ISPAD2012

ORAL SESSION

Oral Session 1 - Diabetes Genetics, Immunology and New Insulins and Pharmacologic Agents

O/1/WED/01

Administration of regulatory T cells preserves β-cell function in children with type 1 diabetes

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Objectives: Type 1 diabetes (DM1) develops as a consequence of destruction of pancreatic islets by self-reactive T cells. Recent studies suggest that this process can be inhibited by a subset of highly suppressive lymphocytes called regulatory T cells (Tregs). Studies on animal models showed that $CD4^+CD25^+FoxP3^+$ Tregs can prevent the autoimmune destruction of pancreatic islets and thus protect from DM1. In the current study we used for the first time in human autologous Tregs to prolong remission in children with new-onset DM1.
Methods: Ten DM1 children (8–16) received Treg infusion within 2 months since the diagnosis. The therapeutic product consisted of autologous $CD3^+CD4^+CD25^{high}CD127^-$ Tregs sorted and expanded under conditions of *Good Manufacturing Practice* (GMP). The patients were followed along with control group that consisted of matched DM1 individuals not qualified for the therapy due to inappropriate venous access.
Results: No adverse effects of the treatment were observed. Since the day of infusion significant increase in the percentage of Tregs in the peripheral blood has been observed. 8 months after DM1 onset (6–7 months since Treg infusion) 2 patients treated with Tregs do not receive insulin therapy and 8 receive significantly lower insulin doses (daily insulin dose ≤0.55 UI/kg.b.w) than non-treated individuals. In addition, fasting plasma C-peptide levels are ~2- fold higher in the treated group as compared to the control individuals [median 0.76 ng/ml vs.0.41 ng/ml, respectively].
Conclusions: These results show for the first time that the administration of Tregs can prolong the remission in DM1 children.

O/1/WED/02

Preserved C-peptide 30 months after GAD-alum treatment of children and adolescents with recent-onset type 1 diabetes

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Glutamic acid decarboxylase 65 kDa isoform (GAD_{65}) is a major autoantigen in type 1 diabetes (T1D). Although alum-formulated GAD_{65} (GAD-alum) induced preservation of residual insulin secretion in a previous clinical Phase II trial, recent Phase II and Phase III trials failed to reach their primary end-points. The European Phase III trial was therefore closed after 15 months, and the 30 months follow-up period was completed only for a minority of the patients. This study aimed to assess whether GAD-alum preserved β-cell function in those recent-onset T1D patients who completed their 30 months visit in the European Phase III trial.
Patients and methods: In the European Phase III trial patients aged 10–18 years with Type 1 diabetes for <3 months, had been randomly assigned into three arms: 4 doses of GAD-alum (4D), 2 doses of GAD-alum followed by 2 doses of placebo (2D), or 4 doses of placebo. Out of 334 patients 45 patients had reached the final visit after 30 months before the study was closed Serum fasting and stimulated C-peptide after a MMTT (AUC) was analysed . The C-peptide data were compared with the results from the Swedish Phase II trial with similar patient population.
Results: Patients in the Phase III trial treated with 2 doses of GAD-alum had less decline of both fasting ($P = 0.040$) and stimulated C-peptide ($P = 0.012$) after 30 months, and a larger proportion of these patients preserved >25% of their initial C-peptide AUC compared to placebo ($P = 0.012$). When patients from the Phase III trial treated with 2 doses of GAD-alum were added to the Phase II trial the difference between actively treated patients ($n = 50$) and placebo ($n = 50$) was highly significant (9 months: $P < 0.037$; 15 months: $P < 0.032$, 21 m: $P < 0.003$; 30 months: $P < 0.004$).
Conclusion: Two-dose regimen of GAD-alum treatment seems to preserve β- cell function at least for 30 months.

O/1/WED/03

Enterovirus infection, microRNA levels and type 1 diabetes: regulation of genes involved in inflammation and human pancreatic islet cell death

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Objective: Type 1 diabetes (T1D) is a chronic autoimmune disorder in which enteroviruses, such as coxsackievirus B (CVB) are putative environmental factors that may trigger or accelerate disease. Growing evidence indicates that microRNAs (miRNAs) are involved in the pathogenesis of β-cell death. miRNAs function as translational repressors and important regulators of key biological processes. We hypothesise that CVB infection of β-cells alters miRNAs abundance, thereby regulating gene expression, inducing pro-inflammatory cytokines and β-cell death.
Methods: Primary human islets were infected with clinical strains of CVB 3,4, and 5. RNA was isolated on Day 1 to 7 post infection and analysed using the TaqMan miRNA Array, resulting in the analysis of 755 miRNAs. miRBase and miRWalk algorithms were used to predict possible target genes of differentially expressed miRNAs in association with T1D candidate genes. Multivariate analysis of miRNAs and non-parametric Spearman's correlation coefficient were used to calculate the pairwise correlation in miRNA level. Hierarchical clustering was used to determine groups of miRNAs with similar expression patterns following EV infection. R software was used for correlation analyses and for creating heat maps.
Results: We identified 21 microRNAs that increased at least 10-fold following infection with all CVBs compared with the no virus control (NVC) and six that decreased at least 10-fold vs. the NVC. Of the up-regulated miRNAs, 19 are associated with genes involved in immune regulation (e.g., IL-2, IL-10, PTPN22, GPR183 and TAGAP), five are transcription regulators (e.g., AFF3, IL2RA and RGS1) and four are in the HLA region (e.g., HLADRB1 and HLADQB1). The down-regulated miRNAs are associated T-cell activation (e.g., CD69) and immune response (e.g., CCR5).
Conclusions: We identified a specific miRNA signature during CVB infection of human islets, with marked differential expression of multiple miRNAs associated with T1D candidate genes. Functional analysis of these miRNAs may further our understanding of the mechanisms underlying CVB induced T1D.

O/1/WED/04

Metabolomic profiles predicting islet autoimmunity leading to type 1 diabetes

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Objectives: Little is known concerning metabolomic changes associated with development of islet autoimmunity and progression to type 1 diabetes (T1D).
Methods: We investigated longitudinal profiles of 382 metabolites in 25 high-risk children who developed diabetes (T1D group), 25 with persistent islet autoimmunity but not T1D (IA group), and 25 controls matched on HLA DR/DQ, sex, and age. Metabolic profiles were analyzed at 4 time points: age <15 months (T1); just prior to IA (T2); after development of IA (T3); and prior to T1D or the most recent sample (T4). Non-targeted metabolic profiling platform included two ultrahigh performance liquid chromatography/tandem mass spectrometry optimized for basic species and acidic species and gas chromatography/mass spectrometry. A repeated measures analysis of variance determined statistically significant changes in metabolites between experimental groups. False discovery rates (q-value) were calculated to account for multiple comparisons.
Results: The major novel findings were significantly lower levels of vitamin C ($P < 0.00001$; $q = 0.0166$) and its metabolite threonate ($P = 0.0002$; $q = 0.0374$) in T1D group, compared to controls at time point T1. Ascorbate levels were also lower in IA group, compared to controls. In addition, at time points T1-T2, multiple metabolites (3-indoxyl sulfate, phenylacetylglutamate, p-cresol) previously associated with altered gut microbiome were significantly elevated in T1D and IA groups, compared to controls, Secondary bile acids: glycodeoxycholate, glycolithocholate sulfate, and taurolithocholate 3-sulfate were also significantly higher in both T1D and IA groups, compared to controls, at T1 through T3.
Conclusion: These results suggest that altered gut microbial activity and/or lower ascorbate levels in early childhood are significant predictors of IA leading to T1D.

O/1/WED/05

The spectrum of autoantibodies in pediatric type 1 diabetes: far beyond β-cells

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Objectives: It has been well established that in type 1 diabetes (T1D) patients autoantibodies to various non β-cell organ-specific autoantigens are detected that only in some cases are associated with clinical symptoms. Here we analyzed a large cohort of young T1D patients for the presence of various autoantibodies.
Patients: A retrospective cohort of 738 sera collected from 434 T1D children was monitored for a series of organ-specific and non-specific autoantibodies including: islet cell autoantibodies (ICA), antibodies to insulin, glutamic acid decarboxylase (GAD), tyrosine phosphatase (IA2), zinc transporter (ZnT8), thyroperoxydase (TPO), thyroglobulin (TG), H^+/K^+ ATPase, anti-transglutaminase (immunofluorescence and RLA), Saccharomyces Cerevisiae (ASCA), neutrophile cytoplasmic antibodies (ANCA), AIE 75 (typical of autoimmune enteropathy).
Results: 313 of the patients (51% boys, 49% girls) had at least one β-cell autoantibody (ICA, anti-insulin, GAD, IA2 or ZnT8). Nineteen of these 313 patients (6.1%) exhibited anti-H^+/K^+ ATPase autoantibodies (35.6% boys, 68.4% girls). Only two of these patients had clinical signs of autoimmune gastritis. In 26% of these 19 patients we observed at least one other associated autoantibody: anti-TPO and anti-TG antibodies in 18.8%, anti-transglutaminase in 5.3% and anti-ASCA in 1 case.
Conclusion: Our results demonstrate that in some patients the loss of immune tolerance associated with T1D goes far beyond β-cell to spread to other endocrine and non endocrine tissues. Although asymptomatic, the presence of multiple

autoantibodies mirrors an upstream process revealing a loss of immune tolerance to a larger repertoire of autoantigens. It is interesting to interpret these data in the context of first, epidemiological findings describing the increasing frequency of T1D in very young children and, secondly, isolated observations of clinical cases of T1D associated to other autoimmune diseases.

O/1/WED/06

Intrafamilial spread of enterovirus infections at the time of clinical onset of type 1 diabetes

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Background: At the clinical onset of type 1 diabetes (T1D), enteroviruses (EVs) of different species are present in 80% of probands (Toniolo et al.,2012).Family spread and geographic clustering of EV infections have been documented (Kogon et al.,1969). At diagnosis, we searched for EV infectivity and genomes in peripheral blood leukocytes (PBL) of diabetic children and first-degree relatives.

Materials and methods: Blood was drawn from 20 children, 16 siblings, 34 parents, 69 healthy controls. EV-susceptible cell lines were co-cultured with PBL of all individuals. RT-PCR assays detecting ≥100 EV serotypes (5′UTR, 5′UTR-VP2, and 3D genome regions) were run on plasma and medium of cell lines co-cultured with PBL for 1 month. Blood glucose, HbA1c, basal and stimulated C-peptide,T1D auto-Abs (IAA, GAD65, IA2, ZnT88), HLA class II haplotypes were determined. Geographic and temporal clusters of T1D cases were identified using Google maps.

Results: EV infectivity and genomes were found in blood of 19/20 (95%) diabetic children, 12/16 (75%) non-diabetic asymptomatic siblings, 20/34 (59%) asymptomatic parents, 3/69 (3%) healthy controls. Virus-positive members of each family shared the same EV species. Clusters of T1D were detected, each involving 2–4 families that shared the same EV species. During 1-year follow-up, 4/16 (25%) siblings of diabetic probands developed T1D. They carried high-risk HLA haplotypes and were EV-positive at the time of their proband's diagnosis. EVs of the B species were predominant. In one family, RNA sequencing credited infection to coxsackievirus A20.

Conclusions: High prevalence of systemic EV infections at T1D onset, familial spread of infection, clustering of cases, development of T1D at high frequency in virus-infected siblings of probands point to EVs in blood as a novel biomarker of T1D. In a multi-hit scenario, the above findings do not exclude the possible contribution of other noxious agents, such as chemicals or viruses other than EVs.

O/1/WED/07

The likelihood of enterovirus viraemia is modified by the type 1 diabetes-associated common polymorphism in *IFIH1*

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Objectives: The putative underlying mechanism of the *IFIH1* association with type 1 diabetes (T1D) involves sensing the double-stranded RNA during virus replication. We therefore investigated whether the rs1990760 polymorphism in the *IFIH1* gene influences the rate of enterovirus viraemia.

Methods: Enterovirus RNA was tested in 1001 blood samples, each from an infant or toddler (taken at median age 12.3 months, IQR 9.2–13.5, 512 males) recruited from the general Norwegian population in the MIDIA study (646 with the highest-risk HLA genotype for T1D, 355 with other HLA genotypes). The viraemia was tested using qualitative nested real-time reverse transcriptase PCR on RNA extracted from frozen cell packs after removal of plasma. Viral loads of enterovirus in concomitant stool samples (collected in a time window spanning 30 days before to 15 days after the blood sample) were available in 417 of the individuals.

Results: Enterovirus RNA was present in 11.5% blood samples. We constructed a regression model having enterovirus viraemia as the outcome, with the *IFIH1* genotypes and known modifiers (calendar year, age of the child) as the predictors. It suggested an increased risk of viraemia in the *IFIH1* 946Ala/Thr heterozygotes (OR=2.2, 95%CI 1.1–4.2, P = 0.023) relative to the Ala/Ala homozygotes, while there was no difference in viraemia between the Thr/Thr and Ala/Ala homozygosity (P = 0.42). This remained unchanged in a model restricted to individuals who had the concomitant stool samples tested for enterovirus (OR of the Ala/Thr 2.2, P = 0.07), and was apparently independent of the enterovirus positivity in the stool (enterovirus in the gut further increased the likelihood of viraemia, OR=2.2, 95% CI 1.3–3.9, P = 0.007).

Conclusion: We observed that the rs1990760 polymorphism, previously confirmed to be associated with the risk of T1D, may affect the likelihood of enterovirus viraemia.

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O/1/WED/08

Human amniotic epithelial cells as a reliable source for diabetes stem-cell therapy

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Objectives: Human placenta is available as a discarded tissue, which provides a rich population of multipotent stem cells. Amongst them, HAECs represent a promising resource for regenerative medicine. In the present study we cultured HAECs in serum-free and defined media preserving their phenotypic and genetic traits. Then we verified the mesodermic differentiation capacity of HAECs and finally evaluated their pancreatic differentiative potential. We hypothesize that HAECs, cultured in such conditions, may show the same or better differentiation rate of HAECs cultured in standardized serum-rich media when induced into insulin producing cells.

Methods: Placenta samples were collected, HAECs were isolated and cultured in standard serum-rich medium and serum-free optimized media. We used RT-PCR to assess stem cell markers. Mesodermic osteogenic induction was performed for each media using the same induction cocktail. Differentiation was evaluated through Alizarin red staining and qPCR for osteogenic gene expression. To study HAECs' pancreatic differentiation ability, Nicotinamide was added to each medium. Pancreatic markers expression and immune-phenotype profile were assessed respectively with qPCR, fluorescence-activated cell sorting analysis or immune-fluorescence.

Results: Serum-free media sustained HAECs' growth and stem cell potential (OCT4, NANOG, SOX2). Alizarin red assay showed mineralization in all the culture conditions, confirmed by qPCR for key osteogenic markers such as OCN, RUNX2 and COL1A1. Preliminary pancreatic induction revealed expression

of stemness marker NESTIN, typical of pancreatic progenitor cells, and pancreatic markers INSULIN and PDX1.
Conclusion: These data indicate that serum is not essential for HAECs culture and differentiation. Serum-free culture conditions could simplify the transition from laboratory to clinical practice. For this reason HAECs might be a reliable, ethical-free source of insulin producing cells in clinical applications.

Oral Session 2 - Diabetes Acute and Chronic Complications I

O/2/WED/01

Adolescents with type 1 diabetes at higher risk of microalbuminuria have higher sympathetic tone

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Objectives: To determine if adolescents with type 1 diabetes at high risk of microalbuminuria (MA) have early cardiac autonomic changes vs those at lower risk of MA.
Methods: Adolescents with >12 months diabetes duration were screened in a multicentre Australian cohort as a part of the AdDIT trial. Standardised albumin:creatinine ratios (ACR) were calculated from 6 early morning urine collections, adjusted for age, gender, and diabetes duration. Adolescents stratified into lower (n = 88) and upper tertiles (n = 144) on the basis of ACR were assessed for heart rate variability (HRV) using LabChart Pro, a continuous 10-minute ECG recording. Derived parameters were: mean resting HR, lower:higher frequency (LF:HF) ratio- an estimate of relative sympathovagal balance, and standard deviation of mean NN intervals (SDNN), where NN=adjacent QRS-complexes, root mean squared difference of successive NN intervals (RMSSD) and triangular index (TI)-estimates of overall HRV.
Results: The higher risk group was younger (14.3 vs. 15.1 years, P = 0.04), had shorter diabetes duration (6.6 vs. 7.6 years, P = 0.04) and higher SBP and DBP (P < 0.05) than the lower tertile group. There were no differences in HbA1c (8.3% vs. 8.2%) or cholesterol levels (4.4 vs. 4.5mmol/L) between groups. Higher ACR was associated with increased baseline HR and LF:HF ratio, which remained significant when age-adjusted. There were no significant associations between ACR and other HRV measures.
Conclusions: Higher ACR in adolescents is associated with increased HR and LF:HF ratio, independent of glycaemic control. This higher sympathovagal tone may contribute to early renal disease.

