abdelrazek[1] & S. Abdelhamid[1]
[1]*Ain Shams University, Cairo, Egypt*

Background: The study was planned to assess effect of physical exercise on bone remodeling in type I diabetics with osteopenia.
Methods: Twenty-four type I osteopenic diabetics (10 females and 14 males) were compared to thirty-eight age- and sex-matched healthy control individuals (20 females and 18 males). Patients and controls were assessed for bone densitometry by Dual Energy X-ray Absorptiometry (DEXA) at neck femur. Laboratory investigations included serum and urinary calcium, inorganic phosphorus, alkaline phosphatase, and serum aminoterminal (N_) propeptide of procollagen I (PINP). Diabetic osteopenic patients and controls were comparable with respect to serum as well as urinary biochemical parameters of bone mass namely, calcium, phosphorus and total serum alkaline phosphatase.
Results: Osteopenic patients displayed lower mean serum PINP than control group (20.11 ± 6.72 μg/dl vs. 64.96 ± 34.89 μg/dl; P < 0.05). A positive correlation was observed between BMD and degree of glycemic control reflected by serum glycated hemoglobin (r = −0.44, P = 0.030). Bone densitometry correlated with serum P1NP (r = 0.51, P = 0.011). After a planned regular exercise for 3 months, serum PINP and BMD levels increased with percentage change of 40.88 ± 31.73 and 3.36 ± 2.94, respectively. Five patients resumed normal densitometry and they were all males.
Conclusion: Diabetic osteopenic patients displayed lower serum levels of procollagen 1 propeptide (n-terminal) which reflects poor bone formation. A 3-months planned exercise program was associated with improvement of bone densitometry and significant increment of serum PINP.

Recent Results in the Epidemiology of Childhood Diabetes

O/3/WED/01

First trimester cytokine levels in mothers to children diagnosed with islet autoimmunity or type 1 diabetes before eight years of age

S. Resic Lindehammer[1], M. Fex[1], K. Marsal[2], Å. Lernmark[1] & Diabetes Prediction in Skåne DiPiS Study
[1]*Diabetes and Celiac Disease, Clinical Sciences, Lund University, Malmö, Sweden,* [2]*Department of Obstetrics and Gynecology, Clinical Sciences, Skåne University Hospital SUS, Lund, Sweden*

Objectives: We tested whether Th1/Th2 cytokines during the first trimester were different between mothers who gave birth to children who developed islet autoimmunity at 1–8 years of age and matched control mothers.
Methods: First trimester serum samples were analyzed for IFNγ, IL-10, IL-12, IL-13, IL-1β, IL-2, IL-4, IL-5, IL-8 and TNFα. We compared 53 non-diabetic mothers (participating in the Skåne Diabetes Prediction Study (DiPiS)) who gave birth to a child who developed at least two islet autoantibodies against either GAD65, IA-2 or insulin with increasing levels at follow-up (a total of 40 children developed type 1 diabetes before 8 years of age) with 106 non-diabetic control mothers which were matched by age, HLA genotype as well as first trimester sampling date. Blood samples were obtained during the first trimester at the time of delivery.
Results: The median of IFNγ ($P = 0.02$) and IL-1β ($P = 0.04$) levels were significantly higher in the index mothers compared to the controls. The mean length of gestation in the index mothers was 275 days compared to 280 days in control mothers ($P = 0.04$). The shortened gestational length was significantly correlated to IL-10 ($P = 0.03$), IL-12 ($P = 0.01$), IL-13 ($P = 0.04$), IL-2 ($P = 0.04$) and IL-5 ($P = 0.008$).
Conclusion: This study revealed that
1) index mothers had elevated Th1 mediated cytokines (IFNγ and IL-1β) during the first trimester;
2) gestational length was significantly shortened in the index mothers; and that
3) several Th2 mediated cytokines were inversely related to the gestational length in the index but not in the control mothers, in first trimester samples.
We therefore conclude that an increase in Th1 cytokine levels during the first trimester may signify gestational infection or stress. Furthermore, we conclude that Th2 cytokines may affect gestational length. In summary, these aberrations may contribute to an increased risk for islet autoimmunity and subsequent development of type 1 diabetes in the offspring.

O/3/WED/02

Changing pattern in incidence of type 1 diabetes in Hungarian children over 1989–2008

E.K. Gyurus[1], G. Soltesz[1]& Hungarian Childhood Diabetes Epidemiology Group
[1]*Pediatrics, Faculty of Medicine, University of Pecs, Pecs, Hungary*

Objective: To analyze secular trends in incidence of type 1 diabetes in Hungarian children aged 0–14 years over the period 1989–2008. To investigate geographical variation in the incidence of type 1 diabetes.
Methods: New cases of type 1 diabetes in children aged 0–14 years were prospectively registered from 1989 to 2008. The level of ascertainment was estimated by the capture-recapture method. Temporal trends in incidence were analysed using Poisson regression models.
Results: A total of 3240 patients (1666 boys; 1574 girls) were identified; the male:female ratio was 1.05. The overall standardized incidence rate was 11.9/100000/yr (95% CI 11.5–12.3) for the 20-year period; 9.8/100000/yr (95% CI 9.3–10.4) from 1989 to1998 and 14.3/100000/yr (95% CI 13.7–14.9) from 1999 to 2008. There was a significant linear increasing trend in incidence over 1989–2008 ($P < 0.001$), showing a mean rate of 4.6% per annum. With a mean rate of 6% the highest relative annual increase was observed in the youngest children (0–4 years). Although the age-group specific incidence rate was still highest in the 10–14-year-old children for the whole period, with a mean rate of 16.5/100000/yr the 5–9 years old girls had the highest incidence rate over the last 10 years. The cumulative risk of the disease was 0.43 per 1000 in the age group 0–4 years, 1.1 in the age group 5–9 years and 1.8 in the age group 10–14 years.
Conclusion: The incidence of type 1 diabetes in Hungarian children continues to increase even faster than before. The incidence trend shows a different pattern as observed earlier, indicating a shift toward an earlier age in girls, but not in boys.

O/3/WED/03

Growth Differences between North American and European Children at Risk for Type 1 Diabetes

A.M. Nucci[1], D.J. Becker[2], S.M. Virtanen[3,4], D. Cuthbertson[5], B. Softness[6], C. Huot[7], R. Wasikowa[8], H.M. Dosch[9], H.K. Akerblom[10,11], M. Knip[12] & The TRIGR Study Group
[1]*Georgia State University, Atlanta, United States,* [2]*Children's Hospital of Pittsburgh of UPMC, Pittsburgh, United States,* [3]*National Institute for Health and Welfare, Helsinki, Finland,* [4]*University of Tempere, Tampere, Finland,* [5]*University of South Florida, Tampa, United States,* [6]*Columbia University College of Physicians and Surgeons, New York, United States,* [7]*CHU Ste. Justine, Montreal, Canada,* [8]*Medical University of Wroclaw, Wroclaw, Poland,* [9]*The Hospital for Sick Children, Toronto, Canada,* [10]*Hospital for Children and Adolescents, Helsinki, Finland,* [11]*Folkhalsan Research Center, Helsinki, Finland,* [12]*Tampere University Hospital, Tampere, Finland*

Objective: The incidence of type 1 diabetes (T1D) is increasing globally, particularly in young ages. Measures of pediatric growth shown to be risk factors for childhood T1D include elevated birth weight, and subsequent increased height, weight and body mass index (BMI). Our objective was to evaluate anthropometric variations in an international population of children with a first-degree relative with T1D and increased HLA-defined genetic risk.
Methods: With recruitment completed, anthropometric indices at birth, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months of age were compared amongst regions and by T1D proband in 2160 children who participated in the TRIGR study.
Results: Children in Northern Europe had the highest weight between birth-12 months of age and the greatest length between 9–24 months ($P < 0.001$). Children in Southern Europe had the lowest weight and length/height at most time points ($P < 0.001$). Using International Obesity Task Force criteria, the obesity rate at 60 months of age was lowest in Central Europe II countries (3.1%) and highest in Canada (8.8%). In children of mothers without T1D the obesity rate at 60 months was lowest in Australia and Central Europe II (0.0%) and highest in the USA (8.6%). This differs from offspring of mothers with T1D in whom the lowest and highest obesity rates appeared in the USA (4.7%) and Canada (14.1%), respectively and is unrelated to their birth

weight. Infants with mothers with T1D had a higher birth weight than those with an affected father or sibling only in NEUR ($P < 0.001$).

Conclusions: There are regional differences in early childhood increases in growth that are consistent with the higher incidence of type 1 diabetes in Northern Europe and Canada as compared to Southern Europe. Our prospective study will allow prospective evaluation of relationships between obesity and the later development of autoimmunity and T1D in this at-risk population of children.

O/3/WED/04

ZnT8 autoantibody specificities at, and 3–5 years after clinical onset, associates with the age at diagnosis and the SLC30A8 gene polymorphism in Danish children with type 1 diabetes

J.S. Sørensen[1], F. Vaziri-Sani[2], F. Pociot[3], K. Kristensen[4], C. Brorsson[3], L. Lyngsoe[5], B. Dolmer[6], N.H. Birkebaek[4]

[1]*Department of Clinical Immunology, Aarhus University Hospital, Skejby, Aarhus, Denmark,* [2]*Department of Clinical Sciences, University Hospital MAS, UMAS, Malmoe, Sweden,* [3]*Hagedorn Research Institute, Copenhagen, Denmark,* [4]*Pediatric department, Aarhus University Hospital, Skejby, Aarhus, Denmark,* [5]*Pediatric Department, Hillerød Hospital, Hillerød, Denmark,* [6]*Pediatric Department, Næstved Hospital, Næstved, Denmark*

Objective: A polymorphism in the SLC30A8 gene encoding the membrane zinc transporter 8 protein (ZnT8) have recently been shown to be important for the specificity of the diabetes specific ZnT8 autoantibodies (ZnT8A). In this study we have reported the prevalence of the three ZnT8A variants at, and 3–5 years after onset of diabetes (T1DM). Further, the associations of the ZnT8A with age at diagnosis and with the SLC30A8 genotypes have been studied.

