Oral Session I: Diabetes Acute and Chronic Complications

O/1/WED/01

Predictors of recurrent diabetic ketoacidosis in children and adolescents with type 1 diabetes. experience from a large multicenter data base

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Objective: Diabetic ketoacidosis (DKA) remains the leading cause of hospitalisation and death in children and adolescents with established type 1 diabetes despite DKA preventing strategies in diabetes education. The aim of the study was to determine risk factors for recurrent DKA in a large cohort of children and adolescents with type 1 diabetes.

Methods: This observational investigation uses DPV (Diabetes-Patienten-Verlaufsbeobachtung) -Wiss data base containing clinical data on 28 770 type 1 diabetic patients < 20 years of age at follow up from Germany and Austria. DKA was defined as pH < 7.3 and/or hospital-admission due to DKA. Data are presented as mean ± SEM of the latest year of therapy if not otherwise stated. DKA at onset was excluded from analysis. DKA rate is given as incidence of DKA/100 patient years. Statistical analyses were performed using Wilcoxon rank sum test and multiple Poisson regression analyses.

Results: Mean age of the study cohort was 14.0 ± 4.0 years (mean ± SD) (47.9% females). 94.2% had no episode of DKA, 4.9% presented with 1 episode and 1.0% with recurrent DKA (≥ 2 episodes). When comparing patients without, with one or recurrent DKA, age at manifestation ($P < 0.01$), HbA1c ($P < 0.01$) and insulin dose ($P < 0.01$) were significantly higher in patients with recurrent DKA. According to multiple Poisson regression incidence of DKA was found to be significantly higher in females (7.3 ± 0.5 versus 5.8 ± 0.3; $P = 0.03$) and in patients with positive migration background (7.8 ± 0.6 versus 6.3 ± 0.3; $P = 0.02$). Children of the age group 10–15 years were at significantly higher risk ($P < 0.01$) as well as children with longer duration of diabetes ($P < 0.05$). No significant association was found with type of treatment or centre size.

Conclusions: In a large cohort of European paediatric patients with type 1 diabetes the rate of DKA was found to be significantly higher in females, in children with positive migration background and in early teenage years.

O/1/WED/02

Complication screening at 2–5 years diabetes duration in adolescents, and changing prevalence over a 17 year period

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Objectives: In this study, we examined risk factors for early diabetes complications and temporal trends.

Methods: Adolescents with type 1 diabetes of 2–5 years duration (n = 821, 55% F, median age 14.4 years [11–17]) were screened for complications at the Children's Hospital Westmead between 1990–2006. Retinopathy (RET) was defined as presence of microaneurysms/haemorrhages on 7-field stereoscopic fundal photography (≥ 21, Airlie House classification). Early nephropathy was defined as mean albumin excretion rate (AER) ≥ 7.5ug/min, and microalbuminuria (MA) as AER ≥ 20ug/min on ≥ 2/3 timed overnight urine collections. Peripheral nerve function was measured by thermal and vibration threshold at the foot. Independent variables examined by logistic regression were HbA1c, gender, age, duration, BMI, blood pressure (BP), number of injections and cholesterol (model 1). Complication rates were compared between successive time periods (model 2).

Results: RET was associated with higher diastolic BP (OR 1.01, 1.00–1.02). AER ≥ 7.5ug/min was associated with older age (OR 1.17, 1.03–1.32) and diabetes duration (OR 1.34, 1.05–1.72). Peripheral nerve abnormalities (PNA) were associated with higher BMI centile (OR 1.01, 1.00–1.08).

	1990–1994	1995–1998	1999–2002	2003–2006	*P*-value
Retinopathy (%)	21	14	7	7	0.002
AER (%) ≥ 7.5ug/min	24	25	21	21	0.74
Microalbuminuria (%)	1	3.7	2.3	3.7	0.49
Peripheral nerve abnormality (%)	14	19	28	23	0.01
Mean HbA1c%	8.7	8.9	8.8	8.4	0.03
Mean BMI centile	66	71	71	73	0.005

[Complication rates according to time periods]

After 1998, there was a significant decline in RET (OR 0.42, 0.25–0.71), increase in PNA (OR 1.62, 1.12–2.33) and unchanged prevalence of MA.

Conclusions: Early complications are still found in adolescents ≤ 5 years diabetes duration, despite more intensive control in recent years. Further investigation is warranted to assess the contribution of BMI in development of complications, particularly in light of secular trends.

O/1/WED/03

Serum and urinary nitrites and nitrates and doppler sonography in young type 1 diabetics for early detection of subclinical diabetic nephropathy

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Background: Diabetes is a condition of oxidative stress and reduced nitric oxide (NO) bioavailability. There is an inter relationship between reduced NO bioavailability and hypoxia in the renal medulla in early stages of diabetes.

Objective: To evaluate serum and urinary NO concentrations in young type1diabetics compared to healthy subjects. And to investigate the possible alteration of intrarenal Doppler resistive indexes (RIs) and its correlation to NO concentrations.