HRV parameter	Coefficient (95% CI)	p-value	Adjusted for age	p-value
Heart rate	0.02 (0.004–0.03)	0.02	0.02 (0.003–0.03)	0.02
LF:HF ratio	0.15 (0.01–0.28)	0.03	0.15 (0.02–0.29)	0.03
SDNN	-0.004 (-0.009–0.002)	0.17	-0.004 (-0.009–0.002)	0.16
RMSSD	-0.003 (-0.007–0.001)	0.12	-0.003 (-0.007–0.001)	0.11
Triangular index	-0.01 (-0.04–0.02)	0.49	-0.01 (-0.04–0.02)	0.48

[Associations between ACR and HRV parameters]

O/2/WED/02

Urinary albumin excretion relates to early atherosclerosis in youth with type 1 diabetes

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Objective: We aimed to identify risk factors associated with accelerated atherosclerosis (aIMT and cIMT) in youth with T1D.
Methods: A cross-sectional analysis of ultrasound measurements of cIMT and aIMT was conducted in 298 youth with T1D (age 14.3 ± 1.9 years, 148 male, diabetes duration 6.8 ± 3.8 years) with clinical and biochemical data. 204 children enrolled in AdDIT had albumin-creatinine ratio (ACR) measured centrally (UK) at baseline in 6 early morning urine samples, and adjusted for age, gender, diabetes duration and age at diagnosis. 94 T1D children had ACR measured in early morning urine samples collected on the study day.
Results: Mean/maximum aIMT and cIMT were higher than in 32 controls aged 14.2 ± 3 years (P < 0.001, P < 0.01). Males had a greater mean/maximum cIMT than females. Multiple regression analysis, including all significant correlates in linear regression, showed associations between IMT and age, gender, waist circumference, systolic blood pressure, total cholesterol and ACR.

Table 1. Multivariable correlates of IMT

	Mean cIMT		Maximum cIMT		Mean aIMT		Maximum aIMT	
	β	p	β	p	β	p	β	p
Age (years) n=298					**0.011**	**0.004**		
Male vs. Female n=298	**0.019**	**0.006**	**0.026**	**0.002**			-0.037	0.070
BMI (kg/m^2) n=298					0.006	0.059		
Waist (cm) n=298	0.0004	0.343	0.0003	0.529	-0.001	0.535	**0.003**	**0.026**
Systolic BP (mmHg) n=298	**0.001**	**0.050**	0.001	0.215	0.001	0.123	**0.003**	**0.016**
Diastolic BP (mmHg) n=298	-0.001	0.341	-0.0002	0.788	-0.001	0.165	-0.003	0.076
Total cholesterol (mmol/L) n=298			**0.010**	**0.018**	**0.023**	**0.003**	**0.033**	**0.003**
HbA1c (%) n=298	-0.003	0.211	-0.004	0.157	0.010	0.169	0.010	0.169
Standardised ACR n=204					**0.011**	**0.046**	**0.020**	**0.011**
ACR n=94					**0.013**	**0.022**	**0.016**	**0.046**

Conclusions: In addition to established cardiovascular risk factors, higher urinary albumin excretion, before the development of microalbuminuria, relates to early atherosclerosis in youth with T1D.

O/2/WED/03

Major risk factors and the course of microalbuminuria in a long-term prospective observational study on children with type 1 diabetes

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Objectives: To assess in the prospective study the prevalence and the course of microalbuminuria (MA) in diabetic children and adolescents and establish the predictors of MA development in pediatric population.

Methods: The group covered 438 children and adolescents, from Malopolska region in Poland, who developed type 1 DM in the years 1985–2004 were followed for 9.2 ± 3.4 years from the diagnosis.

Anthropometric measurements, albuminuria, presence of retinopathy, blood pressure, HbA1c, insulin dose, total cholesterol and triglycerides were assessed annually. MA, defined as an albumin concentration 20–200 μg/minutes in at least two timed, overnight urine collections, in ≥2 consecutive years was regarded as persistent.

Results: During the study period 102 patients (23.3%) developed MA after 8.27 ± 3.3 years of diabetes: persistent - in 29 (6.6%), transient - in 63 (14.4%) and intermittent - in 10 (2.3%) subjects. The prevalence of MA was not dependent on the year of diabetes diagnosis (P = 0.53 in comparison of the pre-1990, between 1990–1995 and 1995–2000 periods). During the follow-up 17 (58.6%) patients with persistent MA reverted to normoalbuminuria after 2–3 years and remained normoalbuminuric until the end of the observation (1–7 years), two of them received an ACE-inhibitor because of concomitant hypertension. We found no difference in the mean HbA1c before the development of MA and during the follow-up period in patients with the normalization of AER (8.25 ± 1.4 vs. 8.28 ± 1.1%). None of the patients developed macroalbuminuria. Independent risk factors for the development of MA which remained in multivariate Cox regression model were presented in the table 1 (Table 1 - Risk factors for the development of MA in diabetic children).

	HR	95%CI	P
Presence of hypertension at onset	1.37	1.01-1.87	0.0433
Mean HbA1c	1.41	1.16-1.71	0.0005
Age at onset of diabetes	1.13	1.05-1.21	0.0009
Daily insulin dose 0.1U/kg	0.86	0.76-0.98	0.0246

Conclusions: MA in type 1 diabetic children and adolescents is reversible in the majority of patients. Major risk factors for developing MA are modifiable underlining the significance of metabolic control and adequate insulin dosage.

O/2/WED/04

Poor glucose control impairs maximal post-occlusive vasodilation in adolescent type 1 diabetes

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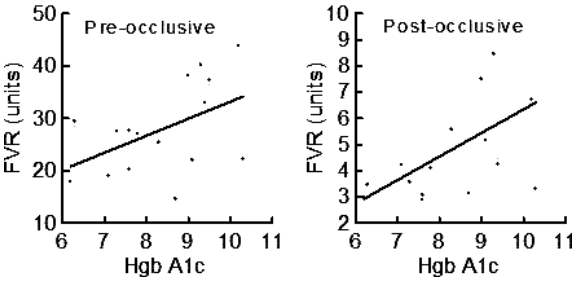
Objective: Endothelial dysfunction plays an important role in the pathogenesis of cardiovascular disease and long-term complications in type 1 diabetes (T1D) and is present in adolescents with T1D. How glucose control affects endothelial function in adolescent T1D is unclear.

Methods: We used venous occlusion plethysmography to measure forearm blood flow (FBF) and forearm vascular resistance (FVR, mean arterial pressure/FBF) before (Pre) and after (Post) 5 minutes of upper arm arterial occlusion in 16 adolescents with T1D (age: 13 ± 2 years; duration; 5 ± 4 years, BMI:20 ± 3 kg/m^2) and assessed their relationship to fasting glucose (FG), 72 hour mean glucose (MG) and standard deviation (STD) (Medtronic Guardian), single hemoglobin A1c (SA1c), and hemoglobin A1c area under the curve (A1cAUC) since diabetes diagnosis.

Results: PostFBF negatively correlated (r = -0.54, P = 0.03) and PostFVR (Figure) positively correlated (r = 0.55, P = 0.03) with SA1c. PostFVR also correlated with MG (r = 0.57, P = 0.03). PreFVR (Figure) tended to correlate with SA1c as well (r = 0.48, P = 0.06). Percent change in FVR from pre to post-occlusion tended to decrease as FG increased (r = -0.49, P = 0.07). Vascular performance was not related to STD, A1cAUC, age, duration, or body mass index.



Conclusion: The results indicate that poor diabetes control impairs maximal, sheer stress-induced, endothelially-mediated vasodilation. Decreased vasodilatory ability may cause poor tissue blood flow and future complications.

O/2/WED/05

Vitamin D deficiency is not associated with retinal vascular calibre

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Background: Identification of early treatable predictors of retinopathy may allow more aggressive management of those at high risk. Higher retinal arteriolar calibre predicted incident retinopathy in a cohort from our centre [1]. We have shown that vitamin D deficiency (VDD) is associated with an increased risk of retinopathy (OR 2.12) [2]. We hypothesised that VDD mediates changes in retinal vascular calibre.

Objective: To examine the association between VDD and retinal vascular calibre measurements.

Method: We assessed 508 young people in the Diabetes Complications Assessment Service at the Children's Hospital at Westmead, Australia in 2009–10. Digitised retinal images were analysed using the Singapore I Vessel Assessment programme. Central retinal arteriolar and venular equivalents (CRAE, CRVE) and arteriolar/venular ratio (AVR) were calculated. 25OHD levels were adjusted for season [2]. VDD was defined as 25OHD <50nmol/L [3]. Quartiles of 25OHD levels were examined to determine if there was a threshold effect for changes in retinal vascular calibre.

Results: Mean (SD) duration was 7.16 (3.47) years and median (IQR) HbA1c 8.4% (1.8). VDD was present in 15.6%. There was

no difference in mean CRAE, CRVE or AVR between those with and without VDD. Those with the highest mean CRAE (fourth quartile) did not have a higher incidence of VDD compared with those with lowest mean CRAE (first quartile) (28.2% vs. 22.5%, P = 0.6). No threshold effect for retinal vascular calibre changes was seen with 25OHD quartiles.

25OHD quartiles	Mean CRAE (SD)	p	Mean CRVE (SD)	p	Mean AVR (SD)	p
1st	165.66 (12.06)	NS	242.57 (19.04)	NS	0.69 (0.05)	NS
2nd	167.46 (20.83)	NS	241.37 (24.98)	NS	0.70 (0.05)	NS
3rd	164.97 (11.76)	NS	239.62 (17.82)	NS	0.69 (0.55)	NS
4th	163.75 (13.63)	NS	240.84 (18.45)	NS	0.68 (0.05)	NS

Conclusion: There was no difference in retinal vascular calibres between those with or without VDD. Changes in retinal vascular calibre may have preceded retinopathy onset. Analysis of the association between other retinal vascular geometry parameters and VDD is warranted.

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3. Munns, C., et al., MJA, 2006. **185**(5): p. 268–272.

O/2/WED/06

Gender differences in retinal microvasculature through puberty in type 1 diabetes (T1D): are girls at greater risk?

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Aim: To longitudinally study gender differences in retinal vascular geometry from pre- to post-puberty in a well-characterized group of patients with T1D.
Methods: Sixty-four pre-pubertal patients with T1D were repeatedly monitored until the end of puberty with Tanner-staging and diabetes complications assessments. Retinal vascular geometry from every visit was assessed using the semi-automated computer program Singapore I Vessel Assessment tool from digitized central retinal photographs by a single grader blinded to clinical patient status. Mean retinal vascular measurements for 3 periods (pre-, during- and post-puberty) were averaged and compared between males and females using ANOVA.
Results: Median age at first visit was 9.8 years [IQR 1.3] in girls and 10.7 [1.2] in boys, with similar diabetes duration (9.3 years vs. 10.7 years, P = 0.2) at study end. Girls had wider arterioles and venules than males pre- and post-puberty (Table). Girls had lower arteriolar length-to-diameter-ratio (LDRa), greater arteriolar tortuosity, greater venular LDR and significantly lower venular tortuosity than males (Table) before and during puberty, but only differences in LDRa persisted post puberty. Girls had higher cholesterol in puberty (4.8mmol/L vs. 4.0, P < 0.001) and post-puberty (4.8mol/L vs. 3.8mmol/L, P < 0.001) than males despite similar glycaemic control.
Conclusion: Girls had significantly more complex arteriolar microvascular network (lower arteriolar LDR and greater tortuosity) and a simpler venular microvascular network (lower venular tortuosity and a trend towards greater venular LDR) pre- and post-puberty. Both these patterns have been associated with greater risk of microvascular complications.

..... .	Pre-Pubertal Female (n=29)	Pre-Pubertal Male (n=35)	P	Pubertal Female (n=29)	Pubertal Male (n=35)	P	Post-Pubertal Female (n=29)	Post-Pubertal Male (n=35)	P
CRAE	169.9(12.9)	162.4(17.4)	<0.00	163.8(16.0)	166.9(15.6)	0.3	169.7(15.8)	163.8(12.1)	0.05
CRVE	247.4(24.0)	238.5(23.9)	1	243.1(26.1)	243.3(23.3)	0.96	249.5(25.8)	244.7(20.0)	0.3
AVR	0.69(0.07)	0.68(0.07)	0.008	0.68(0.06)	0.69(0.06)	0.3	0.68(0.06)	0.67(0.06)	0.00
LDRa	8.26(6.98)	10.48(8.78)	0.4	8.53(7.10)	12.50(8.63)	0.00	8.18(7.17)	13.16(9.64)	2
STa	1.12(0.03)	1.11(0.02)	0.04	1.12(0.03)	1.11(0.03)	2	1.12(0.03)	1.12(0.04)	0.99
CTa	1.23(0.25)	1.12(0.21)	0.001	1.20(0.23)	1.14(0.24)	0.02	1.19(0.22)	1.16(0.27)	0.6
BAa	85.1(9.0)	83.6(9.6)	<0.00	84.6(10.1)	80.9(10.4)	0.1	82.1(8.4)	84.1(9.4)	0.2
LDRv	13.31(6.60)	12.77(8.74)	1 0.2 .	12.56(6.52)	11.49(7.95)	0.03	10.94(4.82)	11.13(7.80)	0.9
STv	1.092(0.011)	1.097(0.013)	0.6 0.003	1.093(0.011)	1.096(0.013)	0.4 0.2	1.095(0.011)	1.097(0.013)	0.4 0.09
CTv	1.028(0.106	1.094(0.179	0.001	1.056(0.109	1.134(0.227	0.00	1.030(0.102	1.085(0.215	0.1
BAv	) 76.0(10.1)	) 78.8(9.7)	0.04	) 78.8(10.2)	) 79.7(12.2)	7 0.6	) 77.2(9.2)	) 79.9(9.3)	0.4

[Retinal Vascular Geometry for 64 Patients with T1D]

O/2/WED/07

Ascorbic acid decreases endothelial activation in adolescent type 1 diabetes

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Objective: To determine the effect of ascorbic acid infusion on endothelial activation during euglycemia and hyperglycemia in adolescents with type 1 diabetes.
Methods: Soluble intracellular adhesion molecule (SICAM) levels were measured in 8 adolescents with type 1 diabetes [age, 14.2 ± 1.5 years(mean ± SD); duration, 5.1 ± 4.2 years; BMI, 22.0 ± 3.3 kg/m^2; HgbA1c, 8.4 ± 1.1%] fasting and during hyperinsulinemic glucose clamp with euglycemia, followed by hyperglycemia on two occasions. On the second occasion ascorbic acid infusion (3 mg/minutes) was begun at the same time as the insulin infusion.
Results: Glucose levels did not differ between the study sessions. Mean baseline glucose for the ascorbic acid study was 206 ± 39 mg/dl and 169 ± 23 for the control study. Levels at the end of euglycemia were 89 ± 2 and 77 ± 4 mg/dl and at the end of hyperglycemia 223 ± 8 and 220 ± 9 mg/dl, respectively. Baseline, fasting SICAM levels did not differ between the two sessions (ascorbic acid session, 144 ± 22; control, 161 ± 27 ng/ml) but were significantly lower following initiation of ascorbic acid during both euglycemia (ascorbic acid, 126 ± 24; control, 154 ± 26, P = 0.001) and hyperglycemia (ascorbic acid, 118 ± 23; control, 148 ± 27, P < 0.001). SICAM fell during euglycemia (P = 0.029) and hyperglycemia (P = 0.034) in both studies but these changes were not affected by ascorbic acid.
Conclusion: The lower SICAM levels demonstrate that acute ascorbic acid infusion lowers endothelial activation possibly by decreasing acute oxidative damage.

O/2/WED/08

Change in pulse wave velocity over 2 years in adolescents with and without type 1 diabetes

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Objectives: Pulse wave velocity (PWV), a measure of arterial stiffness, has been associated with cardiovascular disease risk. Accelerated increase in PWV over time may suggest more rapid vascular aging. Little is known regarding change in PWV over time in adolescents with type 1 diabetes (T1D). We measured PWV at baseline and after 2.2 ± 0.4 years in 194 adolescents with and without T1D. We hypothesized that change in PWV is

accelerated in T1D adolescents compared to their non-diabetic (non-DM) peers.

Methods: PWV was measured at baseline and follow up in the carotid-femoral segment using the SphygmoCor device in 153 T1D adolescents (T1D duration >5 years at baseline) and 41 similar age and sex, non-DM controls. Anthropometric and lab data were also collected.

Results: Subjects were age 12–19 years at baseline and 51% male. T1D subjects were slightly older than non-DM controls (T1D 15.4 ± 2.1 vs. non-DM 14.8 ± 1.6 years, P = 0.04). Gender distribution was similar (T1D 50% vs. non-DM 56% male, P = 0.46). Age-adjusted baseline PWV was similar in T1D compared to non-DM adolescents (P = 0.33). At 2-year follow up, age-adjusted PWV trended higher in T1D subjects but the difference was not statistically significant (P = 0.06) (Table).

Table 1 Baseline characteristics & PWV by diabetes status

Variable (mean ± SD) except where indicated)	T1D (n = 153) Duration = 8.7 ± 3.0 years	Non-diabetics (n = 41)	P-value
A1c (%)	8.9 ± 1.6	5.3 ± 0.3	<0.0001
BMI (kg/m2)	22.5 ± 3.8	22.0 ± 5.1	0.55
LDL-c (mg/dl)	89 ± 28	82 ± 22	0.14
HDL-c (mg/dl)	51 ± 11	47 ± 8	0.003
Triglycerides (mg/dl) (median (IQR))	72 (58–98)	76 (58–88)	0.65
Systolic blood pressure (mmHg)	112 ± 9	109 ± 9	0.06
Diastolic blood pressure (mmHg)	68 ± 7	64 ± 6	<0.001
PWV baseline (m/s) (age adjusted mean ± SE)	5.3 ± 0.1	5.2 ± 0.1	0.33
PWV 2 years (m/second) (age adjusted mean ± SE)	5.8 ± 0.1	5.6 ± 0.1	0.06

Conclusions: These data suggest that vascular aging may be accelerated in T1D adolescents compared to non-DM peers. Further study is needed to determine if differences are significant over a longer period of longitudinal follow up.