Methods: Two hundred and twenty four children and adolescents (114 males) with median (range) age of 13.7 years (4.8–18.9), with diabetes onset before the age of 15 years, and T1DM for 3–5 years, were included. Fifty-two patients were younger than 6 years at diagnosis. Patients were genotyped for the single nucleotide polymorphism, rs13266634 by Taqman assay. ZnT8RA, ZnT8WA and ZnT8QA were assessed at the onset and 3–5 years after the diagnosis of T1DM.

Results: At the clinical onset of T1DM the distribution of ZnT8A was: ZnT8RA – 65%, ZnT8WA – 60%, ZnT8QA – 46%. A total of 73 % were positive for one or more ZnT8A. After 3–5 years the distribution of ZnT8A was: ZnT8RA – 47%, ZnT8WA – 43%, ZnT8QA – 42%. A total of 61% were positive for one or more ZnT8A. Compared to children older than 6 years at diabetes onset, a lower frequency of ZnT8A positivity at debut was found in children with onset before 6 years of age ($P < 0.01$). ZnT8RA correlated to the CC genotype ($P < 0.01$) and ZnT8WA correlated to the TT genotype ($P < 0.04$) at onset and after 3–5 year T1DM.

Conclusion: ZnT8A are important markers of T1DM autoimmunity in children at T1DM onset and after 3–5 years. The ZnT8A positivity is less in the youngest age group. We could confirm the correlation between SLC30A8 genotypes and ZnT8A specificity in Danish children.

O/3/WED/05

Early life determinants of paediatric onset type 1 diabetes mellitus with a focus on low sun exposure

A.-L. Ponsonby[1,2,3], A. Pezic[1], F. Cameron[1,2], C. Rodda[4], J. Ellis[1], J. Halliday[1], J. Carlin[1,2], T. Dwyer[1,2,3]

[1]*Murdoch Childrens Research Institute, Melbourne, Australia,* [2]*Department of Paediatrics, University of Melbourne, Melbourne, Australia,* [3]*University of Tasmania, Menzies Research Institute, Hobart, Australia,* [4]*Paediatric Endocrinology and Diabetes, Monash Medical Centre, Melbourne, Australia*

Objective: To investigate the aetiology of type 1 diabetes mellitus (T1DM) in a location where 95% of vitamin D stores are sunlight-derived.

Methods: A case-control study of children under the age of 15 years residing in Melbourne, Victoria during 2008–2011. Cases have incident T1DM. Community controls are age-matched and selected from randomly selected schools and child health clinics. Hospital controls are day care surgery attendees. Measures include objective measures of past child sun exposure including ultraviolet fluorescence photography of the eye surface, surface casts of the hand, and skin pigmentation by spectrophotometer. Child salivary or plasma 25OHD levels will be measured as well as levels within archived neonatal dried blood spot cards (1).

Results: Cases were more likely than siblings to have lighter skin pigmentation at the upper arm (AOR 0.69 (95% CI: 0.52, 0.90)) and lower infant sun exposure AOR 2.43 (95% CI: 0.91, 6.51). (2) Among cases presenting 2008–2009, (n = 186, 72% of eligible) higher ambient sunlight levels six months prior to diagnosis was associated with lower GAD antibody levels (beta = −0.028, se = 0.011, p value = 0.01, increase in logged 2 GAD units per increase in UVR standard erythemal dose) at first presentation.

Conclusions: These preliminary results add further to the growing evidence that low vitamin D stores or low sunlight exposure in fetal and child life may increase the risk of autoimmune diseases (3) such as T1DM.

References: (1) Eyles DW et al. The utility of neonatal dried blood spots for the assessment of neonatal vitamin D status. Paediatr Perinat Epidemiol 2010; 24: 303–308.

(2) Ponsonby AL et al. A case-sibling assessment of the association between skin pigmentation and other vitamin D-related factors and type 1 diabetes mellitus. Photochem Photobiol 2009; 85: 1267–70.

(3) Staples J et al. Low maternal exposure to ultraviolet radiation in pregnancy, month of birth, and risk of multiple sclerosis in offspring: longitudinal analysis. BMJ 2010; 340: c1640.

O/3/WED/06

Association of the WFS1 gene with disease progression in children with new onset T1D. Results from the Hvidoere study group on childhood diabetes

L.B. Nielsen[1], M.L.M. Andersen[1], J. Svensson[1], S. Pörksen[1], P. Hougaard[2], P. Swift[3], H. Hoey[4], H.B. Mortensen[1], L. Hansen[1] & The Hvidoere Study Group on Childhood Diabetes

[1]*Glostrup and Herlev University Hospital, Herlev, Denmark,* [2]*University of Southern Denmark, Odense, Denmark,* [3]*Leicester Royal Infirmary Children's Hospital, Leicester, United Kingdom,* [4]*University of Dublin, National Children's Hospital, Dublin, Ireland*

Objective: The wolframin gene, WFS1, encodes a glucoprotein involved in the calcium homeostasis of the endoplasmatic reticulum; WFS1 is critical for the function and survival of the pancreatic beta-cells. Genetic variation within the WFS1 gene is

known to be associated with T2D and for rare variants the Wolfram syndrome.
The aim of this study was to investigate the impact of a common genetic variant (rs10010131) of the WFS1 gene on disease progression in a group of children newly diagnosed with T1D.
Methods: The study is a multicenter longitudinal investigation with 18 participating paediatric centres from 15 countries. Clinical information and blood samples were collected from 275 children less than 16 years at diagnosis and at 1, 6, and 12 months after onset. Genotyping of the rs10010131 variant was done by KBioscience using an in-house KASPar assay system. Statistics: C-peptide, HbA_{1c}, $IDAA_{1c}$ and proinsulin were analysed by multiple regression using age at onset, gender, DKA at onset, HLA class II risk groups, and genotypes as explanatory factors in a compound symmetric repeated measurement model.
Results: The genotype frequencies were: 17% (AA), 48% (AG), 35% (GG), where the G allele is the wildtype allele. In a dominant model the G allele carriers of the rs10010131 variant was significantly positively associated with stimulated C-peptide (est.: 1.73, $P < 0.0001$), negatively with HbA_{1c} (est.: −0.49, $P = 0.005$), negatively with $IDAA_{1c}$ (est.: −0.67, $P = 0.02$) and positively with proinsulin (est.: 1.55, $P = 0.005$) the first 12 month after disease onset compared to the AA genotype carriers.
Conclusions: A common variant of the WFS1 gene is highly associated with better residual beta-cell function and corresponding better metabolic control during disease progression in new onset T1D compared to AA genotype carriers. Thus, genotyping WFS1 might serve as a suitable selection tool for patients eligible for beta-cell regenerative intervention studies.

O/3/WED/07

The incidence of childhood onset type 1 diabetes in norway is steadly increasing for both sexes

T. Skrivarhaug[1,2], L.C. Stene[3], H. Strøm[3], A.K. Drivvoll[2], P.R. Njølstad[4], G. Joner[1] & The Norwegian Childhood Diabetes Study Group
[1]*Department of Pediatrics,Oslo University Hospital, Ullevaal, Oslo, Norway,* [2]*Oslo University Hospital, Ullevaal, The Norwegian Childhood Diabetes Register, Oslo, Norway,* [3]*Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway,* [4]*Department of Pediatrics, Haukeland University Hospital, Bergen, Norway*

Objectives: There is a global increase of type 1 diabetes (T1DM). Since 1989 the Norwegian population-based childhood diabetes register is including all newly diagnosed children aged 0–14 yrs. with diabetes. All paediatric departments in Norway reports new cases of childhood diabetes to The Norwegian Childhood Diabetes Register (NCDR). Since 2004 the Prescription Database (NorPD) at the National Institute of Public Health has registered all drug prescription in Norway, including insulin. It has been an increasing trend in the incidence of childhood onset type 1 diabetes during the period 1973–2003 with IR moving from $19.1/10^5$ in 1973 to $28.9/10^5$ in 2001–2003. The aim of the study was to determine the incidence of T1DM in children 0–14 years in Norway, and to calculate the ascertainment in the nationwide NCDR during the same period.
Methods: During the study period 2005–2008, 1232 new cases of childhood onset diabetes were registered by the NCDR. Of these, 1144 were classified as T1DM and age 0–14 years at onset. Information on individual insulin prescriptions was obtained from NorPD, and the first prescription of insulin 2004–2008 was registered and assumed to be at a date close to onset of T1DM. New cases in the NorPD could only be defined for the years 2005–2008. The assumption of source independence and equal probability of capture of each case by these two sources is verifiable. This is the first time these two registries are linked with the purpose to give information about incidence of childhood T1DM and completeness of the NCDR.
Results: In the period 2005–2008, the uncorrected incidence rate of T1DM 0–14 years was $32.4/10^5$/year for both sexes, for boys $34.1/10^5$ and for girls $30.9/10^5$, which indicates an increasing trend compared to previously published incidence rates. The completeness of NCDR is calculated to 92% for the whole study period.
Conclusions: In Norway the incidence of T1DM in children is steadily increasing.