Design: The study included 90 children and adolescent with type 1 DM divided into 2 groups: Group1; (n = 45) diabetics with disease duration < 5 years. Their age ranged between 8–14 years. Group 2; (n = 45) diabetics with disease duration > 5 years. Their age ranged between 8–15 years. They were compared to 45 age and sex matched healthy subjects. History and clinical examinations were done. Laboratory investigations included; random blood

sugar (RBS), glycated heamoglobin (HbA1C), fundus examination, urinary microalbumin and measurement of serum and urinary No levels. Doppler ultrasonographic registration of intrarenal RI was performed.

Results: Compared to controls, both diabetic groups had significantly increased concentrations of serum NO ($P < 0.001$) and urinary NO ($P < 0.001$).Doppler RI values were significantly elevated in both diabetic groups compared to controls ($P < 0.001$).Significant positive correlation was found between serum and urinary NO levels ($P < 0.001$). Serum NO was positively correlated with Doppler RI ($P < 0.002$), HbA1c ($P < 0.012$), RBS ($P < 0.000$), and diabetes duration ($P < 0.004$). Doppler RI was positively correlated with ($P < 0.025$), RBS ($P < 0.000$), and diabetes duration ($P < 0.000$).

Conclusions: In type 1 diabetics, chronic hyperglycemia may act through a mechanism that involves increased NO production and/or action and contributes to generating intrarenal hemodynamic abnormalities, which are detectable by Doppler ultrasonography even before the overt clinical nephropathy.

O/1/WED/04

Longitudinal change in brain volumes with glycemic extremes in youth with type 1 diabetes

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Objectives: Previously, we found that retrospective history of hypo- and hyperglycemia in youth with T1DM was associated with reduced regional brain volumes and specific cognitive functions. Now with a strong longitudinal design, we relate prospective measures of glycemic extremes to changes in brain volume over time.

Methods: T1-weighted MRIs of the brain were acquired in 75 youth (7–16 years old) with T1DM and 25 non-diabetic sibling controls (NC) at study entry and after 2 years. Prospective measures included hemoglobin A1c values (A1c), downloaded glucose meter readings, and reports of severe hypoglycemia (SH; defined as requiring assistance to treat). Percentage of glucose readings below 60 mg/dL (3.3 mmol/L) was used as a measure of mild hypoglycemia (MH). With SPM8b, gray and white matter volumes were calculated and co-registered by DARTEL, a detailed registration algorithm. Whole brain volume and voxel-wise analyses were performed to determine effects of average A1c, SH, and MH on gray and white matter over time.

Results: No significant differences were observed between T1DM and NC. Within T1DM, higher average A1c was associated with greater loss of whole brain gray matter over time ($r = -0.22$; $P < .03$). Gray and white matter volume within specific prefrontal regions also decreased with higher average A1c. Subjects with SH ($n = 15$) were compared to T1DM without SH matched for age, gender and A1c; no differences were found. MH rates ranged from 0.1% to 10.6% of readings (mean 4.9%, SD 2.7) and did not correlate with brain volume change.

Conclusions: Hyperglycemia, but not SH or MH, had measurable effects on gray and white matter change over a 2-year period. Low frequency of SH during follow-up limited the power of analyses; longer-term follow-up on this sample is underway.

O/1/WED/05

Acute painful neuropathy (insulin neuritis) - case report

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Insulin Neuritis is a self limiting iatrogenic complication described mainly in adult diabetic patients following initiation of insulin therapy and associated rapid improvement in metabolic glycaemic control. Very few case reports describe this condition in paediatric patients with Type 1 diabetes mellitus.

We report a 15-year old girl with Insulin Neuritis who had long standing poor glycaemic control and then developed neuritis when her HbA1c dropped from 16 to 10 over a three month period. In addition she also developed an acute massive fatty liver (confirmed on biopsy), insulin oedema and proteinuria. Her previous glycaemic control had been poor over a period of two to three years with her HbA1c over 16, and five emergency admissions for Diabetic Ketoacidosis. The poor control had been attributed to previous variable adherence with health care professionals and insulin therapy compounded by serious psycho-social issues.

She complained of disabling paresthesiae described as burning and shooting pain mainly affecting both lower limbs and sometimes associated with prickles and tingles in her feet causing severe distress. Neurological examination revealed normal reflexes with no objective sensory or motor loss. She declined nerve conduction studies. Various modalities of pain relief were tried without much success. Increasing doses of Pregabalin had no effect and patient unilaterally discontinued the medication. Over a period of six months her symptoms gradually subsided and she was able to resume normal activities in keeping with Insulin Neuritis.