Oral Session 3 - Diabetes and Obesity

O/3/WED/01

Insulin resistance and bone growth in children - a 6y longitudinal study

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Objectives: Two opposing forces influence bone mineral density (BMD) in obesity. Weight loading promotes osteogenesis, while ectopic fat in bone impairs it - so-called 'obesity of the bone'. Obesity is associated with insulin resistance (IR) and ultimately, diabetes. Reports vary on the outcome in obese adults, although bone density is lower and fracture rate higher in those with diabetes. Little is known of this impact in children. Therefore effects of IR and body fat on bone density were investigated longitudinally in a cohort of healthy children.
Methods: We recruited 292 children (147 boys) from randomly selected schools in the UK, and monitored them annually from 9 to 15 years. BMD, lean mass index (LMI = lean mass/height^2) and %body fat (BF) were measured using Dual Energy X-ray Absorptiometry (DEXA). IR was derived fasting glucose and insulin concentrations using the HOMA2 programme. The effects of BF and IR on BMD was explored through response-profile (mixed-effects) modelling, controlling for age-related growth and age-standardised height.
Results: Nearly 20% (55) of otherwise healthy children showed impaired fasting glucose (≥5.6 mmol/l) by 15 years BF had a significant positive effect on BMD in girls ($P < 0.001$) that increased with age and outweighed the effect of LMI, which had a significantly negative effect ($P < 0.001$) up to 10 years. LMI had a positive effect in boys ($P < 0.001$), increasing progressively after 12 years as BF fell and LMI rose. We found only weak evidence for a (negative) association between IR and BMD, confined to girls (0.001g/cm^2 decrease for every 50% increase in IR, $P = 0.03$).
Conclusions: Body fat is associated with denser bones in girls, negatively mediated to a lesser extent by lean mass, whereas in boys, only lean mass is associated with denser bones. Both probably exert their effect through weight loading. Insulin resistance has little impact on bone growth in contemporary children, even though a substantial proportion show impaired fasting glucose.

O/3/WED/02

Children are changing shape - metabolic implications based on a 10 year longitudinal study

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Objectives: BMI cannot assess fat distribution, and is an uncertain predictor of metabolic risk. Waist circumference (WC) is a good predictor of metabolic risk, but only when it reflects intra-abdominal fat. Children are getting fatter, but the relationships between BMI, WC and metabolic risk are unclear.
Methods: We compared the trends of WC with BMI annually from 5 to 15 years in a single cohort of 307 contemporary children (170 boys), and measured their insulin resistance by HOMA-IR. WC and BMI were age-adjusted according to the UK 1990 growth standards.
Results: The change in WC SDS from 5 to 15 years (Δ Girls: 1.10 SDS, Δ Boys: 0.74 SDS) was substantially greater in both genders than the corresponding change in BMI SDS (Δ Girls: 0.18 SDS; Δ Boys: 0.20 SDS). Nearly half the girls (49%) crossed the 91st centile for WC by 15y, while only 21% crossed 91st percentile for BMI (Fig 1). Adjusted linear mixed effects modelling showed a significant, but modest, increase in IR of ~1.20 for each SDS of WC ($P < .001$) in both genders. There was no indication of recovery in the girls by 15 years, whereas the imbalance between WC and BMI resolved in the boys

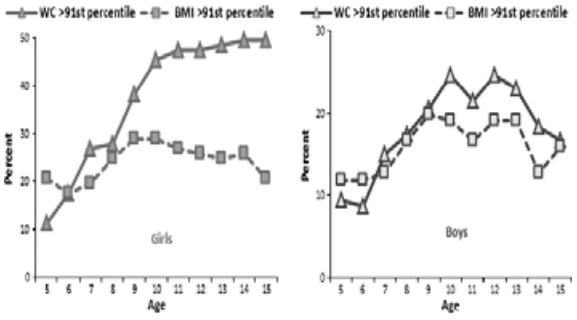

Fig 1: Comparison between WC & BMI >91st centile

Conclusion: Contemporary children, girls in particular, are changing shape. However, the metabolic implications are muted, which may suggest that the expanding waist line of today's adolescent female is largely subcutaneous fat, and not a health threat.

O/3/WED/03

Optimum macronutrient content of the diet for adolescents with pre-diabetes: RESIST, a randomised control trial (ACTRN12608000416392)

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Pre-diabetes and clinical insulin resistance in adolescents are rapidly emerging clinical problems with serious health outcomes. With appropriate management these conditions are potentially reversible.
Objective: To determine the effectiveness of two lifestyle interventions, differing only in diet composition, on insulin sensitivity in obese adolescents with pre-diabetes and/or clinical features of insulin resistance.
Methods: A 12 month RCT at two tertiary hospitals in Sydney, Australia. At baseline adolescents are prescribed metformin and randomised to structured diet which is either high carbohydrate or moderate carbohydrate increased protein. The program commences with an intensive 3 month dietary intervention, followed by a 3 month exercise intervention and a 6 month maintenance phase.[1] Trial endpoints: Insulin sensitivity index (ISI),[2] adiposity, cardiometabolic profile and fitness 6 month outcomes will be available in July and presented; data below are for the first 3 months.
Results: 111 (66 girls) were recruited and 106 completed the 3 month intervention. Over 3 months the mean BMI z-score decreased from 2.4 ± 0.4 to 2.2 ± 0.3, $P < 0.001$ and the ISI increased from 1.4 ± 0.7 to 1.7 ± 0.8, $P < 0.001$ with no

difference between dietary interventions. Overall 51 adolescents lost ≥2 kg (median 3.9[2–13 kg]), 43 maintained weight and 12 gained ≥2 kg (2.8[2–5]). Adolescents who lost weight had an increase ISI (0.4 ± 0.6, P < 0.001) and improved cardiometabolic profile.

Conclusion: Obese adolescents at high risk of developing type 2 diabetes, prescribed metformin, can achieve modest weight loss and an increase in insulin sensitivity over 3 months, irrespective of the macronutrient content of the diet. More radical strategies are required to address pre-diabetes and clinical features of insulin resistance in the young.

References:

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O/3/WED/04

Major differences of impaired fasting glucose prevalence in two nationwide cohorts of obese children

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Impaired fasting glucose (IFG), a prestage to type 2 diabetes in adults, is also present in obese children and adolescents. A large variation of the occurrence has been recorded but the prevalence is unknown due to lack of larger representative cohort studies. This study was implemented to investigate the prevalence of IFG in two large nationwide cohorts of obese children and adolescents, one in Sweden and one in Germany, and to find factors that affect the risk of IFG.

Data were collected from two national registers of obese children and adolescents. The total number of eligible subjects with fasting glucose available were 35 633 samples, 32 907 German and 2 726 Swedish. Subjects included were 2–18 years of age and obese according to international cut-off limits. Two cut-off limits for IFG were used; According to American Diabetes Association 5.6–6.9 mmol/l and according to World Health Organization 6.1–6.9 mmol/l. Variables collected were gender, age, and degree of obesity. Logistic regression was used to calculate odds ratios.

The mean age in the German and Swedish subjects included in this study were 12.5 (SD 2.9) and 11.4 (SD 3.4) years respectively. The total prevalence of IFG among obese children in the German cohort according to ADA criteria is 5.7% and WHO criteria 1.1%. In Sweden the corresponding prevalence was 17.1% and 3.9% respectively. Increasing age and degree of obesity were positively correlated with a greater risk of having IFG.

In conclusion, this study confirms that large regional differences, similar to those observed for type 1 diabetes, occur in IFG prevalence. Due to unknown reasons, Sweden had a 3 fold higher prevalence of IFG according to the ADA criteria and 3.5 fold higher prevalence according to WHO criteria than Germany in obese children and adolescents. Both age and degree of obesity were positively correlated with the risk of having IFG.

O/3/WED/05

HbA1C does not detect glucose impairment in youth: a 10-year longitudinal study

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Objective: An HbA1C threshold of ≥6.5% has been adopted by the ADA to diagnose diabetes in adults, and of ≥5.7% to identify individuals at risk. Little, however, is known behaviour or diagnostic value of HbA1C in youth. Our aim was to evaluate the utility of HbA1C in youth at risk of diabetes.

Methods: HbA1C (DCCT aligned) and fasting glucose were measured annually in 327 children from the age of 5–15 years. Both cross-sectional association and longitudinal trends were examined. ROC analysis was used to determine the diagnostic value of HbA1C among those individuals who had impaired fasting glucose (IFG - glucose ≥5.6 mmol/l).

Results: Cross-sectionally, there were positive associations between HbA1C and glucose throughout (r = 0.11–0.30, P <0.07–0.001). From 10 years, however, HbA1C fell while glucose rose (Figure 1). Some 94 observations recorded IFG, but HbA1C exceeded 5.7% in only seven of them, and the area under the ROC curve was modest at 0.75 (P < 0.001). Maximum sensitivity (65%) and specificity (70%) for predicting IFG corresponded to an HbA1C of 5.3%.

Conclusions: HbA1C is not diagnostically useful in youth with pre-diabetes (IFG) because of low sensitivity and specificity. Although HbA1C retains a positive association with glucose over time, their divergent trends from 10 years suggest that factor(s) beside glycaemia dominate the variance of HbA1C in youth.

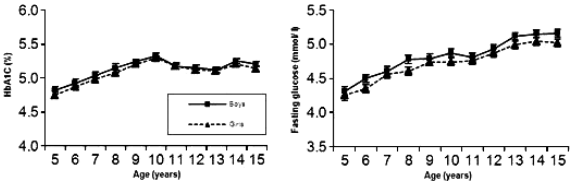

Figure 1. Trends in fasting glucose and HbA1C in children from 5 to 15 years

O/3/WED/06

White UK children are older, more obese and more insulin resistant than non-white UK children at diagnosis of type 2 diabetes: baseline results of the UK National Type 2 Diabetes Cohort

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Objective: Type 2 diabetes (T2DM) has increased in UK children since the first reports in 2000; however it is poorly characterised and management practice varies across the UK. We aimed to describe the characteristics of the first 125 children recruited to the UK national study.

Methods: We recruited children with: a paediatrician diagnosis of T2DM; body mass index (BMI) above 85th centile for age and sex; and other diagnoses such as monogenic diabetes excluded. Clinical data was collected into a national database. Blood was taken for DNA and diabetes auto-antibody status.

Results: We were notified of 256 presumed affected children and have recruited 145 so far. Exclusions: auto-antibody positive (13); secondary diabetes (7). After exclusions the M : F ratio was 1 : 2.6; white UK origin (49%); South Asian (SA) origin (29%); African-Caribbean (A-C) (12%); other (10%). The mean age at diagnosis was 13.2 years and the mean duration of diabetes 3.0 years. White children were older at diagnosis (mean 13.4 years vs. SA (13.2 years), A-C (12 years; white vs A-C $P < 0.04$); fatter at diagnosis (BMI-SDS white (3.2), SA (2.8), A-C (2.7); white vs S-A $P < 0.01$). White children had a trend towards lower HbA1c (white (9.2%, SA 8.7%, A-C 10.5%); and higher fasting C-peptide (white 1594 pmol/L; SA 1229 pmol/L; A-C 935 pmol/L). 19% of A-C children had resting heart rate more than 2 SD's above the mean,versus 8% in SA and 7% in white children. There were no significant differences in resting blood pressure between groups.
Conclusion: White UK children are older at diagnosis than non-White children, more obese, and probably more insulin resistant. African-Caribbean children have poorer metabolic control and signs of cardiovascular dysfunction compared to white and SA children. A significant proportion of children still have raised C-peptide levels soon after diagnosis of diabetes. This raises the possibility of therapeutic intervention to preserve pancreatic β- cell function early in the disease process.

O/3/WED/07

Determinants of BMI increase during the course of diabetes in children and adolescents with T1D: data from the German/Austrian DPV multicenter survey

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Objectives: Weight gain is an important part in the care of children and adolescents with type 1 diabetes (T1D) and has been reported as a side-effect of intensified insulin therapy. Pediatric studies are complicated by the age- and gender-dependency of BMI and by the time trend of increasing obesity during the last decades. The aim of this study was to evaluate factors, related to the increase in BMI during the course of diabetes in children and adolescents with T1D in a large multicenter survey.
Methods: From January 1995 to March 2011, data of 53 108 patients with T1D, aged <20 years, were collected in 248 centres in Germany and Austria within the DPV-Wiss-project. 12 774 patients (53% male, mean age 13.4 ± 3.9 years, mean diabetes duration 4.7 ± 3.0 years, and mean age at diabetes onset of 8.7 ± 4.0 years) were included in this analysis. Population-based German reference data were used to calculate BMI-SDS and define overweight and obesity.
Results: At baseline, 12.5% of T1D patients were overweight and 2.8% were obese. Multiple regression analysis revealed that female gender, longer diabetes duration, pubertal diabetes onset, lower BMI at diabetes onset, more intensified insulin therapy and higher insulin dose (per kg/bodyweight) were related to increasing BMI-SDS during the course of diabetes ($P < 0.0001$; all).
Conclusion: Insulin regimen is one important factor associated with weight gain during T1D course, in addition to demographic variables. Medical and behavioral optimization of diabetes management especially during puberty and in females, might limit weight gain in order to reduce overweight and obesity and to reduce further co-morbidities.

O/3/WED/08

Evidence of early β- cell deficiency in children who develop impaired fasting glucose: a 10-year longitudinal study

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Objective: Type 2 diabetes in children has been ascribed to rising obesity and insulin resistance. A glucose level above 5.6 mmol/l, known as impaired fasting glucose (IFG), is associated with increased risk of diabetes and our aim was to compare the behaviours of BMI, insulin sensitivity and β- cell function in children who developed IFG with those whose glucose levels remained within the normal range.
Methods: BMIsds and fasting blood samples were taken annually from 327 children from 5–15 years. Trajectories of BMIsds, insulin resistance (HOMA-S), and β- cell function (HOMA-B) in children who developed IFG were compared with those in whom glucose remained normal.
Results: Fifty-five children showed IFG, mostly after age 11 year, the majority of whom (39) were boys. Fasting glucose rose progressively in both groups, but was higher throughout in those who developed IFG ($P < 0.001$). IS and BMI correlated as expected ($r = -0.4$, $P < 0.001$), but there was no difference in BMI between those who showed IFG and those who did not ($P = 0.56$). IS rose from 5 year and fell after 7 , but again was the same in both groups ($P = 0.49$). HOMA-B, on the other hand, was lower in those who developed IFG, even at 5 year (82.5 vs. 95.0, $P < 0.001$). Glucose levels of the parents whose children developed IFG were higher than those whose children did not (mother's glucose: 4.9 vs. 4.6 mmol/l, $P < 0.001$; father's glucose: 5.0 vs. 4.8 mmol/l, $P = 0.04$). There was no difference in IS of either parent ($P \geq 0.6$), but the HOMA-B of the mothers whose children showed IFG was lower (112.7 vs. 129.6, $P = 0.02$).
Conclusions: IFG is common in contemporary children, and it appears to result from a defect inβ- cell function, which is already present at 5 year. The parental differences suggest a possible genetic cause, requiring loss of insulin sensitivity to reveal it. As the insulin resistance of puberty recovers, further weight gain is likely to become the determinant of progression to diabetes.

Oral Session 4 - Diabetes Care, Education, Psychosocial Issues I

O/4/THU/01

Training of motivational interviewing to parents improved the glycemic control of the childhood and adolescent type 1 diabetes: a prospective randomized control trial

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Background: The management of the childhood and adolescent Type 1 Diabetes (T1D) was difficult in the both of metabolic and psychological aspect. Especially the conflict with their parents might be one reason which enhanced the difficulties. Motivational interviewing (MI) is a counseling approach developed by clinical psychologists. The concept of MI evolved from experience in the treatment of problem drinkers. Recently, MI is applied to the various health management approaches, such as smoking, obesity, and diabetes. In this study, we have tried to adapt MI to improve the family communication.
Objective: To evaluate whether the training of MI to the parents of the childhood and adolescent type 1 diabetes can improve the glycemic control of patients.
Design: This study was a 12-month randomized controlled trial. Thirty three parents of children and adolescent type 1 patients whose glycemic control were not good (HbA1c >7.5%), were enrolled. Participants were randomly divided to MI group that was trained MI immediately and control group that was trained MI 6 months later. MI group was immediately received the MI training 3 times monthly and 6 month later received 3 times again. Control group was received the diabetes care class 3 times monthly, and 6 month later received the MI training 3 times monthly.
Main Outcome Measures: HbA1c and the score of Children's Depression Inventory (CDI).
Results: At 6 month, HbA1c of MI group was significantly improved compared to that at the beginning (8.3 vs.9.0; $P < 0.01$), and that of control group did not changed (9.6 vs.9.6). At 12 month, HbA1c of MI group was slightly improved to 8.1% ($P = 0.86$), and that of control group was also slightly improved to 9.1% ($P = 0.14$). The score of CDI in control group at 12 month was significantly improved compared to that at the beginning (15.6 vs.16.1; $P < 0.05$).
Conclusions: The MI training to parents of the childhood and adolescent T1D patients improved the glycemic control.