O/3/WED/08

Thirty Years of Prospective Nationwide Incidence of Childhood Type1 Diabetes – The Accelerating Increase by Time Tends to Level off in Sweden

Y.T. Berhan[1], I. Waernbaum[2], T. Lind[1], A. Mollsten[1], G.G. Dahlquist[1], Swedish Childhood Diabetes Study Group
[1]*Umea University, Department of Clinical Sciences, Pediatrics, Umea, Sweden,* [2]*Umea University, Department of Statistics, Umea, Sweden*

Objectives: Over the past decades rapidly increasing incidence of childhood T1D has been reported from many parts of the world. The change over time has been partly explained by changes in lifestyle causing rapid early growth and weight development. In the present 30 years follow up (1978–2007) of the Swedish Childhood Diabetes Register (SCDR) we describe the current time trend by age, sex and birth cohort, and analyze the changes in incidence using statistical models. We also aim to discuss the possibility to predict numbers of new cases of childhood onset T1D using generalised models over long periods of time. For discussion we examine possible correlations between time trend in T1D incidence and indicators that mirror calorie-intake.
Methods: The present analysis involved 14 721 incident cases recorded in the SCDR during 1 January 1978–31 December 2007. Generalized additive models were fitted for poisson distributions and the impact of calendar year at onset in five years age groups, sex and interaction terms were tested.
Results: Age and sex specific incidence rates varied from 21.6 (95% CI 19.4–23.9) during 1978–1980 to 43.9 (95% CI 40.7–47.3) during 2005–2007. Cumulative incidence shifted to younger age at onset over the first 22 years, but from the birth year 2000 a reversed trend was seen. Using a model including all calendar years, age and sex the predicted number of incident cases may almost triple the next 30 years period (648 in year 2007 and 2294 in year 2037). An ecological analysis using soft drink consumption as a marker for eating habits and high energy intake showed a strong correlation with incidence rate in Sweden ($R^2 = 0.84$).
Conclusions: Childhood T1D increased dramatically and shifted to younger age at onset the first 22 years of the study period, but since year 2000 for the first time we report a reversed trend. The predicted almost tripling of incident cases over the next 30 years is thus probably an overestimation.

Psychosocial Issues & Education in Diabetic Youth

O/4/FRI/01

Mental state at diagnosis predicts intellectual outcome in children 6 months after diagnosis of type 1 diabetes

C. Nadebaum[1], S.E. Scratch[1], E. A. Northam[2,3], F.J. Cameron[4] & Diabetic Ketoacidosis and Brain Injury Study Group
[1]*Child Neuropsychology, Murdoch Childrens Research Institute, Melbourne, Australia,* [2]*Department of Psychology, Royal Children's Hospital, Melbourne, Australia,* [3]*Department of Psychology, University of Melbourne, Melbourne, Australia,* [4]*Department of Endocrinology and Diabetes, Royal Children's Hospital, Melbourne, Australia*

Objectives: Children with type 1 diabetes are at risk of impaired intellectual functioning in the years following diagnosis. We aimed to determine whether mental state at diagnosis predicts longer-term intellectual outcomes.
Methods: This study formed part of a larger longitudinal project examining pathophysiology and neuropsychological outcomes in diabetic patients with or without diabetic ketoacidosis. Participants were 25 girls and 38 boys (mean age 11.6 years, SD 2.9 years) who presented with a new diagnosis of type 1 diabetes at the Royal Children's Hospital, Melbourne. Twenty-five children had impaired mental state on the day of diagnosis, as measured by the school-years screening test for the evaluation of mental status (SYSTEMS). Intellectual abilities were assessed six months post-diagnosis using the Wechsler Intelligence Scale for Children – Fourth Edition.
Results: Children with impaired mental state at diagnosis had significantly lower Full Scale IQ at six months compared to those with unimpaired mental state, $F(1.56) = 11.87$, $P = 0.001$. Covariates included gender, age, diabetic ketoacidosis at diagnosis, socioeconomic status, and blood glucose level at the six month assessment, none of which were significant predictors of outcome. More detailed examination of results revealed that Perceptual Reasoning ($P = 0.001$) and Working Memory ($P < 0.001$) indices were significantly lower in the group with impaired mental state. Although Processing Speed scores were not significantly reduced, the group with impaired mental state made significantly more errors on timed tasks ($P = 0.030$).
Conclusions: Mental state at diagnosis is a significant predictor of intellectual function 6 months after diagnosis of type 1 diabetes. Clinicians may consider using a child-specific mental state screening measure such as the SYSTEMS for all newly diagnosed diabetic children to identify children at risk of cognitive sequelae.

O/4/FRI/02

Intervenient variables in the acceptance of a diabetes educational program in children and its impact on the pillars of the treatment. repercussion over metabolic control

A.M. Figueroa Sobrero[1], F. Walz[2], N. Orzuza[1], E. Baraballe[1], A. Perez de Laporta[1], S. Panzitta[1] & J.C. Cernuda[1]
[1]*Hospital M.I. 'San Roque', Entre Ríos, Paraná, Argentina,* [2]*Universidad Nacional del Litoral-Facultad de Bioquímica y Ciencias Biológicas, Departamento Matemático – Area Bioestadística, Santa Fe, Argentina*

Diabetes Education Programs (DEP) have come neither to a universal consensus structure nor reached all patients in the same way demanding, consequently, an analysis of the influence factors and the consequences of its application.
Objectives: To establish associations between family functioning style and school performance in type 1 Diabetic (T1D) children versus the acceptance degree of the DEP; to determine dependence between the DEP acceptance degree and the main variables of the treatment and to compare the glycosylated haemoglobin average levels among the DEP acceptance degree categories.
Methods: A total of 86 T1D patients, aged from 10 to 19 were studied. The degree of acceptance was measured by Licker scale. Intervenient evaluated variables considered for the acceptance of the DEP: school performance and family functioning style. Main variables observed: nutrition, physical activity, theoretical and practical diabetic knowledge. The metabolic control was determined by the HbA1C levels.
Results: School performance and family functioning style had a significant influence in the acceptance of the DEP (P-value = 0.002 and 0.001). A high grade of acceptance of the DEP impacts positively on the main variables: nutrition, physical activity, practical diabetic knowledge (P-value = 0.003, 0.001 and 0.001), but such relationship was not observed with Theoretical Knowledge (P-value = 0.12). The HbA1C average level was significantly lower in patients with DEP high acceptance grade (P-value = 0.001). A positive association was determined between parents' Theoretical Knowledge versus children's within the group with good acceptance of the DEP (P-value = 0.007).
Conclusions: A DEP high level of acceptance leads to a better observance of the treatment resulting in a better metabolic control. When a DEP is presented, it is important to consider the family functioning style and school performance of T1D children because of its relevance in the degree of acceptance.

O/4/FRI/03

Lower achieved A1C among adolescents with lower perceived A1C goal

R.P. Wadwa[1], M.D. Anger[2], F.K. Bishop[1], E. Cruz[1], G.J. Klingensmith[1] & D.M. Maahs[1]
[1]*Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, Aurora, United States,* [2]*School of Medicine, University of Colorado Denver, Aurora, United States*

Debate exists regarding optimal A1C goals for youth with type 1 diabetes (T1D). Scant data are available on how goals relate to achieved A1C. In a cohort of 13–19 year old youth with T1D for >5 years, we hypothesized that youth aware of A1C goals would be more likely to achieve lower A1C levels compared to those not aware of A1C goals. Data from 213 subjects with T1D (53% male, 85% non-Hispanic white, age 16.1 ± 1.7 years, T1D duration 9.0 ± 3.1 years, mean A1C 9.1 ± 1.6%) were obtained by a survey including questions regarding awareness of guidelines for A1C targets. ISPAD guidelines were used to define A1C goal (A1C < 7.5%). Almost all subjects (n = 210) reported they were told their goal A1C by a healthcare provider. Of those claiming to know their goal A1C (n = 190), only 16 (8%) were correct. An additional 10% (n = 20) thought their A1C goal was a range that included the actual goal. In the entire cohort, 32 subjects (15%) had A1C levels in target range. Mean A1C for these subjects was 7.0 ± 0.4% compared to a mean A1C of 9.5 ± 1.5% for the 181 subjects with A1C above goal ($P < 0.0001$). Among subjects with A1C in goal range, none knew the correct goal. However, 84% of subjects in goal (compared to 59% of subjects above goal) thought their A1C goal was lower than the actual goal ($P < 0.01$). Subjects with A1C in goal range were more likely than those with A1C above goal to use insulin pumps (66% vs. 34%, $P < 0.01$). Male subjects with A1C above

goal had lower A1C levels than females with A1C above goal (9.1 ± 1.3% vs. 9.9 ± 1.6%, P < 0.001). In this cohort of adolescents with T1D, few reached A1C goals and subjects who reached A1C goals were more likely to believe their goal A1C was lower than the ISPAD recommended goals. These findings suggest that lower A1C goals may lead to improved glycemic control, although we do not have data on whether lower goals are associated with more severe hypoglycemia or psychosocial distress.

O/4/FRI/04

Parental health literacy and glycemic control in young children with type 1 diabetes

E.R. Pulgaron[1], A.M. Patino-Fernandez[1], D. Wile[1], J. Sanchez[1], L. Sanders[1] & A. Delamater[1]
[1]*Miller School of Medicine, University of Miami. Miami, FL, USA*

Objective: A recent study reported that in adolescents with intensive insulin regimens, parents' health literacy was associated with better diabetes management (Janisse, Naar-King & Ellis, 2010). The present study examined the relationship between parental health literacy and glycemic control in a sample of young children with type 1 diabetes (T1D). We hypothesized that parents with lower health literacy would have children with poorer glycemic control.
Methods: Participants were recruited at their child's regularly scheduled diabetes clinic visits. Fifty-two English-speaking primary caregivers completed a measure of health literacy (Short Test of Functional Health Literacy in Adults; S-TOFHLA), a measure of diabetes-specific numeracy (the PDNT-14), and a measure of diabetes self-efficacy. Caregivers also provided demographic information and the child's medical history were obtained by medical chart review.
Results: Most caregivers were mothers (86%) with a mean age of 38.39 (SD = 6.51). About half of the sample (55%), was receiving financial assistance from the government. The children in the study were 3–9 years old (M age = 6.77, SD = 2.08), diagnosed with T1D for at least one year, and had a mean HbA1c level of 8.46 (SD = 1.38). Higher child HbA1c was associated with lower parent health literacy (r = −0.36, P = 0.02) and numeracy (r = −0.42, P = 0.01) skills. When controlling for maternal education, literacy was still a significant predictor of HbA1c (β = −2.56, P = 0.01) but numeracy was not. Additionally, caregivers who reported lower diabetes self-efficacy had children with higher HbA1c (r = −0.55, P = 0.02), but self-efficacy did not mediate the relationship between health literacy or numeracy and HbA1c.
Conclusions: Parents with low literacy and numeracy skills have children with higher HbA1c, suggesting difficulty with T1D management tasks. Parents would likely benefit from interventions targeting health literacy and numeracy or diabetes education in more practical and simpler forms.