O/1/WED/06

The efficacy of antioxidant systems and the levels of advanced oxidation protein products (aopp) and lipids (tbars) in adolescent children with type 1 diabetes mellitus and in their siblings

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The aim of the study was to evaluate correlations between antioxidant defense mechanisms (SOD, GSHPx, CAT, TAS) and the levels of advanced oxidation protein end products (AOPP) and lipid peroxidation (TBARs) in patients with type 1 diabetes mellitus (DM1) in the period of puberty. The investigated parameters were also evaluated in siblings of diabetic patients and in the control group.

Material and methods: The investigations involved 87 patients with DM1 with the mean age of 13 years and duration of disease - 3.5 years. The siblings group comprised 27 children and the control group - 41 healthy children.

Results: The levels of AOPP and TBARs correlated positively with duration of the disease and with HbA1C. The level of TBARs correlated positively with gender, age and BMI of patients. No correlation was revealed between the activity of antioxidant enzymes and TAS and gender and age of the subjects, duration of the disease and HbA1C. There was a positive correlation between the level of AOPP and TBARs . Patients with DM1 and their siblings did not reveal any correlation between the activity of antioxidant enzymes and TAS, AOPP and TBARs. A significant

negative correlation was observed between the activity of SOD, the main ROS scavenging enzyme, and TBARs in the control subjects.
Conclusions: Lack of correlation between selected parameters of antioxidant defense and AOPP and TBARs accumulation may indicate a pronounced role of other antioxidants in patients with DM1. Increased activity of CAT and unchanged activity of Se-GSHPx may point indirectly to an increased generation of ROS in the investigated group of patients. Similar changes in the activity of these enzymes in the patients' siblings may indicate the participation of genetic factors.

O/1/WED/07

Long-acting insulin analogues elicit atypical igf-i receptor-mediated signals

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Background: In previous investigations (1) we have found that the long-acting insulin analogues Glargine (Lantus®, Sanofi Aventis) and Detemir (Levemir®, Novo Nordisk), unlike regular insulin, exhibit "*in vitro*" profilerative and anti-apoptotic activities in a number of cancer cell lines [colon (HCT116), prostate (PC3) and breast (MCF7)] which resembled IGF-I actions.
Objective: To investigate the signaling events elicited by Glargine and Detemir in a colon cancer cell line, compared to regular human insulin and IGF-I.
Methods: Immunoprecipitation, propidium iodine staining for cell-cycle analysis and confocal microscopy.
Results: Immunoprecipitation assays showed that glargine was able to phosphorylate both the InsR and IGF-IR. Activation of IGF-IR by glargine resembled its activation by IGF-I in terms of doses and time frame. Dose-dependent experiments revealed that glargine activated the IGF-IR at five-fold lower doses than those required to activate the InsR. In addition, glargine induced a sustained InsR phosphorylation whereas it activated the IGF-IR in a biphasic fashion. The ability of both analogues to activate the major signaling pathways, PI3K and MAPK, in terms of kinetics and intensity, are essentially different from those of insulin. Biological studies revealed that the analogues exhibit an IGF-I-like antiapoptotic effect and enhanced the proportion of cells in the S-phase. Finally, confocal microscopy indicates that glargine led to IGF-IR internalization similarly to IGF-I.
Conclusions: Glargine and Detemir exhibit IGF-I-like mitogenic and antiapoptotic activities in cancer cells by interacting with the IGF-IR. The different binding characteristics of the analogues to the IGF-IR, compared to regular insulin, seem to promote atypical signaling events leading to different biological actions. The clinical implications of these findings remain to be established.
Reference: 1. Weinstein D et al. Diabetes Metab Res Rev 2009: 25: 41–49.

O/1/WED/08

Is there an increased risk of Type 1 diabetes in children treated with antibiotics in early childhood?

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There is a worldwide increase in Type 1 Diabetes (T1D) and indication of a similar increase in allergic diseases, the causes of the increase are largely unknown. The use of antibiotics in early childhood has been linked to increased risk of allergy. The aim of the present studies is to examine the use of antibiotics in early childhood and the subsequent risk of developing T1D.
Material: The study is a case-control study based on cases born since 1996 collected from the Danish Registry of Diabetes in Childhood. The cases are compared with four healthy controls selected from the population matched by birth year and area code. Use of antibiotics is collected from the Danish Prescription Registry. The analysis was done using logistic regression with diabetes as outcome and age at prescription of antibiotics and number of antibiotic prescriptions as explanatory variables. The model was adjusted for gender and region.
Results: There were 706 children with T1D in the register born after 1996, 2824 matched controls were selected. The number of children under the age of 2 years treated with broad-spectred antibiotics varied from 30-50% between calendar years, but with no clear secular trend. The hazard ratio of T1D for use of all types of systemic antibiotics before the age of 2 was 1.08 (0.90–1.30) $P = 0.41$ and for broad-spectred 1.18 (0.99–1.40) $P = 0.067$. There was no significant effect of age at first treatment with antibiotics or number of treatments; hazard ratio per year: 0.98 (0.93–1.03), $P = 0.37$, per treatment cycle 1.03 (0.98–1.09), $P = 0.28$.
Discussion: The use of antibiotics in early childhood does not seem to increase the risk of T1DM, though an increased risk of less than 40% in children treated with broad-spectred antibiotics before the age of 2 cannot be excluded. The majority of cases in this study are likely to have high risk genotypes because of their early onset diabetes. This may have diminished our chance of finding an association, because it is more difficult to modulate these children's risk.
Conclusion: There is no support for an increased incidence of T1D in children who are subject to treatment by antibiotics.