O/4/THU/02

Parenting an adolescent with type 1 diabetes mellitus: especially stressful for fathers

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Objectives: To examine the relationship between paternal and maternal parenting stress and depressive symptoms in adolescents with type 1 diabetes mellitus (T1DM) and in adolescents without a chronic disease.
Methods: 151 adolescents with T1DM (mean 14.9 ± 1.7 years) and a comparison group (CC) (N = 122) reported their depressive mood (Children's Depression Inventory-CDI) and behavior problems (Youth Self Report-YSR). Parenting stress (general: Parenting Stress Index (NOSI) and diabetes specific parenting stress) was reported by mothers (T1DM N = 126; CC N = 106), as well as fathers (T1DM N = 105; CC N = 55).
Results: Fathers of adolescents with T1DM report significantly more parenting stress than fathers of the comparison group: $F(1,158)=5.46$, $P = .021$. This difference was not significant for mothers of adolescents with T1DM: $F(1,232)=3.24$, $P = .073$. The age of the adolescent was not associated with general and diabetes specific parenting stress. Both fathers and mothers of adolescents with T1DM at risk for depression as indicated by a score higher than 13 on the CDI, reported significantly more general and diabetes related parenting stress compared to parents of adolescents not at risk for depression.
Parents of adolescents who did not reached optimal levels of metabolic control (HbA1c >7.5%) did not differ in general and diabetes specific parenting stress from parents of adolescents who reached optimal levels of metabolic control (HbA1c <7.5%).
Conclusions: Especially fathers of adolescents with T1DM showed more parenting stress than fathers of adolescents without a chronic disease. Specifically the combination of diabetes and depressive symptoms in the adolescents with T1DM was found to be associated with both paternal and maternal parenting stress. No such relationship was found between parenting stress and depressive symptoms in the comparison group.

O/4/THU/03

Coverage, cost, care and education of type 1 diabetes in children and adolescents in Beijing and Shantou

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Objectives: This mixed methods study strengthens data on the numbers diagnosed, cost, care and education of T1D in Beijing (B) and Shantou (S) among participants <20 years old meeting criteria for T1D. Data was collected as part of the larger 3C Study.
Methods: In the 3C Study, a 3-year retrospective record review in 18 facilities identified 1604 (654 < 20 years) diagnosed with T1D of whom 22 (5 < 20 years) had died and the status of 82 (13 < 20 years) was unknown. Their mortality rate was estimated to be at least twice that of general population. Median age at diagnosis was 13 (B) and 19 (S) and patient contact with health system reduced after 10 years' diabetes duration. Participants were enrolled sequentially from the review as well as inpatient wards and outpatient clinics for face-to-face interviews (n = 849; <20 year, n = 373). Data was also collected via interviews with clinicians (n = 86), medical record audit (n = 786; <20 year, n = 339) and venous blood samples tested locally n = 817; <20 year, n = 362.
Results: Up to 44% of children and 34% of adolescents presented in DKA at diagnosis. Mean A1c at time of study was 8.5% (B) and 10.6% (S). Incidence of DKA by events per 100 pt years was (B) 12.2 in those <13 and 17.6 in the 13–19 age group; 12.5 and 10.7 respectively in (S). 43% of <20 years received <1 hour of

diabetes education following diagnosis. Up to 75% of children reported missing school in previous year, mean days = 84 (B), 26 (S). Mean annual direct medical costs identified are RMB 31389 ($4962), 87% are out-of pocket. Families with a T1D member experience catastrophic payments for medical care (52.3% of mean annual household income). 29% of families are impoverished due to medical expenditures or the person with T1D may not seek needed care.

Conclusion: A larger study is required to confirm incidence. Less than half T1D diagnosis occur in the <15 years group. Cost imposes a burden. There are significant differences in care in Beijing and Shantou with opportunities for improvement.

O/4/THU/04

Training program for diabetes educators and mental health professionals in behavior change, psychosocial support techniques and family dynamics: assessment tools and intervention strategies

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Objective: In this study 6 diabetes educators (RN's and RD's) and 2 mental health professionals (a psychologist & a social worker) were trained in developing new assessment and intervention strategies in the area of behavior change and family dynamics that would help them to feel and become more effective at understanding the link between dysfunctional family coping and poor diabetes control as well as helping them develop more effective intervention strategies based on this new insight. Given the scarcity of training tools for educators in this area it also sought to develop a set of edited training videos with voice over narration and graphics to be used as a teaching tool for other diabetes educators and health care professionals.

Methods: The study took place in the outpatient diabetes clinic at Alberta Children's Hospital (ACH) in Calgary, Alberta, Canada. Educator training sessions were conducted in the context of the regular clinic and specifically assigned one-way mirror consultation and observation rooms, which were outfitted with audio and video DVD recording to record the 1 hour live supervision family sessions. Live family consultation and HCP training sessions were approximately 1 hour in length, with a trainer observing from the one-way mirror observation room. Trainees included 3RN's, 3 RD's, 1 psychologist, 1 social worker. Qualitative data was generated by means of pre-and post questionnaires to the educators.

Results: Qualitative data at study end shows educators reported improved sense of clinical competence and role satisfaction. Edited set of training tapes were developed.

Conclusions: The study provided the diabetes educators with new tools that have enabled them to make more relevant psychosocial coping assessments and interventions for families and patients as well as feeling more professionally competent. This study identifies and provides a new, powerful and effective training tool for diabetes educators in the area psychosocial issues.

O/4/THU/05

Motivational interviewing to improve metabolic control in adolescents with type 1 diabetes: it's worth talking to boys?

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Objectives: To assess the changes in metabolic control after a psychological intervention with elements of motivational interviewing (MI) and cognitive behavioral therapy (CBT) in adolescents with poorly controlled type 1 diabetes (T1DM) after 6 months of intervention in a randomized controlled trial.

Methods: 151 T1DM patients, age 13–20 years, diabetes duration >1 year and HbA1c >8% in the past year from 5 diabetes outpatient clinics in Austria were eligible to participate. 39 refused participation, 37 could not be reached or did not attend their scheduled appointments.

75 patients (male n = 32) were included in the study. Participants were matched for age, sex and contributing clinic and randomly assigned to an intervention group (n = 40) and a control group (n = 35).

In the intervention group (IG) 12 sessions of 45–60 minutes (four of motivational enhancement therapy, eight of CBT) and 10 supportive email exchanges with specially trained clinical psychologists were accomplished during a time span of 6 months. In the control group (CG) treatment as usual was applied with an additional offer of a fortnightly email contact.

HbA1c was assessed at baseline and within 4 weeks after completing.

Groups were compared by using χ^2-test and Wilcoxon-test for statistical analysis.

Results: There was no significant improvement in metabolic control in either of the groups after intervention (IG 9.95% vs. 9.74%, P = .412; CG 9.25% vs. 9.18%, P = .978).

When separated for gender, boys in the IG showed improvement in HbA1c after the intervention (9.74% vs. 9.14%, P = .017), girls did even slightly increase their HbA1c (10.09% vs. 10.14%, P = .475).

In the CG no significant change was found in either gender.

The change in HbA1c in the IG was -0.40% in boys vs. +0.05% in girls (P = .023).

Conclusions: In a 6 month intervention of MI and CBT only a minor effect on metabolic control in adolescents could be achieved directly after intervention. A moderate effect was observed in boys, girls did not improve.

O/4/THU/06

Diabetes related problems and diabetic controls among the school children with type 1 diabetes mellitus living in Istanbul

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Objectives: Adequate glycemic control in children with Type1DM requires optimal conditions guided by diabetes team both at home and at the school since children spend a remarkable time at school. We aim to search problems of

children with T1DM encountered at school related to diabetes and their diabetic controls.
Methods: 114 diabetic children from randomly selected schools from 1st to 12nd grade (6–18 years old) were interviewed and a questionnaire was filled by patients and the parents.
Results: Overall mean HbA1c level was 8.1 ± 1.8% (4.7–13.8%). Glycemic control was good (HbA1c≤7.5%) in 42% of the patients. 68% of the children were followed by a pediatric endocrinologist, 12% by a paediatrician in government hospital and 15% by a pediatrician in private practice. HbA1c levels were lower in patients followed by a pediatric endocrinologist than those followed by a goverment or private base pediatricians (7.9%, 8.7%, 9.1% respectively, $P < 0.05$). 72% of the patients were visiting their doctors at least every 3 months while in 28% doctor visits were less frequent and in 15%, there was no regular follow-up. 27% of the patients were checking their blood sugar(BS) ≤1–2 /day. 55% of children were avoiding BS measurement at school. The classmates and teachers of the patient know that they were diabetic in 95% and 94% respectively. 30% of the children were avoiding injections at school, 33% were injecting at classroom, 15% at infirmary, 11% at cantina and 11% at rest rooms. There was no school nurse in 80% of the schools. 18% of the children reported severe hypoglycemia in the last 1 year. Glukagon was present at the schools in 19% and at homes in 72% of diabetic children.
Conclusion: This survey demonstrated a need for a more vigorous education and organisation for diabetes-care (especially for blood sugar measurement, insulin injections and glucagon) at school environment in Istanbul. It also demonstrates importance of a specialist (pediatric endocrinologist) in care of children with T1DM.

O/4/THU/07

Intrinsic motivation in minority youths with type 1 diabetes

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Objective: Intrinsic motivation (IM) is an important self-determination theory-based construct for understanding regimen adherence (RA). The objective of this study was to develop a self-report measure of IM and evaluate its relationship to RA and glycemic control in minority youth with type 1 diabetes (T1D).
Methods: Participants had a mean age of 13.6 years (range of 12–16 years) and were diagnosed for at least 1 year. This sample of 42 youth (55% male, 90.5% Hispanic and 9.5% Black) had mean A1c of 9.0% (SD = 1.8). Youth completed the Intrinsic Motivation Inventory for Diabetes Management (IMI-DM, developed for this study), and the Diabetes Self Management Profile (DSMP), a measure of RA across several domains (exercise, hypoglycemia, eating, insulin use, BG monitoring). The IMI-DM consists of 12 items each rated on a 7-point scale; six items each comprise the confidence and importance subscales.
Results: Internal consistency of the scale was excellent (Total $\alpha = .92$; Confidence $\alpha = .90$; Importance $\alpha = .80$).There were significant associations between the IMI-DM total and DSMP total scores ($r = .63$, $P < .001$) as well as A1c ($r = -.41$, $P < .01$). The IMI-DM total score was also associated with DSMP eating ($r = .55$, $P < .001$) and exercise ($r = .52$, $P < .001$). The IMI-DM Confidence subscale was associated with the DSMP total ($r = .54$, $P < .001$), DSMP eating ($r = .52$, $P < .001$) and exercise ($r = .47$, $P < .003$), and A1c ($r = -.50$, $P < .001$). The IMI-DM Importance subscale was associated with DSMP total ($r = .66$, $P < .001$), and DSMP eating ($r = .53$, $P < .001$), exercise ($r = .52$, $P < .001$), and BG monitoring ($r = .36$, $P < .03$). IM also predicted better RA ($r = .52$, $P < .008$) and A1c ($r = -.39$, $P < .03$) 6 months later.
Conclusions: These results support the reliability and validity of the IMI-DM in minority youth with T1D, indicate that greater IM for diabetes management is associated with better RA and A1c, and suggest that interventions to increase IM in minority youths with T1D may help improve diabetes management.

O/4/THU/08

The 'to become independent' – educational program for young adolescents. The pilot study of original program

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Objectives: Puberty in adolescents with type 1 diabetes is usually associated with deterioration in metabolic control. In order to avoid such problems, the To Become Independent (TBI) educational program was launched. The aim of this pilot study is to assess the effectiveness of mentioned educational training on glycaemic control.
Methods: The TBI is created for young adolescents (10–14 years) and its aim is to prepare teenagers to become more independent, example in decision making, motivate them to take more responsibility for their diabetes self-management and to learn to live with diabetes as much as their peers without it, as well as to avoid deterioration in metabolic control. Main goal to achieve was to take a part in few-days school-trip. The TBI program is structured, age-appropriate and individualized program of at least 4 1-hour long, face-to-face meetings, with further overview with parents. Trainings took place in diabetes clinic in 2011. In the first stage, analysed data include only results in HbA1c. In next 3 years further analysis are being planned.
Results: The participants were patients aged 10–14 years old (n = 80). Mean age=12 ± 1.5, HbA1C before start of the program: A1C1 = 7.67 ± 1.04, after the program A1C2 = 7.5 ± 1.07, ΔA1C = -0.17 ± 0.82. Those who took a part in the TBI program (n = 30) had better results in decreasing of the A1C comparing to their peers: ΔA1C(TBI) = -0.37 ± 1.19% vs. ΔA1C(noTBI) = -0.05 ± 0.47%. Although there were significant differences in A1C1 between two groups - A1C1 (TBI) = 8.14 ± 1.21% vs. A1C1 (noTBI) = 7.77 ± 1.4%, there were no significant differences in A1C2 after educational intervention.
Conclusions: In short-term analysis participation in TBI program is more effective in avoiding deterioration in metabolic control than lack of it. It is necessary to assess the effectiveness of TBE program by conducting follow-up studies.

Oral Session 5 - Diabetes Acute and Chronic Complications II

O/5/THU/01

Diabetic ketoacidosis: a disease of psyche and soma

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Objectives: To study the impact of uncomplicated diabetic ketoacidosis (DKA) upon brain morphology and function.
Methods: Patients aged 6–18 years with and without DKA at diagnosis were studied at 4 time points: 1, 5 and 28 days, and 6 months after diagnosis. Demographic data and diabetes characteristics were obtained. Patients underwent magnetic resonance (MR) imaging (T1 weighted, diffusion tensor imaging (MD) and fractional anisotropy (FA)) at each time point. MR spectroscopy was undertaken in frontal lobes and left basal ganglia. Several psychometric tests were performed: mental state (SYSTEMS), Test of Everyday Attention – Child Version, the WISC-IV and long-term verbal memory. Groups were compared using ANOVA and ANCOVA (continuous variables) and χ^2 (categorical variables) analyses.
Results: Thirty-six DKA and 59 non-DKA patients were studied. DKA and non-DKA groups had no significant differences in any demographic variables at baseline. Significant findings included: total cortical grey matter volume was lower in the DKA group on day 1 and increased over 6 months; total cortical white matter volume was increased in the DKA group on day 1 and decreased over 6 months; white matter swelling was apparent in the frontal, temporal and parietal cortices on day 1 in the DKA group; lower levels of a marker of neuronal density/activity (NAA/Creatine) were noted on day 1 in the DKA group in the frontal grey matter and basal ganglia; mental state scores were lower in the DKA group on days 1 and 5; changes in total and regional brain volumes in the first 5 days were associated with delayed memory recall, and focused, sustained, and divided attention at 6 months. Multiple regression analysis demonstrated that pH and age at the time of presentation were strong predictors of the aforementioned outcomes.
Conclusions: DKA at type 1 diabetes diagnosis commonly results in morphologic and functional brain changes that are associated with adverse psychometric outcomes in the medium term.

O/5/THU/03

Advanced glycation end-products consumption and skin autofluorenscence in children with type 1 diabetes

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Objective: Advanced glycation end-products (AGEs) burden can be indirectly quantified *in vivo* by measuring skin autofluorescence (SAF). In a recent study, we showed that diabetic children had significantly elevated SAF levels compared with sibling controls and that a highly correlation of SAF levels was observed among siblings (1). Here, we studied the association between AGEs consumption and SAF.
Methods: Individual quantification of nutritional AGEs intake on the last 3 months was performed with a retrospective questionnaire the day of SAF measurement in 40 children with type1 diabetes for more than 1 year.
Results: Patients were aged 5–18 years. In the cohort, HbA1c was 8.1 ± 0.9%, AGEs intake 696 ± 326 kU/3 months and SAF 1.39 ± 0.20. No association was found between AGEs intake and SAF measurement. AGEs intake was correlated with the last HbA1c (r = 0.35, P = 0.026).
Conclusion: With the retrospective questionnaire we used, no association was found in our cohort between AGEs intake and AGEs burden quantified with SAF. AGEs intake was associated with poor metabolic control.
Reference:
(1) Barat P., Cammas B., Lacoste A., Harambat J., Vautier V., Nacka F., Corcuff JB. Advanced glycation end products in children with type 1 diabetes: family matters? *Diabetes Care*. 2012 Jan;35(1):e1

O/5/THU/04

Optic nerve sheath diameter in newly diagnosed children with type 1 diabetes

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Objectives: Newly diagnosed with type 1 diabetes in children, dehydration and metabolic acidosis often occurs. It is life threatening condition. Patient's clinical condition is most commonly monitored by clinical and laboratory evaluation. Another diagnostic tool allowing to obtain detailed patient assessment is ultrasound of the optic nerve sheath diameter (ONSD).
Methods: The study included 28 children with newly diagnosed type 1 diabetes. 3 children could not be examined because of lack of cooperation. The final analysis included 25 children (11 boys) aged 8.1 ± 4.0 years, of which 8 children (3 boys) were admitted in state of diabetic ketoacidosis (pH = 7,22 ± 0,11) and 17 in compensated diabetic ketoacidosis or without ketoacidosis (pH=7, 39 ± 0,02) and one boy with hyperosmolar hyperglycemic nonketotic coma (HHNC) who was examined by bedside ultrasound of ONSD with linear probe on admission and after normalisation of biochemical parameters.
Results: In the whole group significant difference between ONSD on admission and after normalisation of biochemical parameters, was observed, respectively, 3.69 ± 0.59 mm and 3.31 ± 0.33 mm (P = 0.001).
In children with newly diagnosed type 1 diabetes, with compensated metabolic acidosis on admission, an average ONSD was significantly increased (3.64 ± 0.40 mm) comparing to control study (3.39 ± 0.32 mm) (P = 0.021). For children admitted in the state of diabetic ketoacidosis the ONSD (3.74 ± 0.96 mm) was also greater than in control study (3.12 ± 0.32 mm) (P = 0.058).
The patient with HHNC during treatment, the ONSD was decreased from 4.20 mm to 3.25 mm.
Conclusions: Preliminary studies indicate that ONSD is very usefull diagnostic tool in children with new onset of type 1 diabetes.