O/4/FRI/05

Five-factor personality traits, metabolic control, negative affect and coping in adolescents with type I diabetes: a three year longitudinal investigation

D. Waller[1], C. Johnston[1], L. Smith[2], J. Overland[2,3] & K. Hatherly[2]
[1]*University of Western Sydney, Sydney, Australia,* [2]*University of Sydney, Sydney, Australia,* [3]*Royal Prince Alfred Hospital, Sydney, Australia*

Adolescence can be a particularly difficult period for an individual with type I diabetes. People in this cohort often exhibit poor metabolic control and are at increased risk for psychological morbidity. Whilst research has implicated the role of adolescent personality in metabolic control, its links to coping and negative affect in type I diabetes has received little attention. The aim of this study was to investigate the role of personality in metabolic control, coping, and negative emotion in a sample of Australian youth with type I diabetes. A total of 155 children and adolescents with type I diabetes aged between 8 and 19 years at baseline participated in the three year longitudinal study. Participants completed the Five-Factor Personality Inventory for Children (FFPI-C), the Depression Anxiety Stress Scale-21 (DASS-21), and the Coping with Diabetes Inventory (CODI) annually over three years. Annual quantitative data on demographic, family and service factors were also gathered, along with an annual capillary blood sample to determine metabolic control. Initial correlational analyses of data highlighted the potential role of personality factors in negative affect, coping and metabolic control. Conscientiousness and Agreeableness were associated with metabolic control and coping (all p values < 0.05), whilst Emotional Regulation was associated with coping (P < 0.05) and negative affect (P < 0.05). Mixed-modelling was employed to further investigate the associations between these variables. This research suggests that personality appears to have a role, not only in the behavioural management of diabetes, but also in general psychological wellbeing. The researchers argue that coping and negative affect should not only be considered as predictors of metabolic control but as independent outcome measures in type I diabetes research.

O/4/FRI/06

HbA1c tracking in patients with type 1 diabetes – from diabetes onset in childhood, during puberty and adolescence into adulthood

S.E. Hofer[1], A. Naeke[2], A. Herbst[3], J. Rosenbauer[4], D. Dunstheimer[5], E. Lilienthal[6], W. Marg[7], R.W. Holl[8] & DPV Science Study Group
[1]*Department of Pediatrics, Medical University of Innsbruck, Innsbruck, Austria,* [2]*Department of Pediatrics, University of Dresden, Dresden, Germany,* [3]*Department of Pediatrics, Klinikum Leverkusen, Leverkusen, Germany,* [4]*Deutsches Diabeteszentrum Düsseldorf, Abteilung für Epidemiologie, Düsseldorf, Germany,* [5]*Department of Pediatrics, Klinikum Augsburg, Augsburg, Germany,* [6]*Department of Pediatrics, Ruhr University of Bochum, Bochum, Germany,* [7]*Klinikum Bremen Mitte, Bremen, Germany,* [8]*Department of Epidemiology, University of Ulm, Ulm, Germany*

Objectives: Metabolic control remains the most predictive value for the development of micro-and macro-vascular complications in type 1 diabetes.
Methods: This prospective longitudinal survey was designed to follow patients from disease onset in childhood over a prolonged period of time during puberty and adolescence until adulthood. Standardized electronic diabetes patients' documentation system broadly used in diabetes centers in Austria and Germany was used for data collection. Patients were recruited from 294 centers. About 12 095 patients with diabetes onset under the age of 10 were documented. Pre-pubertal, pubertal and post-pubertal HbA1c levels were available for consecutive analysis in 1 255 patients. The main outcome parameter was HbA1c, reflecting metabolic control.
Results: Mean age at diabetes manifestation was 6.6 (± 2.4) years, 52% were male. In the pre-pubertal stage HbA1c was 7.5 ± 1.2% (mean age 10.4 ± 1.1 years, mean diabetes duration 3.8 ± 1.9 years), during puberty HbA1c was 8.0 ± 1.2% (mean age 14.9 ± 0.6 years, mean diabetes duration 8.4 ± 2.5 years) and after puberty HbA1c was 8.4 ± 1.7% (mean age 18.6 ± 0.6 years, mean diabetes duration 12.1 ± 2.4 years). A highly significant correlation was found for pre-pubertal/pubertal (R = 0.54, P < 0.0001), pubertal/post-pubertal

($R = 0.70$, $P < 0.0001$) and pre-pubertal/post-pubertal HbA1c ($R = 0.35$, $P < 0.0001$). Dividing pre-pubertal patients into tertiles (1. good, 2. moderate, 3. poor metabolic control) HbA1c increased in each group, with the steepest increase in the first tertile (1. 6.4% (±0.4) – 7.3% (±0.3) – 7.8% (±1.4), 2. 7.4% (±0.3) – 8.0 (±0.9) – 8.3 (±1.5), 3. 8.8 (±0.9) – 8.8 (±1.3) – 9.1 (±1.9)).
Conclusion: This survey provides convincing evidence for long term tracking of metabolic control from childhood until adulthood and suggests an early focus on metabolic control with close to normal HbA1c levels in children with type 1 diabetes.

O/4/FRI/07

Digital sugarsquare leads to better appreciation of care and better communication between caregiver and adolescent with diabetes

E. Boogerd[1], C. Verhaak[1] & C. Noordam[2,3]
[1]*Department of Medical Psychology, Radboud University Nijmegen, Medical Center, Nijmegen, Netherlands,* [2]*Department of Pediatrics, Radboud University Nijmegen, Medical Center, Nijmegen, Netherlands,* [3]*Childreńs Diabetes Center Nijmegen, Nijmegen, Netherlands*

Objectives: Adolescence is often considered the most difficult phase in life for dealing with diabetes. Usage of new technologies (e.g. telecare or internet programs) in pediatric diabetes care show positive effects on self management of adolescents with diabetes. For the present study we developed an online digital treatment environment: sugarsquare. Sugarsquare facilitates for each user a personal secured treatment overview and an option for low-level individual contact with the treatment team. It also facilitates low-level contact among adolescents with diabetes. We studied the effects of sugarsquare on delivered care and on adolescents' psychosocial wellbeing.
Methods: Participants were 53 adolescents aged 11 to 21 ($M = 15.2$, $SD = 2.1$), who were treated by the Children's diabetes center Nijmegen (KDCN) for type 1 diabetes. Participants were randomly assigned to a control group or an experimental group. The control group received regular care. The experimental group received access to sugarsquare upon regular care. Data were gathered by means of questionnaires prior to (T0) and 9 months following (T1) access to sugarsquare. Questionnaires were aimed at patients' evaluation of care (PEQD), quality of life (PedsQL, diabetes module), confidence in self care (CIDS) and disease knowledge (DKT). Differences between groups were analyzed by means of Students' *t*-tests.
Results: Analyses reveal an increase in patients' evaluation of diabetes care in the experimental group ($t = -2.45$, sig < 0.05) between T0 and T1. The control group shows no change. Further, the experimental group shows an increase in quality of life, with regard to communication with the treatment team concerning diabetes ($t = 2.60$, sig < 0.05), although the control group shows no change. Other variables show no change over time in both groups.
Conclusions: Digital sugarsquare leads to better appreciation of delivered diabetes care and to more satisfaction on communication with the treatment about the disease.

O/4/FRI/08

Sibling's knowledge of diabetes and treatment

E. Goethals[1], D. Verbrugghe[2], T. Havermans[1] & K. Casteels[1]
[1]*Department of Pediatrics, University Hospital Leuven, Leuven, Belgium,* [2]*Department of Psychology, Katholieke Universiteit Leuven, Leuven, Belgium*

Objectives: Siblings of children with type 1 diabetes were tested on their knowledge of diabetes, to determine which topics they were less aware of and whether an education programme was needed.
Methods: A total of 38 siblings (10–18 years, 23 boys) completed a multiple-choice questionnaire of twelve questions constructed around diabetes-related topics (see table 1). Their mean age was 13 ± 2.3. All attended mainstream education (25 in secondary school, 12 in primary school and 1 at university). 22 siblings were younger than the child with diabetes.
Results: A total of 10 siblings (26%) obtained the maximum score of 12 correct answers, 17 scored 10 or 11 (45%), 9 (24%) scored 8 or 9 and 2 (5%) scored 7. Scores were related to age and to rank of sibling as older children had more correct answers ($r = 0.33$, $P < 0.05$ and $r = 0.35$, $P < 0.05$). Scores were not related to gender. Questions receiving the most incorrect answers were related to physical impact of lack of insulin and to the causes of hypoglycemia (see table 1).
Conclusions: This survey on a sample of 38 Belgian siblings of children with type 1 diabetes showed that many are well informed about their brother's or sister's diabetes. However, questions related to insulin deficiency and hypoglycemia were often answered incorrectly (39.5% and 73.7%). This suggests that generally there is good communication within families about diabetes and that siblings are concerned and involved with this issue. Growing up, they seem to learn more about diabetes. The results indicate that an education program on certain topics might be useful.

Table 1. Questions and correct answers

	Questions	% of correct answers
1.	What is diabetes	(97.4)
2.	Origin of insuline	(89.5)
3.	Physical impact of insulin deficiency	(39.5)
4.	Treatment needs	(94.7)
5.	Meaning of hypo	(94.7)
6.	Recognition of hypo	(94.7)
7.	Cause of hypo	(73.7)
8.	Treatment of hypo	(97.4)
9.	Meaning of hyper	(92.1)
10.	Recognition of hyper	(86.8)
11.	Usage of glucagon	(81.6)
12.	Limitations in sugar	(86.8)

Unraveling the Genetic Basis of Diabetes in Children

O/5/FRI/01

Monogenic diabetes in infants: time to extend genetic testing beyond the first 6 months of life?