Oral Session II: Diabetes and Obesity

O/2/WED/01

Decreased llvel of soluble receptor for advanced glycation end-products (s-rage) is an independent risk factor for cimt in obese pre-pubertal children

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Objectives: Advanced glycation end-products (AGEs) and the receptor for AGEs system (es-RAGE and s-RAGE) plays an important role in the onset and progression of atherosclerosis in adult subjects. AGE engagement of RAGE results in cellular signaling including activation of nuclear factor-B, increased expression of cytokines and adhesion molecules, and induction of oxidative stress. Both reduced es-RAGE and s-RAGE are tightly related to the risk of carotid atherosclerosis (cIMT). Therefore, we tested whether impaired es-RAGE and s-RAGE concentrations are related to increased cIMT in obese pre-pubertal children.
Methods: In 44 obese pre-pubertal children (20M/24F, mean age 7.9 ± 1.5 yrs), anthropometric measurements, inflammatory markers (hs-CRP and PGF-2α), es-RAGE and s-RAGE, were evaluated and compared with 41 healthy gender, age and pubertal stage matched subjects (21M/20F, mean age 7 ± 2 yrs). OGTT was performed and insulin resistance (IR) indexes (HOMA-IR, WBISI) were calculated in all patients. High resolution ultrasound techniques were used to evaluate cIMT.
Results: Obese children had lower levels of es-RAGE and s-RAGE compared to healthy subjects ($P = 0.009$ and $P = 0.001$). Fasting insulin levels and HOMA-IR were higher ($P = 0.003$ and $P = 0.001$) while WBISI lower ($P = 0.006$) in obese children than controls. Furthermore, compared to healthy subjects obese children showed increased levels of PGF-2α and hs-CRP ($P = 0.001$ and $P = 0.007$).

In addition, obese children had an increased cIMT ($P = 0.001$). A significant correlations between cIMT and PGF-2α ($\beta = 0.341$, $P = 0.003$), between cIMT and s-RAGE ($\beta = -0.230$, $P = 0.030$), between cIMT and HOMA-IR ($\beta = 0.206$, $P = 0.048$) were detected by multiple stepwise linear regression analysis.
Conclusions: The receptor for AGEs system markers are reduced in obese pre-pubertal children and represent an independent risk factor of cIMT, already during pre-puberty.

O/2/WED/02

The earlybird diabetes study: an emerging perspective on insulin resistance

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Objectives: The accelerator hypothesis proposes that type 1 and type 2 diabetes are both driven by insulin resistance. For nine years, EarlyBird has been monitoring a single cohort of 300 healthy children, to better understand why some develop insulin resistance but not others.
Methods: Annual measures include: detailed anthropometry, body composition, physical activity (accelerometry), metabolic health (fasting bloods) including insulin resistance (HOMA-IR). A summary of the key findings to date is presented below.
Results: 1) Most of the excess weight gained before puberty (> 90% in girls, > 70% in boys) occurs before the age of five (calling into question the relevance of school lunches, physical education, computer time etc.). 2) The obesity epidemic appears largely confined to children whose same-sex parent is obese (these may be acting as early role-models). 3) Children record the same range of physical activity whatever the opportunity (suggesting central, rather than environmental control of activity). 4) The cross-sectional relationship between insulin resistance and BMI strengthens over time, *but* ... 5) time trend analysis shows that obesity leads to inactivity, rather than inactivity to obesity and that insulin resistance is more closely related to inactivity than to BMI (the influence of overweight on insulin resistance may largely be explained by the limitation that excess weight places on physical activity). 6) Disposition plotting over time suggests that early insulin resistance in young children may be associated with beta cell loss.
Conclusions: Risk factors for diabetes in contemporary children are already present at an early age and there is an urgent need to prevent weight centile crossing before the child ever reaches school age. Gender assortative weight gain suggests that targeted parental education is a prerequisite for obesity prevention. Calorie reduction may be key to weight loss, but physical activity to improving insulin sensitivity.