O/5/THU/05

Regulatory T cells with CD62L or TNFR2 expression in young type 1 diabetics: relation to inflammation, glycemic control and micro-vascular complications

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Objectives: Human T regulatory cells (Tregs) play a role in controlling autoimmunity and their dysfunctions may result in ineffective suppression of T cells. We determined percentage of peripheral blood regulatory T cells expressing CD62L and the percentage of regulatory T cells expressing TNFR2 in type 1 diabetics, assessed their relation to the clinicopathological characteristics and micro-vascular complications correlating their levels with markers of inflammation and glycemic control.
Methods: Seventy type 1 diabetics were compared with 30 healthy controls. History with special emphasis on disease duration and insulin therapy, clinical examination and laboratory assessment of high-sensitivity C-reactive protein, glycemic control and the presence of micro-vascular complications were performed. Flowcytometric determination of the percentage of regulatory T cells (Tregs), Tregs expressing CD62L and Tregs carrying TNFR2.
Results: Percentage of Tregs ($CD4^+CD25^{high}$ T cells) and $CD4^+CD25^{high}$ $CD62L^{high}$ cells was significantly decreased while $CD4^+CD25^{high}TNFR2^+$ T cells were elevated in both diabetic groups compared with controls ($P < 0.001$).Complicated patients had significantly lower frequency of Tregs and Tregs expressing CD62L with increased percentage of Tregs carrying TNFR2 than non-complicated counterparts ($P < 0.001$).ROC curve analysis revealed that the cutoff value of Tregs at 7.46%, Tregs expressing CD62L at 24.2% and Tregs expressing TNFR2 at 91.9% differentiate complicated from non-complicated cases. Multiregression linear analysis showed that HbA1c, urinary albumin excretion, and hs-CRP were independently related to $CD4^+CD25^{high}$ T cells in type 1 diabetics while hs-CRP only was independently related to Tregs with CD62L($P < 0.001$).
Conclusions: The alteration in the frequency of Tregs and Tregs expressing CD62L or TNFR2 is associated with increased inflammation, poor glycemic control and increased risk of vascular complications in type1 diabetics.

O/5/THU/06

Young adults with type 1 diabetes: after transition

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Adults returning to paediatric centres for follow-up studies provide the opportunity to review transition outcomes.
Objective: To assess education outcomes and identify issues after transition to adult services, in a cohort recruited for follow-up of microvascular complications[1].
Methods: Prior to assessments 101 adults (Eight anonymously) completed a current health care questionnaire, including knowledge of screening recommendations and individual outcomes.
Results: The median age was 23.3 [IQR: 21.7–25.3] years and diabetes duration15.1 [IQR:12.3–17.8] years; 20 were from rural areas previously accessing tertiary outreach services.
Retinopathy was present in 45/92 (49%), laser therapy required by two; diabetes related eye problems were reported by 16. Recommended retinopathy screening frequency was known by 55%, and not by 45%. Six said they did not have their eyes checked, 3 of whom stated they had no retinopathy, three did not know.
Microalbuminuria was present in 2/82; 5 stated they had kidney abnormalities and were on medication. Recommended renal assessment frequency was known by 43%, and not by 57%.
Eighty-one reported seeing an endocrinologist for diabetes care (3 monthly to 2nd yearly); 20 saw only a general practitioner (GP) (nine rural) and 13 stated they always saw the same GP.Only 66% could recall their last HbA1c value. Median HbA1c was highest (9.1%) in those seeing different GP's for diabetes management, compared to those managed by a single GP (7.7%) or an endocrinologist (8.1%) ($P = 0.005$ Kruskal-Wallis).
Conclusion: Young adults transitioned from paediatric care did not have good recall of previously taught screening recommendations or their current measure of glycaemic control. It is a concern that some do not access a constant health provider and have worse glycaemic control increasing risk for poorer long term health outcomes.
Reference:
1. J Diabetes Sci Technol 2012; **6**: 348–55.

O/5/THU/07

Mortality, morbidity and glycaemic control during transition of diabetes care: The South Glasgow experience

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Objective: The aim of this study was to determine mortality, morbidity and glycaemic control for 5 years following transition from paediatric to adult diabetes care.
Methods: This was cohort study of all persons attending South Glasgow's regional transition service. A total of 90 young people were included (46 males and 44 females) and followed up for a maximum of 5 years from the time of initial transition appointment (mean follow-up 3.19 years). Longitudinal assessments were made of motality, hospital admissions, microvascular complications and glycaemic control.
Results: Three patients (3.3%) died within 5 years of transition: two as a result of diabetic ketoacidosis (DKA) and one related to Pearson's syndrome. There were 113 hospital admissions related to diabetes. 31% (n = 28) of the cohort were admitted with DKA and this accounted for 96% (n = 108) of all diabetes related admissions. The remaining 4% (n = 5) of diabetes related admissions were due to hypoglycaemia. The overall rate of diabetes related hospital admissions were 0.4 per patient/year. 24% of patients developed diabetic retinopathy and 4% developed microalbuminuria. The prevalence of coeliac disease was 4%; 8% had hypothyroidism and one patient developed lymphocytic hypophysitis. Mean HbA1c deteriorated significantly within 6 months of the initial transition clinic from 8.85% ± 1.42 to 9.38% ± 1.8% and this was maintained throughout the follow-up period.
Conclusions: The 5 years period following transition from paediatric to adult diabetes care is associated with significant mortality, frequent hospital admissions predominately with DKA and high rates of microvascular complications.

O/5/THU/08

Mortality in a population-based cohort of early-onset type 1 diabetes

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Objectives: To estimate mortality in children and adolescents with early-onset type 1 diabetes (T1DM) in comparison to the general population in Germany.

Methods: The study cohort was selected from the nationwide diabetes register maintained at the German Diabetes Centre (completeness of ascertainment 94%). Inclusion criteria were T1DM onset occurring from 0–4 years of age during the years 1993–1999. 3179 children (53% male) were followed-up through queries at registration offices, contacts with doctors providing care (DPV database) or direct contact to patients and families. Standardized mortality ratios (SMR) were estimated from observed numbers of death and the background population mortality using person-years at risk analysis taking account of sex, age (<1, 1–4, 5–9, 10–14, 15–20, 20–23 years) and calendar period (1993–1997, 1998–2002, 2003–2007, 2008–2012) during follow-up. Poisson regression was used to compare SMRs by age group, calendar period, duration of diabetes and sex.

Results: 2816 (88.6%) patients could be followed-up with a mean follow-up time of 13.1 years (IQR: 11.8–15.3). There were 10 deaths in the cohort during 36888.9 person-years of follow-up compared with 6.4 deaths expected from the national mortality rate, giving an overall SMR of 1.56 (95% CI 0.84–2.90) (P = 0.160). The SMR did not change significantly with attained age (P = 0.054), calendar period (P = 0.560) and diabetes duration (0.325). The male SMR (1.76; 95% CI 0.84–3.70) was similar to the female SMR (1.23; 95% CI 0.40–3.81) (P = 0.593). Three deaths were related to diabetes (2 diabetic ketoacidosis, 1 pneumonia), 4 deaths had other reasons (1 car accident, 3 due to other diseases); for the remaining deaths no sufficient information was available.

Conclusions: No significant excess mortality existed following early-onset of type 1 diabetes in childhood before the onset of late complications. Older age and longer duration were not significantly associated with increased mortality.

Oral Session 6 - Monogenic Diabetes Forms and their Treatment

O/6/THU/01

Doctor knows best? Performance of clinical and calculator-assisted referral systems for children with potential MODY diabetes

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Objectives: To optimize the use of the MODY probability calculator (MPC) created by Shields et al. (www.diabetesgenes.org/content/mody-probability-calculator) in diabetic children.

Methods: We used the MPC to compute MODY probability for 617 diabetic children suspected for MODY. We evaluated purely clinical selection and second-line screening with different cut-off values for a pediatric population. A group of 851 children with T1DM excluded from screening was used as control.

Results: Children with T1DM had significantly lower MODY probabilities than those selected for genetic testing (0.31 ± 0.22 vs. 0.80 ± 0.17; $P < 0.0001$). Overall 73% of the clinically selected patients would also be picked up by the MPC with the original cut-off (0.4). However, reliance only on the MPC would result in 36 (45 for 0.61 cut-off point) false negative cases omitted by the screening procedure. Genetic diagnosis was established in 181 (29.34%) children selected on purely clinical grounds. The probability of MODY differed significantly between those with positive and negative test results throughout the study period (mean difference of 0.21 ± 0.13; $P < 0.001$). No trends in MODY probability scores throughout the study period could be ascertained, regardless of the outcome of testing ($P > 0.68$). If the patients' selection were to be supported by MPC after the initial screening, positive predictive values (PPV) of such screening would be 0.29 (95% CI 0.25–0.34) with a negative PV of 0.79 (95% CI 0.71–0.84) for the original cut-off value and 0.34 (95% CI 0.29–0.39) and 0.82 (95% CI 0.77–0.87) for the optimized one of 0.61. The two-stage screening protocol would reduce the number of patients unnecessarily referred for genetic screening by 27% [371/436] or 45% [241/436].

Conclusions: MPC can play a useful supportive role in referring children to genetic testing for monogenic diabetes by reducing the number of unnecessary genetic test procedures in patients deemed likely to have monogenic diabetes.

O/6/THU/02

Does continuous targeted medical education increase the rate of referrals for genetic testing for MODY? The Czech experience

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Objectives: To update the 13-years experience of genetic testing for MODY in Czechia and to reveal the impact of continuous training of specialists to recognize candidate families for referral.

Methods: Since 1999, all Czech endocrinologists of pediatric and adult age are being trained in recognition of candidate families for genetic testing for MODY at nation-wide and local meetings, by review articles, chapters in textbooks, website information and by a complimentary booklet for physicians and patients. The genetic testing is offered free of charge, being based on research funding and including direct sequencing, MPLA to detect structural gene derangements, and whole exome sequencing on selective basis.

Results: Between 1999 and April 2012, we have collected DNA samples and clinical data of 1698 subjects (631 families) with suspicion for MODY. Of these, genetic etiology was clarified in 603 subjects (36%) from 265 families (42%), representing 58 subjects per million population and 0.08% of the estimated number of diabetic patients. Genetic findings are listed in Tab.

Conclusions: The prevalence of Czech subjects with genetic diagnosis of MODY is high if compared to many other countries and similar to the UK. It may results from the continuous educational effort among the medical community. However, the total number of subjects identified so far represents only 5% of the conservative estimates of the real prevalence of MODY.

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Table 1 Genetic findings in MODY families

MODY subtype	Subjects (families) identified	% of all genetically clarified MODY subjects
HNF4A-MODY (MODY1)	55 (18)	9
GCK-MODY (MODY2)	402 (184)	67
HNF1A-MODY (MODY3)	107 (48)	18
IPF1-MODY (MODY4)	5 (1)	1
HNF1B-MODY (MODY5; RCAD)	11 (9)	2
NEUROD1-MODY(MODY6)	11 (2)	2
INS-MODY	5 (2)	1
ABCC8-MODY	7 (1)	1

O/6/THU/03

Neurogenin Three deficiency: insights into human pancreatic development from rare paediatric patients

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Objectives: *Neurog3*-null mice fail to develop mature islets and die from diabetes mellitus within the first few days after birth. In addition, they lack all endocrine cells in the gut. Homozygous hypomorphic mutations in humans cause a rare form of congenital malabsorptive diarrhea due to enteric anendocrinosis. We recently reported that biallelic mutations in *NEUROG3* were responsible for the disease in a patient with congenital diarrhea and permanent neonatal diabetes. We now report on *NEUROG3* mutations in a cohort of patients with severe congenital diarrhea with or without diabetes presenting in infancy or childhood.

Methods: The single coding exon of *NEUROG3* was amplified and sequenced from genomic DNA in 4 young patients with severe congenital diarrhea and either diabetes -neonatal, infancy or childhood onset – or enteric anendocrinosis on intestinal biopsies.

Results: Biallelic mutations in *NEUROG3* were identified in all probands, each one inherited from a clinically unaffected parent . The mutations and clinical features of the patients are depicted in the table. Remarkably, neither patient has ever presented with severe hyperglycemia or ketosis, not even during intercurrent illnesses.

Conclusion: NEUROG3 deficiency produces a rare syndrome characterized by severe malabsorptive diarrhea from early life and mild diabetes with a variable age of onset. This finding suggests that *NEUROG3* is important but not essential for β- cell development in humans.

Table 1 Clinical characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Female	Female	Male	Female
Current age	7 year	21 year	14 year	9 mo
Mutations in *NEUROG3*	E28X/ L135P	L135P/ L135P	L135P/ L135P	S171fsX68/ S171fsX68
Birth weight (g)	1910	2250	2250	3040
Severe congenital diarrhea	Yes	Yes	Yes	Yes
Enteric anendocrinosis	Yes	Unknown	Unknown	Yes
Diabetes mellitus	Yes	Yes	Yes	No
Age at presentation of diabetes	3 week	3 week	13 year	-
Subtype of diabetes	Permanent neonatal diabetes	Transient neonatal diabetes, relapsed at 6 year	Permanent diabetes	-

O/6/THU/04

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

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Objectives: We aimed to develop a registry for the rare genetic diseases Wolfram (WS), Alstrom (AS), Bardet Biedl (BBS) and other diabetes syndromes, containing clinical, genetic diagnostic and outcome data. The purpose is to establish the natural history of these diseases; to assess clinical management; to characterize cohorts for future clinical trials; and to establish genotype phenotype relations. This abstract describes the first 50 patients recruited.

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

The age range was 2–44 years (interquartile range 6–20 years). There were 15 patients with WS (median age 18 years (range 9–44 years), 16 with AS (14 years (2–30 years), 17 with BBS (8 years (4–16), 1 with Wolcott-Rollison and 1 with vision and hearing impairment of unknown cause. The prevalences of diabetes and median ages of onset were: WS (14/15; 6 years); AS (5/16; 13 years); BBS (2/17; 10 years); $P < 0.01$ for ages of onset WS vs AS and BBS combined). The prevalences of obesity and median ages of onset were: WS (2/15; 8 years); AS (12/16; infancy); BBS (16/17; 2 years); $P < 0.001$ for obesity prevalence WS vs. AS and BBS combined).

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

O/6/THU/05

Clinical and genetic heterogeneity of neonatal diabetes in Chile

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Introduction: Advances in the understanding of genetics of neonatal diabetes (ND) have allowed to modify the outcome of this condition and to treat some of the children with sulfonylureas.

Aim: To report a complete molecular study in a group of 17 Chilean patients with ND.

Methods: Children with onset of diabetes before 6 months of age were recruited. Patients were classified as either transient (TND, N = 4) or permanent (PND) with or without extra-pancreatic abnormalities (N = 5 and N = 8, respectively). *KCNJ11, ABCC8,* and *INS* were sequenced in all. In TND, chromosome 6q24 abnormalities were also excluded. Whenever a mutation was not identified, other candidate genes (*GCK, HNF1B, IPF1, NEUROD1, FOXP3, NEUROG3 and GATA6)* was carried out according to their phenotype.

Results: In TND, chromosome 6 abnormalities were identified in 2 cases and a further patient heterozygous R1380P mutation in *ABCC8* (N = 1). One proband remained molecularly undiagnosed. Four patients with isolated PND carried a *de novo* heterozygous mutations in *KCNJ11* (E51G, R201L, and R201H (n = 2)). Mutations in *ABCC8* were present in two siblings who were compound heterozygotes for mutations L438/M1290V and a child harboring a heterozygous Q211K mutation. One proband was negative for all tested genes. In PND and associated extra-pancreatic features, 2 unrelated probands with congenital malabsortive diarrhea were

homozygous for L135P mutation in *NEUROG3*. A missense mutation in *GATA6* was found associated with primary hypothyroidism. Two siblings with PND with hyperuricemia and developmental delay tested negative. All the patients with abnormalities in the potassium chanenel genes were successfully transferred to glybenclamide.
Conclusions: A molecular diagnosis was satisfactorily made in 14/17 patients and allowed transfer from insulin to sulfonylureas in 6 children. Despite a high prevalence of *KCNJ11* and *ABBC* genes, other molecular defects are present in an important proportion of the patients with ND.