O. Rubio-Cabezas[1,2], S.E. Flanagan[1], A. Damhuis[1], E.L. Edghill[1], A.T. Hattersley[1] & S. Ellard[1]

[1]*Peninsula Medical School, Institute of Biomedical and Clinical Science, Exeter, United Kingdom,* [2]*Hospital Infantil Universitario Niño Jesús, Endocrinology, Madrid, Spain*

Objectives: It is widely accepted that permanent diabetes presenting within the first 6 months of life is monogenic and mutations in three genes (*KCNJ11*, *ABCC8* and *INS*) account for over 50% of cases. In contrast, diabetes diagnosed after 6 months is most likely classic autoimmune type 1 diabetes although there may be a few patients with monogenic diabetes in the 6–12-month age range. We aimed to explore the prevalence of monogenic diabetes in infants presenting during the first year of life in order to define a more accurate cut-off age to consider genetic testing.

Methods: We studied a consecutive international series of 551 patients with diabetes diagnosed before 12 months. All had isolated diabetes or associated neurological features suggesting K_{ATP} channel mutations (developmental delay, epilepsy). Children with pancreatic agenesis and complex multisystemic syndromes were excluded. *KCNJ11*, *ABCC8* and *INS* were sequenced in all patients presenting before 6 months (n = 372) and in infants diagnosed thereafter whose pancreatic antibody status was negative or unknown (n = 141).

Results: Mutations were identified in 246 patients diagnosed before 6 months and in 18 diagnosed between 6 and 12 months (66% vs. 13%; P < 0.0001). *INS* mutations are the commonest cause of monogenic diabetes after 6 months (61%). K_{ATP} channel mutations were found in seven patients (39%), all diagnosed between 6 and 9 months. Monogenic diabetes was more common in infants presenting between 6 and 9 months than in those presenting between 9 and 12 months (20% vs. 2%, P = 0.004). Testing for monogenic diabetes in probands presenting up to 9 months of age increased sensitivity to 99.6% as compared to 93.2% using the current cut-off at 6 months.

Conclusions: We recommend that all infants presenting before 9 months of age be tested for monogenic diabetes. Although chances of treatment with oral sulphonylureas are lower in probands diagnosed after 6 months, there is still a possibility for a successful transfer.

O/5/FRI/02

Using clinical criteria to improve the use of genetic testing in diabetes

T. McDonald[1,2], B.M. Shields[1], S. Ellard[1] & A.T. Hattersley[1]

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

Background: Maturity-onset diabetes of the young (MODY) is often misdiagnosed as Type 1 diabetes (T1D) or Type 2 diabetes (T2D). A correct genetic diagnosis of MODY is important, as these patients need different treatment from other types of diabetes.

Aim/methods: We aim to determine clinical criteria that could be used in young onset diabetes (diagnosed < 35 years) to discriminate MODY (n = 522) from T1D (n = 348) and T2D (n = 253) and produce a probability model for predicting a patient's likelihood of MODY. Data was available on BMI, age at diagnosis, duration of diabetes (year), treatment, family history of diabetes, and HbA1c. Logistic regression analysis was used to determine clinical characteristics predictive of MODY. Regression equations were derived to calculate probabilities of MODY. ROC curves were used to determine cutoffs for sensitivity and specificity.

Results: The key discriminator of T1D and T2D was insulin treatment from diagnosis (99% vs. 0.4% respectively). Therefore, T1D vs. MODY comparisons were carried out in those insulin treated at diagnosis, and T2D vs. MODY comparisons tested in the rest. The optimal model for T1D vs. MODY (Model 1) produced a logistic regression equation for a log odds ratio (logOR) of 0.32 + (1 × Sex) + (0.1 × Age diagnosis)) - (0.6 x hbA1c) + (three if one parent affected) – (0.1*age) (area under the ROC curve = 0.967). The best T2 vs. MODY model (Model 2) provided the regression equation for logOR of 12 + (0.7*Sex) – (1xBMI SDS) – (0.3 x age diagnosis) + (1.1*diet) – (0.5*HbA1c) + (1.8*parent affected) - (0.03*age) (area under the ROC curve = 0.975). Given a prevalence of 1%, these models would give post-test probabilities for MODY of 20% and 15% respectively.

Conclusion: Clinical criteria can discriminate MODY from T1D or T2D and could improve selection of patients for genetic testing. The considerable benefit of making a correct diagnosis of MODY, the post-test probabilities of 15% and 20% would represent appropriate levels at which to request expensive molecular genetic testing.

O/5/FRI/03

Sex differences in the development of diabetes in mice with deleted Wolframin (Wfs1) gene – an animal model for Wolfram syndrome

K. Noormets[1], S. Koks[2,3], M. Muldmaa[1], L. Mauring[1], E. Vasar[2,3] & V. Tillmann[1,4]

[1]*Paediatrics,University of Tartu, Tartu, Estonia,* [2]*Physiology, University of Tartu, Tartu, Estonia,* [3]*Centre of Translational Research of the University of Tartu, Tartu, Estonia,* [4]*Tartu University Hospitals, Children's Clinic, Tartu, Estonia*

Background: Wolfram syndrome caused by mutations in the gene encoding wolframin (Wfs1) is characterized by juvenile-onset diabetes mellitus, progressive optic atrophy, diabetes insipidus and deafness. Diabetes starts usually earlier in boys. Common variants in the Wfs1 gene have been shown to be associated with Type 2 diabetes

Aims: To investigate the sex differences in longitudinal changes in blood glucose concentration (BGC) in Wolframin deficient mice (Wfs1KO) and to compare their plasma proinsulin and insulin levels with the wild-type (wt) mice.

Subjects and methods: Non fasting BGC was measured weekly in 42 (21 males) Wfs1KO and 42 (21 males) wt mice from 9 weeks of age. Intraperitoneal glucose tolerance test (IPGTT) was done at 30th week and plasma insulin, c-peptide and proinsulin levels were measured at 32th week.

Results: At 32nd week Wfs1KO males had increased BGC compared to wt males (9.40 ± 0.60 mmol/l vs. 7.91 ± 0.20 mmol/l; P < 0.05). Opposite tend was seen in females. Both male and female Wfs1KO mice had impaired glucose tolerance on IPGTT. Wfs1KO males had significantly lower mean plasma insulin level than wt males

(57.78 ± 1.80 ng/ml vs. 69.42 ± 3.06 ng/ml; $P < 0.01$) and Wfs1KO females (70.30 ± 4.42 ng/ml; $P < 0.05$). Wfs1KO males had higher proinsulin/insulin ratio than wt males (0.09 ± 0.02 vs. 0.05 ± 0.01; $P = 0.05$) and Wfs1KO females (0.04 ± 0.01; $P < 0.05$). Plasma c-peptide levels measured only in males were lower in Wfs1KO mice (mean 55.3 ± 14.0 pg/ml vs. 112.7 ± 21.9 pg/ml; $P < 0.05$).

Conclusions: Male Wfs1KO mice compared to females have increased risk to develop diabetes. Low plasma insulin concentration, but increased proinsulin/insulin ratio in Wfs1KO males indicates possible disturbances in converting proinsulin into insulin rather than in insulin secretion itself. Further investigations are needed to clarify the mechanism for the sex differences in the development of diabetes in Wolfram syndrome.

O/5/FRI/04

Two ancestral mutations in a large number of Czech families with glucokinase diabetes

P. Dusatkova, S. Pruhova, J. Lebl & O. Cinek

2nd Faculty of Medicine, Department of Pediatrics, University Hospital Motol, Charles University in Prague, Prague, Czech Republic

Objectives: Most families with glucokinase diabetes (GCK-MODY) carry their private heterozygous mutation in the *GCK* gene, while ancestral mutations have been reported only in small numbers of kindreds. However, we have recently detected a considerable number of apparently unrelated Czech families with identical *GCK* mutations. The E40K was carried in 21 families, L315H and G318R in 12 each, and V33A in 7 families; moreover, the E40K and L315H were geographically restricted. The aim of our study was to investigate whether this mutation clustering reflected a common origin of the respective mutations.

Methods: We genotyped 128 mutation carriers from 52 families, as well as 95 population controls using 11 SNP markers that cover a 14 Mb region centered around the *GCK* gene and that are not in linkage disequilibrium in the general population ($r^2 \leq 0.05$ for all pairs). The haplotypes were inferred using PHASE and Haploview, and the mutation age was analyzed using the DMLE+ program.

Results: The 51 subjects with the E40K mutation carried a haplotype spanning up to 8 Mb, which gave strong evidence ($P = 3 \times 10^{-6}$) for a common origin of this mutation arising about seven to nine centuries ago. Similarly, although less convincingly ($P = 8 \times 10^{-4}$), the founder effect was documented for the L315H that was carried on a haplotype spanning about 1.5 Mb; the estimated mutation origin was eight to ten centuries ago. Using the current marker set, we were unable to rule out an independent origin of the G318R and V33A mutations.

Conclusions: We present a large number of families carrying ancestral mutations causing GCK-MODY. In accordance with previous reports of groups up to six families (e.g. from Norway, the UK, and Spain), the Czech 21 families with E40K and 12 families with L315H show GCK-MODY as a disease that does not significantly decrease the reproduction fitness. This raises a question whether *GCK* mutations in general might represent some degree of potential evolutional advantage.

O/5/FRI/05

Frequency of polymorphisms of KCNJ11, INS VNTR and NR3C1 genes in children with small gestational age in polish population

M. Szalapska[1], M. Borowiec[2], K. Antosik[2], W. Mlynarski[2], R. Stawerska[1,3], M. Hilczer[1,3] & A. Lewinski[1,4]

[1]*Department of Endocrinology and Metabolic Diseases, Polish Mothers' Memorial Hospital – Research Institute, Lodz, Poland,* [2]*Department of Pediatrics, Oncology, Hamatology and Diabetes, Medical University of Lodz, Lodz, Poland,* [3]*Department of Pediatric Endocrinology, Medical University of Lodz, Lodz, Poland,* [4]*Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland*

Objectives: Insulin and cortisol are hormones which influence fetal growth process. It is well known that the E23K variant of KCNJ11, encoding for the pancreatic beta-cell adenosine 5′-triphosphate-sensitive potassium channel subunit Kir6.2, is associated with hypersecretion of insulin and insulin resistance (IR) in children. INS VNTR class III allele was associated with IR, as well. Polymorphisms in codons 22 and 23 of the glucocorticoid receptor gene (ER22/23EK of NR3C1 gene) were shown to decrease sensitivity to glucocorticoids and production of insulin. The aim of the study was to identify whether the polimorphism E23K of KCNJ11 gene, INS VNTR class III allele, and polymorphism ER22/23EK of NR3C1gene are associated with small birth weight in Polish population.