O/2/WED/03

Role of es-rage and s-rage and insulin resistance in liver steatosis in obese pre-pubertal children

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Objectives: The AGE-RAGE pathway has been recently implicated in the pathogenesis of several pathological conditions, including insulin resistance (IR) and liver injury. Recently, the endogenous soluble-RAGE (es-RAGE) and soluble-RAGE (s-RAGE) have been shown in human plasma and have emerged as reliable biomarkers in a number of RAGE-mediated disorders. The aim of the study was to evaluate both es-RAGE and s-RAGE levels in obese pre-pubertal children with and without liver steatosis.
Methods: A large group of 100 obese pre-pubertal children was recruited. Anthropometric measurements, an oral glucose tolerance test (OGTT), es-RAGE and s-RAGE levels, transaminase values and a hepatic ultrasound scan were performed in all subjects. HOMA-IR and WBISI were used as indexes of IR. According to the ultrasound presence or not of liver steatosis the children were divided into group 1 (52 subjects; mean age 8.95 ± 1.69 years) and group 2 (48 subjects; mean age 8.09 ± 2.01 years), respectively.
Results: s-RAGE (1013.43 ± 274.60 versus 1361.52 ± 553.60 pg/ml; $P = 0.02$) and es-RAGE levels (0.75 ± 0.46 versus 1.09 ± 0.62 ng/ml; $P = 0.03$) were significantly lower in group 1 than in group 2. HOMA-IR was significantly higher (4.01 ± 2.91 versus 2.26 ± 1.20; $P = 0.0001$) while WBISI (3.72 ± 1.97 versus 6.95 ± 3.84; $P = 0.0004$) was significantly lower in group 1 compared to group 2. Furthermore, in a multiple linear regression analysis, es-RAGE and HOMA-IR were independently related to liver steatosis ($\beta = -2.667$, $P = 0.01$ and $\beta = 0.369$, $P = = 0.003$, respectively).
Conclusions: Decreased s-RAGE and es-RAGE levels have been shown in obese pre-pubertal children affected by liver steatosis. The relationship between s-RAGE and liver steatosis suggests an independent role of AGE-RAGE pathway in the development of liver injury, already in pre-pubertal obese children.

O/2/WED/04

Serum high-sensitivity c-reactive protein (hs crp) levels as a marker of micro and macroangiopathy in diabetic children and adolescents

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Background: Diabetes mellitus (DM) and obesity are risk factors for atherosclerosis, and asymptomatic low grade inflammation occurs prior to overt vascular lesions. High-sensitivity *C*-reactive protein is known as a novel marker of low grade inflammatory state, which characterizes atherosclerotic process in its early stages.
Objectives: To assess serum Hs CRP in diabetic children and adolescents in relation to hypertension, obesity, degree of glycemic control, lipid profile and diabetic micro and macrovascular complications.
Methods: This study was carried out on 54 children and adolescents with type 1 DM (mean age 12.83 ± 2.95 years) recruited from the Pediatric Diabetes Clinic, Ain Shams University Hospitals, 23 of whom with microvascular complications (MCV) and 31 without microvascular complications. According to body mass index (BMI), diabetics were subdivided into 10 obese and 44 non obese. The study also included 36 non diabetic subjects: 10 simple obese (mean age 13.2 ± 2.74 years) and 26 non obese controls (mean age 11.77 ± 3.66 years). Patients were subjected to clinical examination and assessment of HbA1c, urinary microalbumin, lipid profile and serum Hs CRP using ELISA technique. The data were analyzed using SPSS (version 15).
Results: Serum Hs CRP levels were significantly higher in diabetic patients compared to normal controls (2.18 ± 1.37 μg/ml versus 1.5 ± 0.7 μg/ml) ($P = 0.02$); significantly higher in diabetic patients with MCV compared to those without (2.63 ± 1.31 μg/ml versus 1.8 ± 1.27 μg/ml) ($P = 0.02$); significantly higher in obese diabetic patients (median = 3 μg/ml) and obese controls (median = 3.75 μg/ml) compared with non obese subjects of relevant group (median = 1.93 and 2.05 μg/ml) ($P < 0.05$). Serum Hs CRP was correlated with total cholesterol, triglycerides, LDL and BMI in diabetic patients ($P < 0.05$).

Conclusions: High levels of Hs CRP might reflect low grade inflammation in diabetics and might indicate increased risk of cardiovascular disease, being correlated with lipid profile and BMI.

O/2/WED/05

Analysis of resistin serum concentration in relation to body fat mass in children with type 1 diabetes

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Objectives: Adipose tissue is an endocrine organ, secreting biologically active peptides called adipokines, that may influence insulin synthesis and its action. Resistin is an adipokine known to increase insulin resistance in mice, but the same role of resistin in humans is still controversial. Insulin is one of the major factors regulating adipose tissue function. In patients with type 1 diabetes mellitus (t1DM) endogenous insulin secretion is replaced with exogenous insulin therapy. Aim of the study was to establish resistin serum concentration, and its relation to body fat mass in children with type 1 diabetes mellitus.