O/6/THU/06

Effectiveness of GLP-1 receptor agonist in MODY3 and mitochondrial diabetes

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Objective: Patients with MODY3 and mitochondrial diabetes (MD) have impaired ATP production in mitochondria and decreased endogenous insulin secretion as the disease progresses. The first treatment in uncontrolled patients with these two types of diabetes should be insulin-secretion enhancers such as sulfonylureas (SUs). However, the patients show a gradual decline in endogenous insulin and finally require insulin treatment. On the other hand, a new drug for type 2 diabetes (T2D), the GLP-1 receptor agonist, is known to be effective in some patients with T2D via a mechanism involving increased insulin secretion proportionate to concentrations of blood glucose and suppression of glucagon, etc. We treated pediatric patients with MODY3 and MD using a GLP-1 receptor agonist (GLP-1 RA).
Cases: A 12-year old girl with MODY3 (mutation of HNF-1 alpha gene: c.1054delT) was treated with insulin from the time of diagnosis for 6 months and achieved adequate glycemic control. Besides, a 16-year old girl with MD (point mutation of mtDNA at the position of 3243) had been treated with SUs for 2 years, but did not achieve optimal glycemic control. Genetic analyses of these two patients suggested that treatment could be switched to GLP-1 RA. After the introduction of GLP-1 RA, the MODY3 patient maintained good glycemic control with HbA1c levels of 6–7.5%, and the MD patient improved HbA1c levels from 9.1% to 7.6%, and both showed increased postprandial CPR levels from 2.5–3 ng/mL to 3–6 ng/mL. No adverse events associated with GLP-1 RA were observed.
Conclusions: Patients with MODY3 and MD may achieve good glycemic control with GLP-1 RA. This effect is not caused by increased ATP production, which is impaired in these two types of diabetes, but rather via a sub-pathway of insulin secretion in response to increased c-AMP production. GLP-1 RA could be used first in place of SUs, for MODY3 and MD patients with residual insulin secretion.

O/6/THU/07

Heterogenous phenotype of patients with mutations in the HNF1B gene causing renal cyst and diabetes syndrome (RCAD, MODY5)

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Objectives: Heterozygous mutations in the *HNF1B* gene cause hereditary diabetes (MODY) and nondiabetic renal lesions named as Renal Cysts and Diabetes (RCAD) syndrome. Aim of our study was to investigate the *HNF1B* gene in the different cohorts of patients.
Methods: The *HNF1B* gene was investigated by MLPA (Multiplex Ligation Probe-dependent Amplification) and direct sequencing in a total of 148 patients from 3 cohorts:
(1) 116 children with various cystic kidney diseases (median of current age 16 years, IQR 11–21),
(2) two patients with RCAD and
(3) 30 patients with MODYX (clinical picture of MODY with no mutations in the known genes and without nondiabetic renal disease).
Results: Heterozygous anomalies in the *HNF1B* gene were identified in 11 patients. In 8 of 116 children (6.9%) with cystic kidney diseases mutations V61G, IVS1-1G > C, R165H, or whole gene deletions were detected. Five of them suffer from chronic renal insufficiency, two underwent kidney transplantation at the age of 2 and 5 years. Diabetes was observed only in two patients: a 17-year old patient manifested diabetes during the growth hormone therapy and in a 11-year old girl impaired glucose tolerance was subsequently detected. Both patients with RCAD carry heterozygous whole gene deletions, one of them, a 53-year old patient also suffer from pancreas atrophy. In one out of 30 MODYX families, novel mutation R235W was found in a 26-year old patient and her 51-year old mother, both treated with insulin since 17 and 30 years, respectively.
Conclusions: We found very heterogenous phenotypes associated with mutations in the *HNF1B* gene ranging from chronic renal failure without glucose homeostasis impairment, over combination of diabetes and cystic kidney diseases, to patients with diabetes exclusively. In contrast to other subtypes of MODY, the progression and treatment of patients with mutations in the *HNF1B* is difficult to predict.
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O/6/THU/08

Prevalence of MODY among diabetic children and adolescents without islet autoantibodies in Sweden, the BDD study

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The prevalence of monogenic β-cell diabetes (MODY) among children with diabetes is thought to be 1–2% of all types of diabetes but due to lack of systematic studies of large cohorts the true prevalence is unknown. Better Diabetes Diagnosis (BDD) is a prospective study including almost all children below the age of 18 at diagnosis of diabetes in Sweden. A total of 4120 children were diagnosed with all types of diabetes between May 2005 and December 2010. The analysis of autoantibodies against insulin, GAD65, IA-2 and three variants of ZnT8 showed 391 (9%) children without islet autoantibodies (ab). In 302 of these children, the MODY genes for glucokinase (GCK), hepatocyte nuclear factor 1 α (HNF1A) and 4 α (HNF4A) were successfully sequenced at the University of Exeter. Before the systematic sequencing of MODY genes in this study these 302 patients were

classified as type 1 diabetes (T1D)(154), T2D (61), MODY (26), unclear diabetes (28), secondary diabetes (25) and 8 had hyperglycemic episodes without diabetes. Sequencing showed mutations in the 3 MODY genes studied in 39/302 (13%). 44% had mutations in GCK, 28% HNF1A and 23% HNF4A. Two subjects had mutations in both the GCK and HNF1A genes. In the T1D group 8/154 (5%) were genetically MODY positive, in T2D 8/61 (13%), in MODY 21/26 (81%), and unclear diabetes 2/25 (7%). No MODY was found among subjects with secondary diabetes or episodic hyperglycemia. Among MODY positive subjects with T1D diagnosis parental diabetes was present in 5 of 8 subjects and among T2D in 5 of 8.

In Conclusion, MODY was found in 1% of all and 13% of ab negative children. Genetically positive MODY was found among subjects previously classified both as T1D and T2D. Since treatment of MODY differs from both T1D and T2D treatment, sequencing of MODY genes among islet autoantibody negative subjects with diabetes should be considered.

Oral Session 7 – Diabetes Care, Education, Psychosocial Issues II

O/7/FRI/01

Improving the care of young people with T1DM and poor glycaemic control (HbA1c>10%)

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Objectives: Provision of best practice T1DM care is difficult and diabetes teams struggle in particular to help young people with sustained (>3 m) HbA1c>10% and psychosocial co-morbidities. Causes include staff burnout and lack of expertise in dealing with these co-morbidities. We examined the effectiveness of a continuing education program and a management pathway to help diabetes teams care for young people with HbA1c>10%.
Methods: Seven teams (5 non-tertiary) across Queensland in 2011 provided care for 1113 young people with diabetes (49.9% female, mean age 11.9 ± 4.0 year, duration 4.3 ± 3.7 year, mean HbA1c 8.5 ± 1.6%, 155 (14.4% of total) with HbA1c>10%).
Continuing education program; initial site visit by an experienced health psychologist followed by monthly videoconference case studies facilitated by a child psychiatrist to give education on assessment and care of psychosocial co-morbidities.
Management pathway for young people 12–18 year with T1DM and HbA1c>10% for >3 m; developed by multidisciplinary expert team, based on NHMRC and ISPAD guidelines, provided a mechanism to formulate the psychosocial co-morbidities, promoted multidisciplinary team and patient-centred care.
Results: The project made a positive difference to health care practice in 61% of health professionals; 96% felt that the continuing education had met their needs, in particular the videoconferences to non-tertiary centres with limited access to mental health services. 123 subjects were eligible for the Management Pathway; 48 were provided this extra care. There was, in these patients, a mean 1.3% reduction in HbA1c in the 9 m of the project.
Conclusion: We have identified and addressed unmet needs by providing continuing education and a management pathway for the care of this difficult patient group (>10% HbA1c). On-going support via regular videoconferences appears vital to assist diabetes teams to work with young people to achieve positive outcomes in difficult circumstances.

O/7/FRI/02

The effect of automated bolus calculators on HbA1C in children with type 1 diabetes

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Introduction: Adult data shows flexible intensive insulin therapy and automated bolus calculators (ABC) significantly improved HbA1c[1]. There is no published data regarding ABCs in children with type 1 diabetes (T1DM) to date.
Objective: To investigate the effect of ABCs on HbA1c in children with T1DM on multiple daily injection regimes, at a UK children's hospital.
Methods: ABCs were predominantly offered to children with suboptimal glycaemic control. Patients were trained in using the device, including insulin bolus advice for meals and correction doses, with no insulin regime changes. Those within 12 months of diagnosis (potentially in partial remission phase) were excluded. HbA1c was recorded prior to ABC use, 1–3 months and 3–6 months after.
Results: 31 patients were identified (age 7–16 years, M:F 18:13) with duration of diabetes 1–14 years. There was a 7 mmol/mol (0.6%) reduction in median HbA1c at 3–6 months post ABC use (median HbA1c pre ABC- 74 mmol/mol (8.9%) interquartile range (IQR) 64–84, 3–6 months post- 67mmol/mol (8.3%) IQR 56–81). Patients with HbA1c in target <58 mmol/mol (7.5%) increased by 14% (pre ABC 7% and 3–6 months 21%).
Conclusion: This preliminary data shows a noticeable reduction in HbA1c with ABC use and a substantial increase in patients with a HbA1c within target. We believe there may be great potential for using ABCs to vary insulin to carbohydrate ratios through the day and improve confidence in insulin sensitivity factor calculations to correct hyperglyceamia, thus improving control. ABCs, when used with appropriate training, may also increase independence for children and support families in self-management of T1DM. A randomised control trial with larger patient numbers and long term outcome measures is needed to determine the overall impact of ABCs on clinical outcomes.
Reference:
1. Schmidt S. et al., Use of an automated bolus calculator in MDI-treated type 1 diabetes. Diabetes Care, published online diabetes http://care.diabetesjournals.org

O/7/FRI/03

Multiple daily injection therapy in children with type 1 diabetes: effectiveness of carb counting and automated bolus calculator

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Objective: To investigate the effect of CarbCount (CC) with or without an automated bolus calculator (ABC, AccuCheck Expert, Roche) in children with type 1 diabetes (T1D) treated with multiple daily injections (MDI).
Methods: This was a 18-month prospective, controlled, observational study of 58 children aged 6–16 years with T1D from 1–13 years. The patients were divided in 4 arms: control (n = 10), experienced CC (n = 11), experienced CCABC (n = 12), not experienced CCABC (n = 25). Experienced CC children were using CC since diabetes onset, while patients without CC experience were educated to CC at the start of the study. HbA1c, insulin requirement, glycemic variability, (HBGI and LBGI) were evaluated at baseline and after 6 and 18 months.
Results: At baseline age, disease duration, BMI and HbA1c were not different in the 4 groups, while insulin requirement was higher in patients with CC experience (P = 0.016). HBGI and LBGI were also higher in patients with CC experience (P = 0.005 and P = 0.000, respectively). For the first 6 months ABC was settled according to manufacturer standard setting, while in the following 12 months ABC setting were personalized according to patients' features. At 6 months, the HbA1c did not significantly change among groups (pNS), while after 18 months we observed a significant HbA1c improvement in experienced CCABC patients, but not in other groups (P = 0.000). BMI and insulin requirement were not significant throughout the study. HBGI was higher in patients with vs without CC experience (P = 0.001 and P = 0.000, respectively by ANOVA). LBGI was higher in the

same group onlty after 6 months (P = 0.000), but not after 18 months (pNS), due to personalization of ABC setting.
Conclusions: CC since the onset of diabetes seem to be the pivotal factor to improve glycemic control in TID children using MDI. ABC with a correct personalized setting demonstrated to improve both HbA1c and LBGI values, when compared to patients using only CC or controls.

O/7/FRI/04

Health related quality of life among Norwegian children and adolescents with type 1 diabetes on intensive insulin treatment: a population based study

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Objectives: To examine HRQOL in children and adolescents with type 1 diabetes based on their own report and that of their parents. The Norwegian Childhood Diabetes Registry covers 98% of all patients in Norway. 99% use intensive insulin treatment.
Methods: All patients 8–19 years of age were invited. The DISABKIDS paperbased, questionnaires previously evaluated for Norway were filled in by the responders. High scores indicate better HRQOL.
Results: 978 patients, 48% of the total eligible patient population, responded and were included in the study. 1032 parents responded. Mean diabetes duration was 5.0 years (SD 3.3). 51% were girls. 56% used insulin pumps, 43% used multiple insulin injections, predominantly long acting insulin analogs and rapid insulin analogs. Mean HbA1c 8,5% (SD 1,3). The responders had slightly lower HbA1c (-0.3%), and were slightly younger (1 year) then the non-responders of the total registry population. No significant differences were found in regard to comorbidities and acute or chronic complications. HRQOL scores were between 76 and 84 on DISABKIDS subscales and total HRQOL score were 78. Girls scored generally lower than boys. Parents scored significantly lower on most DISABKIDS subscales. Increased HbA1c are related to lower score on HRQOL. Regression analyses demonstrated significant relation between HRQOL score HbA1c and gender. No significant differences in HRQOL score was found between insulin-pump users and those on multi-injection treatment.
Conclusions: The Norwegian childhood diabetes population seem to have HRQOL score similar to other European DISABKIDS studies. Diabetes teams should be encouraged to use HRQOL instruments to uncover which patients need greater effort in order to apply personalized treatment regimes. Insulin pump treatment does not seem to positively affect HRQOL compared to intensive injection treatment.

O/7/FRI/05

Ninety minute and fasting C-peptide are reliable and practical alternatives to a full mixed meal tolerance test in pediatric type 1 diabetes

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Objective: The mixed meal tolerance test (MMTT) area under the curve C-peptide (AUC CP) is the gold standard measure of endogenous insulin secretion in Type 1 diabetes but is intensive and invasive to perform. Ninety minute MMTT stimulated serum CP ≥ 0.2 nmol/l (90 CP) is related to improved clinical outcomes and CP ≥ 0.1 nmol/l is the equivalent fasting measure (FCP). We assessed whether 90 CP or FCP are alternatives to a full MMTT.
Methods: C-peptide was measured during 1334 MMTTs in 421 Type 1 diabetes patients aged <18 year at 3, 9, 18, 48 and 72 months duration.
We assessed: (1) Correlation between mean AUC CP and 90CP or FCP
(2) Sensitivity and specificity of 90CP ≥ 0.2 nmol/l and FCP ≥ 0.1 nmol/l to detect peak CP ≥ 0.2 nmol/l and the equivalent AUC CP.
(3) How the time to reach the CP peak varied with age of diagnosis and diabetes duration.
Results: AUC CP was highly correlated to 90CP ($r_s = 0.96$, $P < 0.0001$) and strongly correlated to FCP ($r_s = 0.84$, $P < 0.0001$). AUC CP ≥ 23 nmol/l/150 minutes was the equivalent cut-off for peak CP ≥ 0.2 nmol/l (98% sensitivity/97% specificity). 90 CP ≥ 0.2 nmol/l correctly classified 96% patients using AUC or peak CP, whereas FCP ≥ 0.1 nmol/l classified 83% and 85% patients, respectively. There was only a small difference seen between peak and 90 CP (median 0.02 nmol/l). The CP peak occurred earlier in patients with longer diabetes duration (6.1 minutes each 1 year increase in duration) and younger age (2.5 minutes each 1 year increase).
Conclusions: 90 CP is a highly sensitive and specific measure of AUC and peak CP in children and adolescents with Type 1 diabetes and offers a practical alternative to full MMTT.

O/7/FRI/06

Diabetes management among children under excellent control in the T1D Exchange Clinic Registry: how do they do it?

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Objectives: Optimizing glycemic control in type 1 diabetes (T1D) is important to minimize the risk of complications. We used the T1D Exchange database from 58 U.S. clinics to identify differences in patient characteristics and in diabetes management techniques by comparing patients with excellent control versus those with poorer control.
Methods: Among registry participants 6–17 years old with diabetes duration >1 year, those with HbA1c levels <7% (excellent control, N = 724) were compared with those with HbA1c levels ≥9% (poorer control, N = 2570). Chi-square tests were employed to examine the association between participant characteristics and the two HbA1c groups.
Results: The excellent control group had more non-Hispanic white than the poorer control group (84% vs 71%), higher parent

education (72% vs 37% with a bachelor's degree or higher), higher income (69% vs 39% with annual income ≥$75,000) and more private insurance coverage (85% vs 59%). The two groups also differed substantially on their diabetes management behaviors (Table). These relationships appeared similar across ages.

Conclusions: Individuals with excellent glycemic control tend to be of higher socio-economic status than those with poorer control. They also tend to manage their diabetes differently with respect to insulin delivery modality, frequency of blood glucose monitoring, timing of meal boluses, use of insulin:carbohydrate ratios, and require lower insulin doses on average.

	HbA1c <7%	HbA1c ≥9%	P-value
Using insulin pump	69%	43%	<0.001
Gives insulin bolus prior to starting meal	66%	52%	<0.001
Varied insulin:carbohydrate ratio at the three meals	58%	33%	<0.001
Blood glucose measurements ≥6 times/day	66%	34%	<0.001
Always checks blood glucose before bolusing	75%	54%	<0.001
Never or rarely (<once/week) misses insulin doses	89%	54%	<0.001
Always gives bolus for daytime snacks	43%	25%	<0.001
Exercises >3 days/week	86%	76%	<0.001
Insulin use units/kg/day, mean ± SD	0.8 ± 0.4	1.0 ± 0.5	<0.001

O/7/FRI/07

Managing diabetes in the context of emerging adolescence

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Objectives: Conduct focus groups to obtain consumer perspectives of challenges and enablers for adolescents living with diabetes and their parents to inform the adaptation of a resilience building program for adolescents with diabetes.