Methods: Two groups of subjects were selected on birth data: SGA (birth weight below 3rd percentile for gestational age and sex; n = 123) and AGA (appropriate for gestational age, birth weight between 25th and 75th for gestational age and sex; n = 132). Genomic DNA was isolated from peripheral blood lymphocytes. All subjects were genotyped for: E23K variant of KCNJ11, rs689A/T single nucleotyde polymorphism of INS VNTR and for polymorphism in codons 22 and 23 (22/23EK) of NR3C1 gene.

Results: We did not find any statistical differences in frequency of analysed polymorphisms in both groups. Variant E23E of KCNJ11 gene was observed in 47.8% of SGA vs. 46.0% of AGA, variant E23K in 40.6% of SGA vs. 40.5% of AGA and variant K23K in 11.6% of SGA vs. 13.5% of AGA. Variant T/T of INS VNTR locus was observed in 56.5% of SGA vs. 53.2% of AGA, variant A/T in 37.7% of SGA vs. 39.7% of AGA and variant A/A in 7.3% of SGA vs. 7.1% of AGA. Variant G/A of NR3C1 (ER22/23EK) was observed in 5.1% of SGA vs. 4.0% of AGA (ns).

Conclusion: Polymorphisms E23K of KCNJ11 gene, INS VNTR locus class III and ER22/23EK of NR3C1 gene were shown do not to be associated in any essential way with SGA in Polish population.

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O/5/FRI/06

The first nationwide multicenter study on the HLA-DRB1, DQB1, DPB1 genotypes in Japanese children with type 1 diabetes and their families

S. Sugihara[1], S. Amemiya[2], T. Ogata[3], T. Kawamura[4], T. Urakami[5], N. Kikuchi[6] & The Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes (JSGIT)

[1]*Tokyo Women's Medical University Medical Center East, Tokyo, Japan,* [2]*Pediatrics, Saitama Medical University, Saitama, Japan,* [3]*National Research Institute for Child Health and Development, Tokyo, Japan,* [4]*Pediatrics, Osaka City University, Osaka, Japan,* [5]*Pediatrics, Nihon University, Tokyo, Japan,* [6]*Yokohama City University, Yokohama, Japan*

Objectives: The genetic effect of HLA-DRB1 and DQB1 in Japanese patients with type 1 diabetes has been suggested to

be different from Caucasian patients. The present study is the first nationwide multicenter study for genetic factors in Japanese children with T1DM including their families.

Methods: Four hundred and thirty-one patients (158 boys and 273 girls) who were GADAb and/or IA-2Ab-positive (Type 1A), and 67 patients (28 boys and 39 girls) who were negative (Type 1B) were recruited into the present study. In addition DNA samples from 83 siblings of Type 1A and 150 parent-child torios were analyzed. HLA typing was performed with a Luminex Multi-Analyte Profiling system using the WAKFlow HLA typing kit.

Results: In the case-control study, the susceptible alleles for Type 1A were DRB1*0901,*0405,*0802, DQB1*0303,*0401,*0302, and DPB1*0201,*0301. The protective alleles were DRB1*1501,*1502,*0803,*0406, DQB1*0601,*0602,*0301, and DPB1*0901,*0402. The prevalences of DQB1*0601 and *0602 were higher in Type 1B, and DRB1*1302-DQB1*0604-DPB1*0401 haplotype was higher in Type 1B than in Type 1A. The prevalence of DQB1*0601 was higher in siblings. In the transmission disequilibrium test (TDT), the susceptible DRB1 and DQB1 alleles, and the protective DRB1, DQB1 and DPB1 alleles were confirmed. Transmission of DRB1*0901 from the mother was seen more frequently than from the father, but was not significant. The DRB1 allele frequencies in four-age groups according to onset (0–1, 2–5, 6–9, and 10–16 years) in Type 1A diabetes children were significantly different.

Conclusions: This study confirmed previous data on the DRB1-DQB1 haplotypes and demonstrated new findings on DPB1. Comparison of Type 1A with Type 1B and their siblings suggested the role of protective alleles, and a part of Type 1B had a unique haplotype. TDT suggested no genomic imprinting of HLA. These results may provide fundamental data for further genetic study of T1DM in Japanese children.

O/5/FRI/07

Specific clinical pattern for glucokinase gene mutations in MODY families

M. Borowiec[1], K. Antosik[1], W. Fendler[1], G. Deja[2], P. Jarosz-Chobot[2], M. Misliwiec[3], A. Zmyslowska[1], A. Szadkowska[1], M. Malecki[4] & W. Mlynarski[1]

[1]*Department of Pediatrics, Oncology, Hematology and Diabetes, Medical University of Lodz, Lodz, Poland,* [2]*Department of Pediatrics, Endocrinology and Diabetes, Medical University of Silesia, Katowice, Poland,* [3]*Department of Pediatrics, Oncology, Hematology and Endocrinology, Medical University of Gdansk, Gdansk, Poland,* [4]*Department of Metabolic Diseases, Medical University Colegium Medium Jagiellonian, KCracov, Poland*

Introduction: Defect of genes involved in beta cell function lead to the manifestation of diabetes. Glucokinase enzyme activity is closely linked to insulin secretion, as the enzyme functions primarily as the main glucose sensor of beta cells. Genetic defect of GCK reflects frequently in diabetes with a mild hyperglycemia observed in MODY families.

Aim: The study aimed to identify mutations in the GCK gene sequence among patients with monogenic diabetes.

Material: Genetic evaluation of GCK mutation was performed in 194 diabetic probands of MODY families with clinical characteristics suggestive of MODY2. Mutation was identified by direct DNA sequencing and MLPA.

Results: A total of 43 GCK mutations were detected among 194 probands recruited by means of the Polish Registry of Monogenic Diabetes. The mutations were present in 68 individuals. Twenty patients had novel mutations:A282fs, D198V,E158X,G246V,G249R, I348N,L165V,L315Q,M115I,N254S, P284fs,Q338P,R377L,R43C, R46S,S212fs,S212P,T255N,V406A, Y214D. All of these mutations segregated the disease in the studied families and were not present in over 200 non-diabetic children who served as a control group. Median age at examination was 15 years and 2 months, while the median age at diagnosis equaled 8 years and 10 months. Among 35 patients positive for dominant mode of inheritance diabetes was present in the father in 20 cases and in 19 in the mother. Correlations of age at onset and duration of diabetes with glycated hemoglobin levels were not statistically significant ($R = -0.07$, $P = 0.63$, $R = -0.01$, $P = 0.92$ respectively). Among 10 patients treated with insulin at the time of examination, median daily dose equaled 0.2 units/kg and ranged from 0.11 to 0.75 units/kg. Diabetic complications were detected in three patients:

1) microalbuminuria,
2) macroangiopathy,
3) preproliferative retinopathy.

Conclusions: Based on above mentioned clinical features we have established a model in logistic regression, which may serve as a surrogate of genetic testing.

O/5/FRI/08

A novel Wolcott-Rallison syndrome mutation in two members of an Irish consanguinous family

M. White[1], C. Costigan[1] & D. Cody[1]

[1]*Our Lady's Children's Hospital, Diabetes & Endocrinology, Dublin, Ireland*

Background: Wolcott-Rallison syndrome (WRS) is a rare recessive disorder characterized by early-onset diabetes, skeletal abnormalities, and liver dysfunction. Diabetes is usually the first manifestation of the syndrome. It results from mutations in the gene encoding the eukaryotic translation initiation factor 2-a kinase 3 (EIF2AK3) and it accounts for almost 24% of permanent neonatal diabetes (PND) in consanguineous pedigrees. The indigenous population of the Irish travelling community is one in which consanguinity is common, with a high rate of recessive disorders.

Case studies: We present two cases of PND in one Irish family. The first is a male, who presented in diabetic ketoacidosis at 7 months of age. He was the first child of well parents who were members of the Irish travelling community and were first cousins. There was no known family history of diabetes. Islet cell and GAD antibodies were negative, as was genetic analysis for Kir6.2 and SUR1 mutations. The second case, a female infant and the sibling of our proband, presented with Type I Diabetes aged 11 months, again in DKA. She too was antibody and Kir6.2/SUR1 negative.Subsequently, our proband developed significant liver dysfunction in the context of a mild viral illness at 23 months of age. Liver biopsy demonstrated fibrosis and cell necrosis.

Results: Our proband, was found to be homozygous for a novel missense mutation in exon 12 of the EIF2AK3 gene (V6391). Both of his parents were found to be heterozygous carriers of this mutation, and although his sibling's genetic results are outstanding at this time, it may be assumed that she may be affected by the same mutation. Both patients continue on insulin therapy.

Conclusion: In addition to testing patients with a clinical presentation suggestive of Wolcott-Rallison syndrome, *EIF2AK3* mutation should be tested for in patients with isolated neonatal diabetes in consanguineous pedigrees.