Methods: The study comprised of 75 children with t1DM (30 boys and 45 girls, mean age 12.5 ± 3.5yrs; mean disease duration 4.9 ± 3.1yrs) without acute disease complication. Control group comprised of 20 children (10 boys and 10 girls, mean age 12.5 ± 2.7yrs). All children had height and body weight measured. Bioelectrical impedance analysis (BIA) was performed to establish body fat mass. Patients had blood samples for resistin (RIA) taken in the morning, fasting.

Results: Mann–Whitney's statistics (nonparametric test) has confirmed the significantly lower resistin concentration in diabetic children if compare to their healthy coevals (mean ± SD: 577 ± 561 versus 861 ± 628 pg/ml; $P < 0.001$). Moreover, in the group consisting of diabetic children, there was negative correlation between blood resistin level and absolute fat tissue mass ($r = -0.265$; $P = 0.022$). The controls did not reveal such a correlation.

Conclusions: Type 1 diabetes induces diminished morning resisitin concentration in fasting children and adolescents. This finding is in unexpected negative correlation with fat tissue mass, what is the next difference in relation to controls. Non-physiological therapy with exogenous insulin seems to be responsible for changes in adipo-insular regulations in type 1 diabetes, which are not like those known in healthy individuals or in obesity for example.

O/2/WED/06

Testing the accelerator hypothesis in type 1 diabetes mellitus (t1dm): an italian multicentre study

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Objectives: The accelerator hypothesis argues obesity an environmental factor hastening the clinical onset of diabetes mellitus. Obesity-induced insulin-resistance may upregulate β-cells, which become more susceptible to autoimmunity in genetically predisposed individuals. Younger patients at T1DM diagnosis showed higher BMI-SDSs than older ones.

Methods: Our multicentre study enrolled 485 T1DM patients (284 m) recruited from Italian Pediatric Diabetes Centres of Genoa, Rome, Naples, Bari, Brindisi, Oristano and followed between 1990–2007. In all patients gender, severity of ketoacidosis (DKA) were recorded at T1DM diagnosis, while BMI (converted to SDS according to Italian reference standards) has been recorded at least 2 months after diagnosis to avoid the confounding effect of DKA. Mean age at T1DM diagnosis was 8.4 ± 4.1 yrs (M ± SD). Patients were divided into 4 groups, age-based: G1 (n = 112): 1–4.99 yrs, G2 (n = 170): 5–9.99 yrs, G3 (n = 164): 10–15.7 yrs, and G4 (n = 20): 15–20 yrs.

Results: At T1DM diagnosis, BMI-SDS was within the normal range in all patients. BMI-SDS was higher in G2 than G3 ($P = 0.018$); no difference was observed among other Groups. No correlation was found between BMI-SDS and severity of DKA, age at diagnosis and calendar year of T1DM diagnosis. BMI-SDS was re-evaluated after a 5-year follow-up in 174/385 (35.9%) T1DM patients, and was increased from baseline values ($P < 0.0001$).

Conclusions: In contrast to accelerator hypothesis, obesity is not common in newly diagnosed Italian young patients. As regards BMI as a risk factor, it should be established if patients are more insulin-resistant than healthy peers. There might be a threshold at which obesity determines earlier onset of type 1 diabetes, already not reached in our Italian patients. The increased BMI-SDS 5 years after diagnosis could be related to over-insulinization due to intensive insulin therapy and deserves attention as a risk factor for the late development of microangiopathy.

O/2/WED/07

Effects of a ketogenic diet as compared to a hypocaloric diet on metabolic parameters and oxidative stress in obese children (c) and adolescents (a)

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Objectives: To compare the effect of a high-protein, low-carbohydrate ketogenic diet (K) and a hypocaloric diet (HC) on metabolic parameters and oxidative stress in obese C and A. Obesity causes insulin resistance, increases oxidative stress and disrupts antioxidant defenses. Adiponectin increases insulin sensitivity, malonydialdehyde (MDA) is an index of lipid peroxidation. Ferric reducing antioxidant power (FRAP) and Ferric reducing ascorbic acid (FRASC) estimate antioxidant capacity.

Methods: Forty-five obese (OC) and 47 lean (LC) C and A were studied. Anthropometric measurements, blood pressure, fasting glucose, insulin, lipidemic profile, MDA with fluorescence detection, assessments of FRAP, FRASC and high molecular weight adiponectin, (Ad) measured by ELISA, were obtained. In the OC an oral glucose and insulin tolerance test was performed. Whole body insulin sensitivity (WBISI) and HOMA-IR were also determined. The OC began a K or HC diet. Changes were assessed after at least a 10% weight loss.

Results: 45% of the OC followed the K diet and 65% of them lost ≥ 10% of their ideal body weight (iBW) whereas 55% of the OC followed the HC diet but only 35% of them lost ≥ 10% of their iBW. The mean weight loss, fat mass loss and waist circumference (WC) reduction were −10.1 ± 4.1 kg, −7.5 ± 4.6 kg, and −10.7 ± 4.3 cm respectively, for the the K and −5.02 ± 2.4 kg, −4.24 ± 3.2 kg and −7.6 ± 2.6 cm respectively for the HC. Only after the K diet, HOMA-IR and WBISI decreased ($P = 0.005$ and 0.01), Ad increased and MDA decreased ($P = 0.04$). The total antioxidant capacity, (FRAP and FRASC) improved more after the end of the K diet.