Method: Adolescents aged 13–14 years, and their parent/s were invited to participate in separate focus groups to share their experiences of living with diabetes (adolescents) or parenting an adolescent with diabetes. Dialogue transcribed by a stenographer (adolescents) or audio recorded and transcribed (parents) was analysed using a qualitative methodology with Nvivo 9 software.

Results: Thematic analysis identified enablers and challenges to living with diabetes or parenting an adolescent with diabetes. The frequency of reported challenges exceeded perceived enablers. The most frequently reported challenges for parents included parenting issues such as managing their child's independence within the context of diabetes, providing support for their child's diabetes management and maintaining ''vigilance''. For adolescents, the most frequently reported challenges related to the tasks required to manage their diabetes, negative parental support, demands on their time to manage diabetes and feeling different from their peers. Peer support, positive parental support and not feeling different from peers were most frequently reported by adolescents as enablers to living with diabetes. For parents, the most frequently reported enablers to parenting an adolescent with diabetes included maintaining contact and communication with their child when away from home and obtaining peer support for parents.

Conclusions: Negotiating developmentally appropriate emerging adolescent independence with the need for vigilance around diabetes management created challenges for both adolescents and their parents. Peer support was a key enabler for both adolescents with diabetes and their parents, as was good communication between parent and adolescent.

O/7/FRI/08

Type I diabetes and Ramadan: safety and efficacy of fasting in relation to different diabetic regimens

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Objectives: Considering diabetic children and adolescence with type I diabetes that want to fast Ramadan, this study is designed to asses the safety and metabolic effects of Ramadan in relation to different insulin regimens to provide them with the best regimen that make fasting safe.

Methods: During Ramadan 2008, 41 children and adolescents with Type-I diabetes agreed to participate in this study. Twenty one patients maintained multiple daily injections (MDI) regular insulin (RI) and insulin NPH (NPH), 10 patients maintained on MDI [(RI and insulin glargine (IG)] and 10 patients on pre-mixed insulin 30/70 (PMI).

Pre and post-fast evaluation of fructosamine, HbA1C and lipid profile in comparison to different modulated diabetic regimens during Ramadan.

Results: Out of 41 patients 17 (41.5%) patients fasted the whole month of Ramadan and the remaining 24 (58.5%) patients fasted 25–28 days. There was significant decrease in the values of fructosamine (pre-fast compared to post-fast) in all insulin regimens. No significant difference in the values of HbA1c, HDL in all regimens. Cholesterol, LDL and triglycerides (TG) were significant increase in post-fast value compared to pre-fast value variably in relation to different diabetic regimens.

Conclusion: Whatever the insulin regimen, diabetic children use; it can be modulated and adjusted during Ramadan to fast safely with improvement in metabolic control. Much consideration to the type and amount of food offered to our children during this month to guard against the changes in lipid profile.

Oral Session 8 – Pumps and Sensors

O/8/FRI/01

Adolescents' expected and experienced benefits and risks at using a closed loop system during a 3 days pilot study (DREAM project)

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Objectives: To assess the subjective expectations and experiences of young people with T1D associated with the use of a wireless artificial pancreas (DREAM project, Israel, Slovenia, Germany).

Methods: In the German DREAM substudy, before and after being connected with the artificial pancreas 18 adolescents completed a structured questionnaire on their feelings associated with the new system. The questionnaire consists of nine items (5-point-Likert-scale) on expected/experienced benefits (e.g., metabolic control, security), risks (e.g., hypoglycaemia, impairment) and confidence. Two open questions focus on additional (dis-) advantages and the willingness to use the system on the long run. Clinical characteristics and data on metabolic control were taken from medical history.

Results: The sample consists of 18 adolescents with T1D on CSII (mean age 14.2 ± 1.5 year; 33% female; mean DMduration 8.0 ± 2.6 years; CSII use since 5.7 ± 1.8 years; mean HbA1c 8.2 ± 0.9%). Before starting the closed loop system 67% of the patients expected mostly better metabolic control, 61% more security, 50% less hypoglycaemia. 83% of the patients expected no or a low risk of hypoglycaemia, 95% deterioration of metabolic control. 17% expected mostly impairment of daily activities, 11% sleep disturbance. 78% confided mostly in the system, 95% rated the system as reliable. After one night connected with the system, the feeling of security increased significantly (3.9 ± 1.0 vs. 4.4 ± 0.5, P = 0.046). The ratings of benefits remained unchanged on a high level, the ratings of risks on a low level. 89% of the participants would like to use the system constantly, but 78% criticize the system size. In addition 28% of the young people anticipated a relief of burden of self-management tasks.

Conclusion: The first German participants using the closed loop system during the DREAM CAMP felt secure, their level of fear was low. They expect benefits in quality of control, security and in reducing the burden of therapy in daily life.

O/8/FRI/02

Adherence to the Warsaw School of Pump Therapy and using of different types of boluses for meals in children and adolescent with type 1 diabetes

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Objectives: Insulin pumps gives possibility to use different types of boluses: normal, square or dual-wave (S/DW). The Warsaw School of Pump Therapy (WSPT) includes an educational program on insulin dosage for Fat-Protein Units (FPU) along with Carbohydrate Units. The aim of this study is to assess the patient's adherence to WSPT recommendations and its effect on glyceamic control.

Method: WSPT is well-defined. Every patient of our outpatient diabetes clinic is familiar with this method. Analysis include data collected prospectively (12 weeks) from glucose meters and insulin pumps. Frequency of S/DW boluses/day, no. of boluses /day, BG tests/day, hemoglobin A1C, percentage of hyper-, hypo- and normoglycaemia were analyzed.

Results: Participants (n = 95, F-M 50/45, mean age 11.5 ± 3.5, diabetes duration - 5.8 ± 3.6 years, mean A1C – 7.26 ± 1.26%, mean Total Daily Dose (TDD) – 37 μ ± 18, mean basal-to-bolus rate: 35–65%) were dosing average 7.7 ± 2.8 boluses, 1.6 ± 1.3 S/DW and testing BG 7 times a day. Only 3 of 95 participants were not using any of S/DW bolus, 30 was using rarely: 0.2 < 1/day. 62 of 95 were using more than ≥1 S/DW bolus a day and were called ''adherent'' to WSPT recommendations. There were significant (P < 0.001) differences between ''adherent'' and ''non-adherent'' participants in A1C: 7 ± 0.8% vs. 8.2 ± 1.7%, ratio of S/DW boluses to boluses/day: 27% vs. 8%, percentage of normoglycemia: 58% vs. 42% and hyperglycemia: 32% vs. 49%. There were no differences in duration of diabetes, percentage of hypoglycemia and TDD. There were no significant differences between age groups (≤9, 10–14, ≥15 years) in any of analyzed factors.

Conclusions: Most of the participants of WSPT educational program were adherent to WSPT method and dosed at least 1 D/SW bolus a day. Adherence to the method is related to better glyceamic control.

O/8/FRI/03

Real-time CGM is necessary to improve hypoglycemia detection in children younger than 7 years with T1DM

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Objective: To investigate how and when hypoglycemia is detected in children younger than 7 years of age with T1DM.

Methods: Twenty three children (12 girls, 18 on CSII and 5 on MDI, mean age 4.5 years, mean diabetes duration 2.0 years, year mean HbA1c 58.8 mmol/mol, 9.7 SMBG/day) used CGMS Gold (Medtronic). The sensor system was applied and calibrated according to instructions from the manufacturer. The monitor was blinded. Data on symptoms of hypoglycemia and p-glucose values were collected via a logbook. Data from p-glucose meters were uploaded via Diasend (Aidera). Families were asked to provide data from two weeks, one in autumn and one in spring. Hypoglycemia was defined as a glucose value ≤3.9 mmol/L.Detection was defined as a measured p-glucose value ≤3.9 mmol/L in meter memory or logbook. Night was defined as 22.00–06.00.

Results: Mean CGM registration time was 204 hours, with a total of 4689 hours available for analysis. The frequency of CGM-registered hypoglycemia was 2.1/24 hours. There were 443 hypoglycemic events with glucose levels ≤3.9 mmol/L; 65% had a nadir glucose ≤3.6 mmol/L and 33% ≤3.0 mmol/L. Data on detection and symptoms were available on 387 of 443 events. 35% of hypoglycemic events were concordantly recorded by CGM and SMBG, 5% only by CGM and 8% only by SMBG. On 52% of events there was no SMBG.

Conclusions: Only 2% of night time hypoglycemia and 10% of all hypoglycemia in children younger than seven years with T1DM are symptomatic.The most common cause of detection of hypoglycemia was scheduled or random measurement of p-glucose. Despite frequent SMBG, half of hypoglycemic events go undetected and only a fifth are detected within 30 minutes. Real-time CGM is necessary to improve hypoglycemia detection in children younger than 7 years with T1DM.

O/8/FRI/04

Characterization of metabolic responders on insulin pump treatment amongst children and adolescents in Denmark from 2007–2012

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Aim: The purpose of this prospective follow-up study was to identify responders vs. non-responders amongst children and adolescents with insulin pump treated Type 1 diabetes mellitus.

Methods: The following parameters were collected from six Danish centres: gender, age at pump initiation, diabetes duration, indication for pump treatment, HbA_{1c} level, number of SMBG, number of insulin boli, number of pen injections and the use of carbohydrate counting (CHOC) prior to initiation and during follow-up for 24 months of pump treatment amongst 562 children and adolescents (255 males). Response was defined as a decrease of ≥1% in HbA_{1c} level or a decrease to the recommended treatment goal of HbA_{1c}<7.5%.

Results: At pump onset prepubertal stage, ≥5 daily SMBGs, >4 pen injections and CHOC were all associated to lower HbA_{1c} (mean HbA_{1c} 8.3%). After 12 months of pump treatment 38% were categorized as responders (HbA_{1c} 7.4%) decreasing to 29% after 24 months (HbA_{1c} 7.3%)(P = 0.044). At 24 months, stratifying for age at onset, 47% of the children < 6 years of age qualified as responders vs. 23% of the children aged 6–12 years and 25% of the adolescents aged 12–19 years (P = 0.019). High (>9%) HbA_{1c} at pump initiation was associated with more responders at both 12 and 24 months follow-up (P < 0.0001, P = 0.0005). ≥7 daily boli was associated with a lower HbA_{1c} after 12 and 24 months, (51 vs. 85%, P < 0.0001, 36 vs. 67% P = 0.002), whereas ≥5 daily SMBGs only associated with a lower HbA_{1c} after 24 months (72 vs. 92%, P = 0.004). No differences between responders and non-responders were observed for gender, pump indication, diabetes duration or CHOC over time.

Conclusion: Age <6 years or high HbA_{1c} at insulin pump initiation were associated independently with a better metabolic outcome, however, even within this age group more than half of the population did not achieve a HbA_{1c} <7.5%. Responders were characterized by measuring ≥5 daily SMBGs or taking ≥7 daily boli.

O/8/FRI/05

Efficacy of automatic insulin pump suspension in youth with type 1 diabetes

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Objectives: The ASPIRE study evaluated the glycemic impact of the Low Glucose Suspend (LGS) feature of the Veo insulin pump system in youth and adults with type 1 diabetes. The LGS feature automatically stops insulin delivery for 2 hours when a low sensor glucose (SG) threshold is met.

Methods: Pediatric (age 17 year), young adult (age 18–21 year), and adult (age 22–58 year) subjects underwent at least 2 experiments to induce hypoglycemia by exercising. In LGS-ON experiments, basal insulin was suspended once SG reached ≤70 mg/dL. In LGS-OFF experiments, basal insulin continued. Experiment order was randomly assigned. A successful experiment was defined by YSI glucose values <70 and >50 mg/dL with an observation period up to 4 hour. Duration and severity of hypoglycemia were compared between LGS-ON and LGS-OFF experiments.

Results: The Table shows the reduction in both duration and severity of hypoglycemia with LGS-ON compared to LGS-OFF in all age groups. Hypoglycemia was less prolonged among young adults than among other age groups. Differences between

	Pediatric	Young Adult	Adult	All Subjects
n	4	4	42	50
Duration, LGS-ON (min, mean±SD)	171.8±55.55	58.5±44.09	143.0±76.85	138.5±76.68
Duration, LGS-OFF (min, mean±SD)	224.5±16.98	96.8±94.55	172.6±73.44	170.7±75.91
P value (duration)	0.07	0.15	0.018	0.006
Severity, LGS-ON (mg/dL, mean±SD)	58.3±4.85	64.5±3.55	59.1±5.82	59.5±5.72
Severity, LGS-OFF (mg/dL, mean±SD)	54.6±2.62	61.8±4.70	57.4±5.82	57.6±5.69
P value (severity)	0.145	0.086	0.049	0.015

[Hypoglycemia in the ASPIRE study, by age group]

age groups may be an artifact (due to the small number of subjects) or may represent physiologic differences in response to exercise or hypoglycemia as an effect of age.
Conclusion: The LGS feature of the Veo pump system reduced hypoglycemia in all subjects, including pediatric and young adult. The automatic shut-off of insulin delivery at a predetermined threshold glucose value may benefit youth by mitigating hypoglycemia.

O/8/FRI/06

Acceptability and glycemic impact of the mySentry Remote Monitor

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Objectives: mySentry is the first commercial device to relay real-time pump and continuous glucose sensor (CGM) information for display elsewhere in the house. We evaluated the mySentry system in 35 children with type 1 diabetes to assess its acceptability and glycemic impact.
Methods: The mySentry system works with the Revel sensor-augmented insulin pump. The mySentry monitor receives pump and CGM data and is typically placed in a parent's bedroom for monitoring a child's data at night. Data related to battery life, remaining insulin, current and recent CGM values, and alarm conditions are displayed. An evaluation was performed in 35 patients and parents. After a run-in period of 1 week, families set up and used the mySentry system for 3 weeks. Data were uploaded to the CareLink Clinical database and surveys were conducted before and at 3 weeks. The study was not powered to detect changes in nocturnal glycemic control.
Results: The subjects had a mean age of 11.9 years and mean age at pump start of 7.1 years. At baseline, parents reported fear of unawareness of nocturnal glucose excursions. At 3 weeks, they reported greater confidence in managing diabetes. The mySentry system met predefined acceptability criteria for general experience, product usability, and training materials. Respondents found the monitor menu easy to use and understand, alarms and alerts loud enough to hear during sleep, and displays easy to interpret. Retrospective evaluation of glycemia showed reductions in nocturnal hypoglycemia and hyperglycemia in subjects with episodes in both study phases. There were no unanticipated device-related adverse events.
Conclusion: The mySentry system met all predefined criteria for acceptability and did not demonstrate any safety issues. Alerting parents to abnormal glucose values or trends may attenuate nocturnal hypoglycemia and hyperglycemia in children with type 1 diabetes by prompting appropriate and timely intervention.

O/8/FRI/07

Predictors for better metabolic outcome in children treated with CSII

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Objectives: During recent years CSII treatment has become more prevalent among Danish children with type 1 diabetes. We want to rule out possible factors at pump initiation associated to a better metabolic outcome.
Methods: A national register-based study including children and adolescents <17 years from Denmark diagnosed with Type 1 Diabetes (T1D) followed from 2005 till 2011 both years included. Clinical data was prospectively recorded, including gender, diabetes duration, age, HbA1c and ethnicity.
Results: There were 1497 females and 1486 males. A number of 1602 individuals were treated with MDI thorugh all the years, and 1381 individuals changed from MDI to CSII in the period. Before pump initiation, there was a significantly lower HbA1c in those offered pump treatment ($P < 0.001$), except for those younger than 5 years of age ($P > 0.05$). Hba1c before pump initiation was the most important factor associated with HbA1c on pump treatment ($P < 0.0001$). Also, there was a significant better HbA1c in patients, initiated on pumps in recent years ($P = 0.03$). No association with age, diabetes duration, gender or etnicity.
HbA1c increased with increasing diabetes duration in both MDI as well as CSII treated patients. However the increase was significantly lower in the CSII treated group ($P < 0.01$).
Conclusions: This is a observational, prospective, national register study, including approximately 3000 patients. The study shows that HbA1c at pump initiation is a major predictor for metabolic control on CSSI, and the results point in the direction that Danish Diabetes Centres for children seem to promote a better pump education to the patients and deliver more intensive pump treatment in recent years.

O/8/FRI/08

Waking effectiveness of a non-invasive nocturnal hypoglycaemia monitor for young people with type 1 diabetes

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Objectives: Determine the waking effectiveness of the alarm on a non-invasive nocturnal hypoglycaemia monitor for young people with type 1 diabetes.
Methods: Young people with type 1 diabetes were provided with a HypoMon system that non-invasively detects and alerts the user or carer giver to nocturnal hypoglycaemia. During the night, subjects used the HypoMon in addition to their current diabetes management. When a hypoglycaemia physiological signature was detected by the HypoMon, an audible and escalating alarm sounded. The users response was measured by the HypoMon with a time stamp registered when the user silenced the alarm via the touchscreen or alarm bar.
Results: Twenty seven subjects (type 1 diabetes, 10–25 years of age, 16 male and 11 female) had 170 alarms from 944 nights. 100% of alarms were silenced 76.6% via touchscreen, 21.9% via alarm bar and 1.5% via the power button. The fastest reaction time was around 3 seconds, for a hypo alarm and the slowest reaction time was 11 minutes and 6 seconds. Average time to silence the alarm was 1 minute 20 seconds with a median time of 37 seconds.
Conclusions: In young people with type 1 diabetes, the HypoMon alarm system is effective and well designed to ensuring users and carers giver wake when the hypoglycaemia alarm is trigged.