Update in Clinical Care of Pediatric Diabetes

O/6/FRI/01

Subcutaneous use of rapid insulin analog: an alternative treatment for patients with mild to moderate diabetic ketoacidosis

I. El Ebrashy[1], M.H.M.F. El Hefnawy[1], A. Basyouni[1] & H. Mahfouz[1]
[1]*National Institute of Child Health Karachi, Pediatric, Cairo, Egypt*

Background: Diabetic ketoacidosis (DKA) is a life-threatening condition that requires hospitalization in children with type 1 diabetes. Many reports have indicated that low-dose insulin therapy is quite effective regardless of the route of administration, whether, intramuscular, or subcutaneous.
Aim of the work: The aim of this study was to look for technical simplification and economic efficiency in the treatment of diabetic ketoacidosis (DKA) with subcutaneous use of the rapid-acting insulin analog and compare its use with regular intravenous insulin treatment.
Subjects & methods: A total of 80 consecutive patients admitted with DKA were randomly classified into four groups: Group 1: Patients with DKA on regular insulin by infusion pump, (infusion pump, n = 20), group 2: Patients with DKA on subcutaneous rapid onset of action-aspart insulin analog (Novolog; Novo Nordisk)/2 hours, sc-2 hour, n = 20), group 3: Patients with DKA on subcutaneous rapid onset of action-aspart insulin analog (Novolog; Novo Nordisk)/1 hour, (sc-1hr, n = 20), and group 4: Patients with DKA on rapid insulin analog by continues subcutaneous insulin pump (CSII, n = 20).
Results: The results of this study showed that there was no statistical difference between the four groups as regarding age in years, blood glucose in mg/dl before the starting of management of DKA, pH, serum HCO3, serum K, anion gap, urine acetone and time needed for resolution of DKA by hours. Conclusion: It could be concluded that management of any patient with mild to moderate DKA with good tissue perfusion can be treated with subcutaneous rapid insulin analog every 1 or 2 hours or to be treated by continuous insulin infusion pumps, if available with same results as giving regular insulin by intravenous infusion pumps.
Keywords: Diabetic ketoacidosis (DKA), Insulin analog and continues subcutaneous insulin infusion (CSII).

O/6/FRI/02

Glycemic variability in pediatric patients with diabetes mellitus type 1; a comparison between treatments and its relation with oxidative stress

M. Angulo[1,2], M. Torres[1], R. Cardona[1], C. Valls[1] & A. Gomez[1]
[1]*Pediatric Endocrinology, Hospital Sant Joan de Deu, Barcelona, Spain,* [2]*Pediatric Endocrinology, Clínica Valle del Lili, Cali, Colombia*

Introduction: Many in vitro experiments have shown a direct relation between oxidative stress and glycemic variability. Our hypotheses were that pediatric patients with DM type 1 receiving treatment with insulin pump have lower glycemic variability and that those patients with high glycemic variability, regardless of their HgA1c, have an increased risk of presenting high levels of oxidative stress markers.
Methods: We studied 40 patients between 9 and 16 years of age with diabetes mellitus type 1 diagnosis. The children were divided into two groups according to the treatment they were undergoing at the time: Insulin pump and insulin analog (bolus-basal) in multiple subcutaneous injections. Each patient carried a glycemic sensor for 5 days. To evaluate the glycemic variability, multiplicative standard deviation (MSD) and MAGE were calculated. Additionally, a blood sample was taken the same day the sensor was installed in order to evaluate the oxidative stress markers.
Results: The group of patients with insulin pump treatment had lower glycemic variability. This result was found in both methods (MSD and MAGE), though a statistically significant result P = 0.003 was found only with MAGE. We obtained a statistically significant relation between TNF Alfa levels and glycemic variability levels. Levels of MSD when compared with levels of TNF Alfa showed a Pearson correlation = 0.46 with P = 0.003. A qualitative variable was established with mean values of MAGE and MSD in High variability (HV), Moderate variability (MV) and Low variability (LV). The three groups were compared using the TNF Alfa values. We found a significant relation U = 0.036 when HV was confronted with MV and U = 0.032 when HV was confronted with LV.
Conclusions: Both of our hypotheses were confirmed: Glycemic variability is better controlled with the insulin pump treatment and there is a statistically significant relation between glycemic variability and oxidative stress when measured with TNF Alfa.

O/6/FRI/03

Improved metabolic control and treatment satisfaction in patients using an integrated infusion pump system for continuous subcutaneous insulin infusion (CSII)

G.E.M. Storms[1], R.P.L.M. Hoogma[2], D. Kerr[3], A. Buhr[4] & B. Petersen[5], on behalf of the Study Investigators
[1]*Diabetes Centrum St Antoniushospital, Utrecht, Netherlands,* [2]*Groene Hart Ziekenhuis, Gouda, Netherlands,* [3]*Royal Bournemouth Hospital, Bournemouth, United Kingdom,* [4]*Roche Diabetes Care AG, Medical Affairs, Burgdorf, Switzerland,* [5]*Roche Diagnostics GmbH, Mannheim, Germany*

Objectives: To evaluate the effects of day-to-day use of a new integrated infusion pump system on metabolic control, treatment satisfaction and patient safety.
Methods: Adult patients on CSII therapy for ≥6 months with HbA1c ≤ 10% were included in this prospective study conducted at nine sites in the United Kingdom and the Netherlands. Subjects were trained on the Accu-Chek Combo system comprising of an infusion pump and a smart blood glucose meter integrating various advanced features including bolus advice, data management, data analysis, reminder functions and remote control of the pump. HbA1c values were measured at baseline and at months 1, 3 and 6. Blood glucose and insulin data were downloaded at study visits. The standardized Diabetes Treatment and Satisfaction Questionnaire (DTSQ) and additional questionnaires were used to assess the patientś perception of the new system.
Results: A total of 86 patients (73 Type 1 , 13 Type 2) were enrolled and 80 patients completed the study. HbA1c was 7.9 ± 0.9% at baseline with a mean change of −0.34 ± 0.67% after 6 months (n = 74; P < 0.001, signed-rank test). The frequency of severe hypoglycemia (defined as an intervention requiring third party help) was 0.08 events per patient year. There was no case of ketoacidosis. A new more sensitive occlusion detection mechanism triggered 54% of the occlusion alarms. Treatment satisfaction at baseline was high (DTSQ status score 31.3 ± 3.8; scale score 0–36) and increased further to study end (DTSQ change score 10.6 ± 7.2; scale score −24 to +24). Overall satisfaction with the system was high with 5.9 ± 1.6 on a 1–7 scale.

Conclusions: The new integrated infusion pump system proved to be safe in everyday use. It contributed to an improvement in metabolic control and an increase in treatment satisfaction. The new, more sensitive occlusion detection mechanism allows earlier therapeutic intervention, which is particularly important in children with low insulin requirements.

O/6/FRI/04

Glucose excursions in children and adolescents in the STAR 3 study: a 1-year randomized controlled trial comparing sensor-augmented pump therapy to multiple daily injections

R.H. Slover[1], W.V. Tamborlane[2], T. Battelino[3], A. Criego[4], M. Daniels[5], C. Foster[6], R.C. McEvoy[7], C. Orlowski[8], S. Weinzimer[2], N.H. White[9], S. Willi[10] & M.A. Wood[11]

[1]*University of Colorado Denver, Barbara Davis Center for Childhood Diabetes, Aurora, United States,* [2]*Department of Pediatrics, Yale University School of Medicine, New Haven, United States,* [3]*Pediatric Endocrinology, University Children's Hospital, Ljubljana, Slovenia,* [4]*Park-Nicollet Clinic, Minneapolis, United States,* [5]*Pediatric Endocrinology, Children's Hospital of Orange County, Orange, United States,* [6]*Pediatric Endocrinology, University of Utah Diabetes Center, Salt Lake City, United States,* [7]*Childreńs Hospital and Clinics, Diabetes Center, Saint Paul, United States,* [8]*Pediatric Endocrinology, University of Rochester School of Medicine, Rochester, United States,* [9]*Division of Endocrinology and Metabolism, Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, United States,* [10]*Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, United States,* [11]*DeVos Children's Hospital, Grand Rapids, United States*

Objectives: Sensor-augmented pump (SAP) therapy may reduce hyperglycemic excursions compared to multiple daily injections (MDI) without increasing hypoglycemia.

Methods: STAR 3 compared SAP therapy to MDI therapy; 156 subjects age 7–12 and 13–18 wore blinded continuous glucose monitoring (CGM) sensors for six days at baseline and were randomized to SAP or MDI. Subjects in the MDI group again wore blinded CGM sensors for 6 days at one year. Using CGM data, areas under the glucose concentration-time curves (AUC, mg × dl^{-1} × minutes) for hyperglycemic excursions (>180 mg/dl and >250 mg/dl) and hypoglycemic excursions (<70 mg/dl and <60 mg/dl) were compared between treatment arms and age groups.

Results: At 1 year, A1c levels in the SAP group were significantly lower than the MDI group in both pre-teens and teens at 1-year. In both age groups, SAP lowered A1c by reducing hyperglycemic AUCs without increasing biochemical hypoglycemia. The magnitudes of improvements in metabolic control with SAP were similar in both age groups. The standard deviation (SD) of sensor glucose values, an indicator of glycemic variability, was significantly lower in teens and preteens in the SAP vs. MDI group.

Conclusions: Switching directly to SAP therapy is an effective strategy for improving glycemic control in youth with T1D who have elevated A1c levels on glargine-based MDI therapy.

		Age 7–12 years (n = 78)			Age 13–18 years (n = 78)		
		Baseline	1 year	p-value*	Baseline	1 year	p-value*
A1c (%)	SAP	8.2 ± 0.6	7.7 ± 0.8	0.021	8.3 ± 0.5	8.0 ± 1.0	0.011
	MDI	8.2 ± 0.5	8.2 ± 0.8		8.4 ± 0.5	8.7 ± 1.1	
AUC > 180	SAP	43.08 ± 22.05	32.04 ± 17.75	0.012	34.79 ± 20.66	27.88 ± 16.85	0.002
	MDI	51.24 ± 18.46	44.05 ± 18.4		37.95 ± 20.2	46.65 ± 31.84	
AUC < 70	SAP	0.16 ± 0.29	0.23 ± 0.45	0.94	0.38 ± 0.48	0.23 ± 0.38	0.92
	MDI	0.12 ± 0.23	0.24 ± 0.38		0.35 ± 0.57	0.25 ± 0.44	
SD Score (mg/dl)	SAP	77.34 ± 16.23	70.12 ± 16.13	0.009	75.66 ± 16.23	66.01 ± 14.67	0.002
	MDI	83.79 ± 13.7	80.61 ± 12.59		74.35 ± 12.54	81.81 ± 18.29	

[Mean (±SD) CGM parameters at baseline and 1 year]
*SAP vs. MDI comparisons at 1 year

O/6/FRI/05

Doubled rate of hypoglycemic events detected by CGM compared to frequent SMBG in children <7 years of age

F. Sundberg[1] & G. Forsander[1]

[1]*The Sahlgrenska University Hospital, The Queen Silvia Childreńs Hospital, Gothenburg, Sweden*

Background: Numerous hypoglycemic events (HG) in small children destabilize glycemic control, increase the level of family anxiety and impair the cognitive development of the child.