Conclusions: The K diet revealed better results in body weight, fat mass and WC reduction. Insulin Resistance and MDA showed a reduction, Ad increased and FRAP and FRASC improved only with the K diet. These results infer that the K diet may be able to better improve the metabolic profile and oxidative stress of obese children than the HC diet.

O/2/WED/08

Metformin therapy to reduce weight gain and visceral adiposity in children and adolescents with neurogenic or myogenic motor deficit

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The aim of this randomized, placebo-controlled study was to explore the effect of metformin in children with a neurogenic or myogenic motor deficit, who are therefore prone to develop overweight, adiposity and insulin resistance.

Patients with neurogenic or myogenic motor deficit were included if they met the following inclusion criteria: older than 8 years of age, fat mass > 30% (absorptiometry) or insulin resistance (screened by fasting glucose (mg/dl) over insulin < 7 (mU/l)). Placebo and metformin capsules had the same appearance, and were given in the evening at a dose of 425 mg/d (age < 10 yr) or 850 mg/d (age ≥ 10 yr). Patients and investigators, except for the study statistician (SF), remained blinded to intervention.

Study participants (N = 42) had a mean age of 15.5 yr, a short stature (height −2.4 SD), a relatively high BMI (+1.7 SD) and a high body fat fraction (41.9% or +2.8 SD). Abdominal CT confirmed the high fat mass and disclosed a high fraction of visceral fat. As expected, insulin resistance was increased.

As compared to placebo, metformin therapy exerted a beneficial effect on insulin sensitivity (HOMAR, $P = 0.044$) and had a significant beneficial treatment effect over placebo on weight ($= 0.0072$) and BMI ($P = 0.016$). Metformin did not result in a significant reduction in total body fat (measured by DEXA or CT scan) but interestingly, there was a highly significant beneficial effect on visceral fat ($P = 0.0008$), suggesting that the weight loss was primarily due to a reduction in visceral fat. Results were similar across diagnostic subgroups.

In conclusion, metformin treatment for 6 months was associated with a rise in insulin sensitivity and with a reduction of visceral adiposity in children and adolescents with a primary muscle disorder or with a neural tube defect. These findings suggest that insulin resistance underpins, at least partly, the overweight and visceral adiposity of these patients, who are not necessarily obese.

Oral Session III: Diabetes Care, Education, Psychosocial Issues

O/3/WED/01

Emotional competences: an asset in the treatment of type 1 diabetes in children and adolescents

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Objectives: The study examines the respective contribution of demographic characteristics, diabetes duration and emotional (in) competences (alexithymia and emotional awareness) of young diabetics on their glycaemic control. Alexithymia was recently found to be associated with poor glycaemic control in an adult population.

Method: The study included 102 type 1 diabetic young people (8–18 years). Mean of glycated hemoglobin (HbA1c), number of severe hypoglycemias and of hospitalizations for hyperglycemia were collected for the previous 12 months. Each young completed the Alexithymia Scale for children (AS-20-C) and the Levels of Emotional Awareness Scale for Children (LEAS-C).

Results: In correlational analyses, we found that higher emotional awareness ($P < .01$) and higher parental education ($P < .01$) are negatively linked to HbA1C. Higher alexithymia ($P < .01$) and higher duration of diabetes ($P < .01$) are positively linked with HbA1C.

For the children (8–12 years, N = 45), a hierarchical regression confirmed that demographic variables-namely marital status & parental education ($P < .05$), as well as duration of diabetes ($P < .05$), predicted HbA1c. Importantly, one alexithymia factor (Difficulty to Describe Feelings) was found to be an additional predictor over and above them, ($P < .01$), explaining an additional 12% of the total variance.

Conclusions: Confirming results already observed for adults, the present findings indicate for the first time that children who have difficulties expressing their feelings to others are more at risk for glycaemic control. In the future, it seems important to detect the diabetic young people with deficits in emotional competences and to consider specific care for them.

O/3/WED/02

Experience of parents of children with diabetes in primary schools in England 2008

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Objectives: To explore the experience of parents of children with diabetes who have to enter school daily to monitor and/or give injections.

Methods: Semi-structured face to face interviews were held with 10 parents of children with diabetes (aged 5–11). Respondents were recruited using a purposive sample in England based on findings from an earlier survey of primary schools and LEAs [1]. Questions explored the day to day management of diabetes (including the parents' role), participation in school activities, communication and relationships, education, knowledge and barriers to support. Interviews were recorded, transcribed and analysed using the Framework Approach.