Oral Session 9 - Diabetes Epidemiology

O/9/FRI/01

Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign – joint epidemiologic report of the PolPeDiab Collaboration and the TEAM Programme

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Objectives: To study dynamic changes in the prevalence of different types of diabetes in paediatric populations in Poland, with a specific focus on monogenic diabetes (MD).

Methods: Using epidemiologic data (PolPeDiab Collaboration) and nationwide genetic test results (TEAM Programme) we compared the prevalence of T1DM, T2DM, cystic fibrosis-related diabetes (CFRD) and MD. Genetically confirmed MD included MODY, neonatal diabetes, Wolfram and Alström syndromes. The study covered all children aged 0–18 years treated for diabetes between 2005–2011 in three regions inhabited by 23.7% (1 989 988) of Polish children with a low prevalence of childhood obesity (<5%).

Results: The prevalence of T1DM increased from 96 to 138/100 000 children, partially due to a decreasing number of children in Poland. The prevalence of T2DM and CFRD also increased, from 0.3 to 1.01/100 000 and from 0.1 to 0.95/100 000, respectively. The prevalence of MD was stable between 4.2 and 4.6/100 000, accounting for 3.1%–4.2% of children with diabetes, with glucokinase (*GCK*)-MODY being the most frequent type.

Conclusions: The prevalence of MD in a paediatric population with a low prevalence of obesity is nearly fivefold higher than that of T2DM and CFRD, justifying a need for increased access to genetic diagnostic procedures in diabetic children.

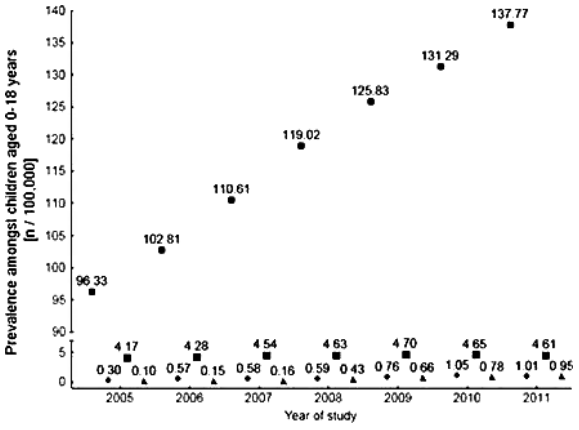

Figure 1 - Prevalence of type 1 (circles), type 2 (diamonds), monogenic (squares) and cystic fibrosis-related (triangles) diabetes amongst children in Poland.

O/9/FRI/02

Antibiotics and risk of type 1 diabetes in early childhood: preliminary results from the Norwegian Prescription Database

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Background: The role of the gut immune system in the development of type 1 diabetes (T1D) has previously been discussed. Exposure to different food or microbial agents may influence on gut immunity and further development of tolerance or autoimmunity. Antibiotics are known to disturb the natural gut microbial environment, and animal studies have found associations between uses of antimicrobial agents and T1D development. We aimed to study the effect of early exposure to antibiotics on T1D development in a cohort of Norwegian children.

Methods: The Medical Birth Registry of Norway (MBRN) was linked to The Norwegian Prescription Database (NorPD) for children born between January 1,2004 and December 31, 2010. Children with T1D and time of onset were identified by first prescription of insulin. Registered use of antibiotics in the time period was identified for the children. Preliminary results were analysed using a Cox-regression model with time-dependent exposure to antibiotics (non-exposed up to the first antibiotics prescription and exposed thereafter).

Results: In a cohort of 4 24 817 children, 277 were identified with T1D during a median follow-up of 3.4 years (range 0.02–6.9). Among children with T1D 47.3% had one or more prescriptions of antibiotics before diagnosis compared to 50.0% in the general population. The hazard ratio was 0.94, not significant. Similar results were found using logistic regression [odds ratio 0.89 (0.71–1.14)].

Conclusion: We found no association between use of antibiotics in early childhood and development of type 1 diabetes in these preliminary analyses.

O/9/FRI/03

Prediciting honeymoon length in newly diagnosed children with type 1 diabetes mellitus based on age, initial HbA1c, and pH; a review of a tertiary hospital database

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Objectives: The honeymoon period in type 1 diabetes mellitus (T1DM) is a period of ongoing endogenous insulin secretion and represents an opportunity for immuno-modulatory interventions. Glycaemic control in the first 12 months is also correlated with risk of long-term complications. The aim of this study was to investigate whether easily obtainable; baseline data are predictive of honeymoon duration.

Methods: Baseline (age at diagnosis, HbA1c, pH) and 12 month post-diagnosis data from 01/01/2005 to 31/12/2010 was extracted from a tertiary children's hospital T1DM database. Honeymoon status was defined by an insulin adjusted HbA1c [IDAA1C = HbA1c + (4 x Insulin/kg)] of <9.

Results: Examination of the baseline data revealed a diabetic ketoacidosis (DKA) rate (pH < 7.3) of 34%. The mean HbA1c in the DKA subgroup was greater than the non-DKA subgroup (12.67% vs.11.34%, P < 0.001). Bivariate analysis demonstrated that patients no longer in honeymoon at 12 months post diagnosis were younger at diagnosis (8.23 vs. 10.21 years, P = 0.028) and had a higher initial HbA1c (11.58% vs. 9.96%, P = 0.014) than patients still in honeymoon. No significant inter-group difference in pH was detected, although the trend indicated a lower pH in the honeymoon group (P = 0.07). There was also no correlation between age at diagnosis and baseline HbA1c.

Conclusions: The results suggest that a younger age at diagnosis and a higher baseline HbA1c independently predict a shorter honeymoon in children with T1DM. If confirmed these findings support close monitoring and intensive treatment of younger patients with a high initial HbA1c (>10%) as it is known that a shortened honeymoon is associated with an increased risk of complications. Given the higher DKA rate and the associated trend towards a shorter honeymoon, public health action could be recommended to reduce the incidence of DKA in first presentation and therefore the burden of disease.

O/9/FRI/04

Tissue transglutaminase antibodies in children with newly diagnosed type 1 diabetes and their first-degree relatives

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Objectives: As type 1 diabetes (T1D) and celiac disease (CD) cluster in individuals and in families, we set out to determine the prevalence of transglutaminase antibodies (TGA) and CD in newly diagnosed children with T1D and their first-degree relatives. We tested the hypothesis that HLA class II genotypes, islet autoantibodies, or clinical characteristics at T1D diagnosis differ between TGA-positive and negative subjects.

Methods: This cross-sectional observation study included 745 newly diagnosed index children with T1D and their 2692 first-degree relatives from the nationwide Finnish Pediatric Diabetes Register. Questionnaires provided information on the prevalence of CD, and a radiobinding assay was used to measure TGA. The register included information on the clinical characteristics at diagnosis, HLA class II genotypes, and islet autoantibodies.

Results: Among the index children, 5.0% had TGA, but only 0.7% known CD. Among the relatives, 3.0% had TGA (5.0% of the mothers, 2.6% of the fathers, 2.1% of the siblings), and 0.5% CD (1.2% of the mothers, 0.4% of the fathers, 0.2% of the siblings). Among the 118 subjects positive for TGA, 64% carried the DR3-DQ2 haplotype, and among the 20 subjects with CD 65%. Positivity for TGA associated with this haplotype (P < 0.001) and with history of autoimmune diseases (P = 0.001). An association with female gender (P = 0.02) was observed only in adults. Among the first-degree relatives, TGA associated with GADA positivity (P = 0.02). In the index children, having TGA did not affect their clinical characteristics.

Conclusions: In children with newly diagnosed T1D and in first-degree relatives, TGAs were six-fold more common than was known CD suggesting a considerable proportion of possible silent CD. Positivity for TGA associated with the DR3-DQ2 haplotype, history of autoimmune diseases, and GADA., although in children with newly diagnosed T1D, it had no effect on autoantibody profile or clinical characteristics.

O/9/FRI/05

Use of electronic health records to estimate 5-year incidence of diabetes among Health Maintenance Organization (HMO) members <20 years of age: the SUPREME-DM project

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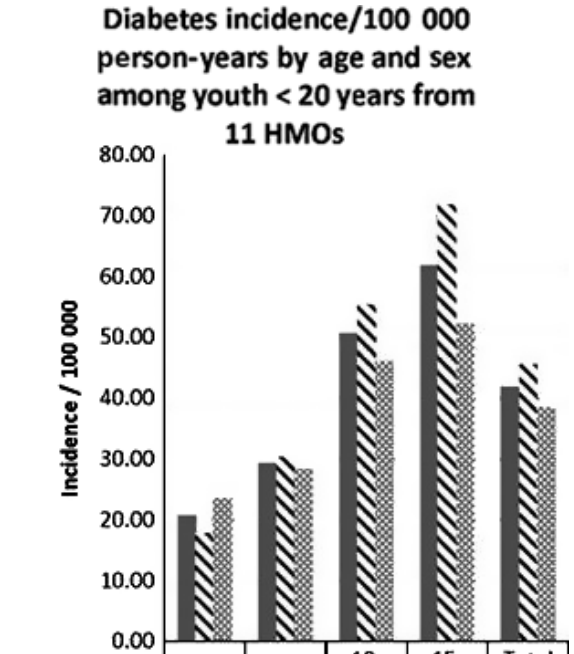
Objective: To estimate total diabetes (DM) incidence rates using electronic health records (EHR) for youth <20 years of age from 11 health maintenance organizations (HMO) in 10 US states.

Methods: The denominator was all HMO members <20 years of age from 1/1/2005 to 12/31/2009. To be an incident DM case, youth required ≥6 months of membership without DM prior to diagnosis, which was defined as ≥2 lab results indicating DM; ≥1 inpatient or ≥2 outpatient DM diagnosis codes; or dispensing of a glucose-lowering medication other than metformin, outside of pregnancy. Follow-up was censored on the earliest date of DM diagnosis, death, disenrollment, or 12/31/2009.



	0-4 Years	5-9 Years	10-14 Years	15-19 Years	Total 0-19 Years
Total sample	20.71	29.39	50.62	61.92	41.90
Girls	17.77	30.42	55.32	71.84	45.49
Boys	23.51	28.41	46.10	52.31	38.45

Results: We identified 4 118 DM cases in 9.8 million person-years of follow-up for a 5-year DM incidence of 41.9/100 000 person-years. DM incidence increased with age and was higher for girls than boys in the 2 older age groups. The prevalence of insulin use only, oral agents ± insulin use, and no use of any glucose-lowering medication in the diagnosis year was 58%, 23%, and 19%, respectively, for those 10–14 years; and 26%, 48% and 25%, respectively, for those 15–19 years.
Conclusions: We report DM incidence rates for 10–14 and 15–19 year olds that are higher than other US studies, perhaps due to our inclusion of some undiagnosed type 2 DM cases in our estimate of total DM incidence. EHRs provide comprehensive data for case identification and may support low-cost, continuous surveillance of childhood DM in the US.

O/9/FRI/06

Frequency of ketoacidosis at onset of type 1 diabetes in children and adolescents in France. A 1 year study in 146 pediatric centers

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Objective: To assess the prevalence and predictors of ketoacidosis at diagnosis of type 1 diabetes (T1D) in children and adolescents in France.
Methods: The following data were collected in a single year for 1299 young (<15 years) beginning T1D in 146 Pediatric centers : age, sex, duration of symptoms, course of the patient, clinical and biological parameters, family history of T1DM. Ketoacidosis was defined as pH <7.30 or an RA <15 mmol/l, severe ketoacidosis as pH <7.10 or RA <5 mmol/l.
Results: At diagnosis, 26% of the population had 0–5 years, 34% had 5–10 years and 40% had 10–15 years. The prevalence of ketoacidosis was 43.9% (0–5 years : 54.2%, 5–10 years : 43.4% and 10–15 years : 37.1%). The frequency of severe ketoacidosis was 14, 8% (0–5 years : 16.6%, 5–10 years : 14.4%, 10–15 years : 13.9% and 25.3% before 2 years). Severe Ketoacidosis was more common when the child was hospitalized at the initiative of the family (26.6%) than by a general practitioner (7.6%) or a pediatrician (5.1%). They represent respectively 30.6%, 53.7% and 9.2% of the patients. With a family history of T1D, the prevalence of ketoacidosis was 20.1% (4.4% severe). Polyuria-polydipsia was present in 97% of cases, enuresis in 56% of children with 26.9% for the 10–15 years patients. In multivariate analysis, age, patient's journey, duration of polyuria-polydipsia (<1 week) and family history of T1D are correlated with the prevalence of ketoacidosis. The age and the background are correlated with severe ketoacidosis.
Conclusion: Ketoacidosis at diagnosis of diabetes in children and adolescents is common and often serious. The age, the route to diagnosis and knowledge of diabetes are the main factors influencing the prevalence of ketoacidosis. These data support the implementation of a campaign to prevent ketoacidosis at diagnosis and will help to evaluate their effectiveness.

O/9/FRI/07

A population-based investigation of the role of life course factors in the onset of type 1 diabetes mellitus

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Objectives: To examine how life course factors may be associated with risk of paediatric T1DM onset.
Methods: Case recruitment of the type 1 diabetes cases commenced in 2008 and finished in 2011 (response rate 77% (333/434) Hospital control (day surgery attendees with minor conditions) participation rates were also high -full questionnaire data and venous blood samples available on 87% (573/661) of eligible children). Community control recruitment was also conducted 2008–2011.
Results: Adjusting for age and sex, T1DM cases compared to hospital controls, were more likely to be Caucasian (AOR) 2.28(1.42, 3.65);have fairer skin; $P < 0.001$ and a blue/grey eye colour; $P < 0.001$. Similar phenotype patterns were observed between T1DM cases to community controls. With regard to parent reported life course sun exposure, patterns were less evident but there was some indication, adjusting for age sex, skin type and ethnicity, that higher sun exposure during winter holidays was associated with decreased T1DM risk compared to hospital controls particularly in early adolescence (p trend per category increase (<1 hour, 1–2 hour, 2–3 hour, more than 3 hours) = 0.84 (0–2 years), $P = 0.06$ (3–5 years); $P = 0.69$ (6–9 years) and $P = 0.03$(11–15 years respectively). Our preliminary analysis of archived neonatal blood spots ($n = 184$), indicates ambient UVR levels in the 6 months before birth accounts for 23% of the variation of 25OHD levels in the dried blood spots. Analysis of a second biomarker, sun-induced eye corneal change, is ongoing but our preliminary analysis indicates an increase in biomarker level with age and history of past sun exposure. During 2012, viral and cytokine profiles and candidate gene variants will be assessed.
Conclusion: T1DM cases have a different skin phenotype than healthy controls at presentation. Further work will assess how this reflects sun exposure, sun sensitivity and vitamin D levels at birth and at the time of first T1DM presentation.

O/9/FRI/08

Two decades of new onset diabetes mellitus in children younger than 6 years at an academic medical center in the USA

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Objective: To compare the presentation, family history, and biochemical status at diagnosis of diabetes mellitus (DM) in children under age 6 years who presented in the decade of the 1990's in comparison to children presenting with DM in 2000–2009.
Study design: We conducted a retrospective chart review of patients age <6 years presenting with NODM from 1990 through 2009 at a pediatric academic medical center.
Results: In the first decade, 43% of patients presented in diabetic ketoacidosis (DKA) and in the second decade, 31% presented in

Age at onset (years) n (%)			DKA at Diagnosis n (%)		Family History of T1D in First-degree Relative n (%)	
	1990-1999	2000-2009	1990-1999	2000-2009	1990-1999	2000-2009
<2	64 (24)	84 (16)	50* (78)	57* (67)	8 (12)	10 (12)
2-3.99	91 (34)	181 (35)	37* (41)	57* (31)	8 (8.8)	17 (9.4)
4-6	109 (40)	247 (48)	27** (25)	43** (17)	10 (9.2)	29 (11.9)
Total	264	512	114= (43)	157= (31)	9.8%	10.9%

DKA. In the first decade two children died of cerebral edema, whereas no child died in the second decade.

Over the past 20 years, the percentage of preschool age children presenting with DM who have a first-degree family member with T1D has not changed. The proportions of patients <2 years and 4–6 years presenting in DKA at diagnosis between decades as well as overall proportion of patients younger than 6 years, respectively, have decreased significantly, i.e., Chi Square(df=1) =5.972, $P < 0.025$; 5.34, $P < 0.025$ and 11.9, ($P < 0.006$), respectively.

Conclusions: The number of children <6 years of age diagnosed with diabetes at this tertiary care center has doubled in the past decade. Although the proportion of children <6 years presenting with DKA at diagnosis from 2000–2009 is significantly less than in the decade of the 1990's, 2/3 children <2 years and nearly 1/3 diagnosed between 2 and 4 years of age presented critically ill. Parents, daycare providers and preschool teachers, and clinicians must be taught to recognize the symptoms of diabetes in a young child.