Objective: To prospectively compare the frequency and detection rate of hypoglycemia in children<7 years with T1DM during one year with SMBG and CGM.

Methods: Of a population of 35 patients aged <7 years, T1DM duration >3 months, attending the Gothenburg pediatric diabetes unit 7M/6F aged 4.7 (1.8–6.9) years with a diabetes duration of 2.4 (0.6–5.2) years complied with ≥5 days of CGM registration (CGMS Gold from Medtronic), most complied twice, and uploaded >300 days of SMBG data. In total 103 days of CGM registration were collected with a mean value of 7.9 (5.5–11.7) days per child. HbA1c was measured at the study start and ≥4 times during the year. Nights were defined as between 10 PM–6 AM. Hypoglycemia was defined as p-glucose <4 mmol/l. Severe hypoglycemia was defined as seizure or coma.

Patients: Eleven were treated with CSII, two with MDI. P-glucose testing was performed daily 7.8 (3.2–14.2) times of which 1.4 (0.2–2.5) per patient during nighttime.

Results: The average mean HbA1c was 7.8 (7.1–8.5) % (DCCT). Half of the patients had a mean HbA1c ≤ 7.5%. One child reported two and one child reported one severe hypoglycemia (23 events per 100 patient years) during the study period. No DKA was reported.

SMBG: The mean daily frequency of hypoglycemia was 0.7 (0.4–1.1). The yearly mean number of nights with detected hypoglycemia was 22 (4–42).

CGM: The mean daily frequency of hypoglycemia was 1.4 (0.5–3.4) of which 0.4 (0.09–0.74) occured during night time (27%).

Conclusion: Given that the accuracy of CGM at low levels of glucose is valid, this would mean that half of the hypoglycemic events in children <7 years with T1DM, and free access to SMBG, are never detected. Improvement in the HG detection rate is essential in order to further improve glycemic control in a secure way.

O/6/FRI/06

Diabetic Ketoacidosis at Onset of T1DM Associates to Future HbA1c Levels

J. Johannesen[1], L. Lyngsøe[2], H. Rida[1], M.L. Andersen[1], M.H. Lauridsen[3], B. Hertz[3], N.H. Birkebæk[4], B. Olsen[1] & J. Svensson[1]

[1]*Department of Paediatrics, Glostrup and Herlev University Hospital, Glostrup, Copenhagen, Denmark,* [2]*Hillerød Hospital, Hillerød, Denmark,* [3]*Viborg Hospital, Viborg, Denmark,* [4]*Department of Paediatrics, Skejby University Hospital, Aarhus, Denmark*

Introduction: Since 1996 The Danish Childhood Diabetes Register has collected data from all Danish paediatric diabetes centres treating type 1 diabetic patients aged 0–15 years. All newly diagnosed type 1 diabetic patients <15 years have been enrolled since 1996. Here we report the frequency and severity of DKA at onset and its association to future metabolic control.

Methods: DKA status was defined as:
(i) none: $HCO_3 \geq 15$ or pH ≥ 7.3;
(ii) mild: $HCO_3 < 15$ or pH < 7.3;
(iii) moderate: $HCO_3 < 10$ or pH < 7.2 and
(iv) severe: $HCO_3 < 5$ or pH < 7.1 from blood gas analyses.

Central HbA1c determination from all participants were analysed by means of multiple regression using age, gender, ethnicity, diabetes duration and DKA status as explanatory variables in a compound symmetric repeated measurement model.

Results: A total of 2939 recordings (1414 girls (48.1%) and 1525 boys (51.9%)) in 3364 persons were included in the analysis as 425 individuals did not have complete DKA data sets. 2422 individuals (82.4%) presented without DKA, whereas 237 (8.1%), 233 (7.9%) and 47 (1.6%) presented in mild, moderate and severe DKA, respectively. The multiple regression analysis revealed association of higher HbA1c levels over time (average diabetes duration 4.49 years) of 0.10%, 0.21% and 0.47% ($P = 0.002$) for mild, moderate and severe DKA presentations compared to no DKA at onset. The HbA1c levels increased significantly with age ($P < 0.001$) and was higher in the immigrant population. There was no effect of gender.

Conclusion: Presentation of T1D in DKA associates to higher HbA1c years ahead. Possible explanatory factors e.g. residual β-cell function or adherence to treatment needs further exploration.

O/6/FRI/07

Analyses of the rate of decline in stimulated c-peptide 12 months after diagnosis in children with newly diagnosed type 1 diabetes. results from the Hvidoere study group on childhood diabetes

M.L.M. Andersen[1], S. Pörksen[2], L.B. Nielsen[2], J. Svensson[2], J. Johannesen[2], P. Hougaard[3], J.V. Jørgensen[4], J. Thomsen[5], N.T. Hertel[6], J.S. Petersen[7], A.E. Karlsen[7], L. Hansen[2] & H.B. Mortensen[2]

[1]*Department of Paediatrics, Glostrup and Herlev University Hospital, Glostrup, Denmark,* [2]*Glostrup and Herlev University Hospital, Glostrup, Denmark,* [3]*University of Southern Denmark, Odense, Denmark,* [4]*Skejby University Hospital, Aarhus, Denmark,* [5]*Kolding Hospital, Kolding, Denmark,* [6]*Odense University Hospital, Odense, Denmark,* [7]*Novo Nordisk A/S, Maaloev, Denmark*

Objectives: Direct measurement of C-peptide has been recommended to provide the most appropriate primary outcome in trials evaluating the efficacy of therapies to preserve beta-cell function. The aim of the present study was to quantitatively characterize the natural history of disease progression as assessed by stimulated C-peptide the first 12 months after diagnosis in children with new onset T1D in two independent cohorts collected over a time interval of 6 years. Furthermore the purpose was to assess whether the natural history of disease has changed over time.

Materials and methods: The International Hvidoere cohort, year 1999–2000: 275 children from 22 paediatric centers; the Danish cohort, year 2005–2006: 130 children from 4 paediatric centers. All patients went through a 90-minutes Boost-test 1, 3 (only the Danish cohort), 6, 12 months to characterize the residual beta-cell function. All samples were centrally analyzed. The linearity of the slope of decline in stimulated C-peptide was analyzed from 3–12 months on a logarithmic scale. Linear mixed-effect models were used to determine cohort differences.

Results: Maximum values of stimulated C-peptide were reached at a duration of three months. Thereafter there was a linear decline in stimulated C-peptide for all age groups above 5 years in both cohorts. The mean value for the disappearance rate in stimulated C-peptide was 7.2 ± 0.9%/month for the Hvidoere and 9.4 ± 0.8%/month for the Danish cohort (NS, $P = 0.12$). The combined slope for both cohorts was calculated to 8.0 ± 0.7%/month.This is in the same range as the value reported of 0.019 nmol/l/month (1982-1985) by Wallensteen corresponding to a relative change of 9.5%/month.

Conclusion: Thus, the natural history of disease progression during the first 12 months after diagnosis has not changed considerably in new onset T1D populations during the last 20 years, despite more intensive insulin treatment regimens has been introduced during this period.

O/6/FRI/08

Long-term follow-up in children and adolescents with type 1 diabetes and abnormal urinary albumin excretion (UAE)

S. Salardi[1], S. Zucchini[1], C. Balsamo[1], G. Maltoni[1], M. Scipione[1], A. Rollo[1], S. Gualandi[1] & A. Cicognani[1]

[1]*S.Orsola-Malpighi Hospital, Pediatrics, Bologna, Italy*

Objectives: To verify spontaneous normalization of abnormal UAE, therapy effectiveness and consequences of its withdrawal in pts with abnormal UAE followed-up from 1984 to 2008. To evaluate relationship between UAE, HbA1c and lipid profile.

Methods: In the whole case series of 490 type 1 DM patients, 44 (9%) pts with persistent abnormal UAE were found and 41 of these with a complete follow-up were included in the study: 32 with microalbuminuria and 9 with macroalbuminuria. In the years 1984–1990 no pts received ACE inhibitor therapy, whereas after 1990 24 pts received ACE inhibitors: 17 with microalbuminuria and 7 with macroalbuminuria (treatment duration with enalapril 6 ± 4.3 years). Age at first abnormal UAE was 12.9 ± 3.8 years and diabetes duration 4.2 ± 4.7 years.

Results: Remission occurred in 33 (82%) of pts: 14/15 (93%) of untreated microalbuminuric pts and 13/17 (76%) of treated microalbuminuric pts, 0/2 of untreated macroalbuminuric pts and 6/7 (86%) of treated macroalbuminuric pts. Duration of abnormal UAE before regression was 5.6 ± 4.6 years and therapy duration before regression was 6.0 ± 3.8 years.

HDL cholesterol levels were significantly higher in the whole group of microalbuminuric pts than in a group of 134 normoalbuminuric control pts (62.4 ± 13.6 vs. 51 ± 11.4 mg/dl, $P < 0.001$).

Conclusions: We confirm the high percentage of spontaneous remission in diabetic children and adolescents. The similar result between treated and untreated pts is probably due to our decision to treat only pts with the highest and long-lasting values. Therapy seems fundamental in pts with macroalbuminuria. UAE tend to normalize in pts with better HbA1c and higher HDL cholesterol.

	Normalized (n = 33)	Persisting (n = 8)	
UAE (mg/day)	136.9 ± 107.5	286.7 ± 141.8	$P < 0.02$
HbA1c during abnormal UAE (%)	7.5 ± 1.0	9.4 ± 1.2	$P < 0.0001$
HDL cholesterol (mg/dl)	52.5 ± 11.3	42.7 ± 8.5	$P < 0.05$
Triglycerides (mg/dl)	71.6 ± 33.9	102.8 ± 47.2	$P < 0.05$

[differences between normalized and persisting pts]