Results: Respondents reported a wide variation in support both geographically and within schools. Parents stated that their children are subject to a range of exclusions from: attending school, taking part in physical activity, reading aloud in class and are treated differently on account of their diabetes. Most parents entered school to monitor and give injections and some altered optimum insulin regimes to reduce exclusions. Barriers included lack of staff knowledge and training, discriminatory attitude of key staff, lack of exact policy guidance and poor communication. The impact on parents is significant. Some are unable to maintain employment; use of anti-depressants; unable to leave the locality as the school requires them to be 'on-call' at all times.

Conclusion: Attending school daily has an immense emotional, psychological, financial and social impact on parents. Schools must develop an inclusive attitude and allow full participation in school life for children with diabetes. Effective daily care can improve the quality of life, and reduce the risk of developing complications [2].

References: 1. Survey of Children with Diabetes and Primary Schools, Diabetes UK 2008.
2. Department of Health. Making every young person with diabetes matter: Report of the Children and Young People Working Group, April 2007.

O/3/WED/03

Stress and coping in type 1 diabetes: adapting a psycho-educational program to improve health and wellbeing in adolescents with type 1 diabetes

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Objectives: Adolescents with type 1 diabetes mellitus (T1DM) are at increased risk for psychiatric disorders, yet standard diabetes care does not routinely offer skills-based psychosocial training to minimise behavioural and psychological difficulties that often appear in adolescence. To assess usability of an existing psycho-educational program *The Best of Coping* (BOC), focus group discussions were held with adolescents with T1DM. The focus groups aimed to: (1) explore diabetes-specific stressors and coping strategies, (2) assess usability and acceptability of the BOC in order to adapt the program before implementation in T1DM.
Methods: Thirteen adolescents aged 13–17 years were recruited from the diabetes clinic at a tertiary pediatric hospital. Four age-appropriate focus groups were held. A semi-structured interview was developed and the focus groups were facilitated by an experienced researcher. Transcripts were coded and analysed using Thematic Analysis. Coping strategies were also grouped according to the 18 categories identified in the Adolescent Coping Scale.
Results: The most frequently cited diabetes-specific stressors included parent/adolescent conflict and blood testing. Key non-productive coping strategies included 'ignore the problem' and 'tension reduction' (specifically using alcohol, cigarettes and food to reduce stress). Productive coping skills included 'seek social support' and 'physical recreation'. Participants' reactions and feedback to the BOC consistently indicated a desire to learn more about coping skills and for the program to focus on diabetes-related stressors and incorporate self-management skills, as well as indicating the appeal of participating in a program with a strong social support component.
Conclusions: Findings demonstrate the value of providing a forum for adolescents to meet peers with diabetes, as well as the importance of providing the opportunity to acquire coping skills adapted to promote diabetes self-management.

O/3/WED/04

Family environment, psychosocial adjustment and metabolic control in pre-teen girls with type 1 diabetes

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Objectives: To examine the relative contribution of family environment and psychosocial adjustment to metabolic control in pre-teen girls with type 1 diabetes.
Methods: In this longitudinal study based at the Hospital for Sick Children in Toronto, Canada, 75 girls with T1D 9–13 years of age completed self-report measures of attachment to parents, depression and self-esteem, and an interview for eating disturbances, at study baseline (Time 1) and one year later (Time 2). Both parents completed the Family Environment Scale (FES). Multiple linear regression was used to predict Time 2 A1c; independent variables were the Time 1 factors listed above, controlling for Time 1 age and A1c. The temporal relationship between A1c and the predictor variables identified in the first regression was then examined with a cross-lagged effects model.
Results: A1c levels rose over one year. Time 1 age and A1c, entered in Block 1 of the regression, were significantly associated with Time 2 A1c ($R^2 = 0.25$). Block 2 of the stepwise regression identified father's FES cohesion, moral/religious and achievement scores, and mother's FES intellectual/cultural orientation score (cumulative $R^2 = 0.46$), as significant predictors. These variables were not significantly associated with Time 1 A1c, and similarly, there was no significant association between Time 2 A1c and these FES variables at Time 2. This suggests that the results do not simply reflect a cross-sectional relationship between family environment and A1c.
Conclusion: Findings highlight the relationship between diverse aspects of the family environment, as identified by both parents, and A1c in the pre-teen years. Of note, family factors predicted A1c one year later, while individual factors, namely depressive symptoms, self-esteem and eating disturbances, did not. Findings support the further development and refinement of interventions supporting family cohesion and cooperation in the optimization of A1c in the pre-teen years.

O/3/WED/05

Depressive symptoms and psychological care in dutch youth with diabetes: a web-based survey

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Objectives: The prevalence of depression in youth with diabetes is found to be elevated, but research is sparse. Less is even known about the psychological care received by adolescents with depression and how this care is appreciated. The aim of this study was to investigate the prevalence of depressive symptoms in youth with diabetes (age 9 - 20 years) and received psychological care.
Methods: A web survey for youth with diabetes across the Netherlands was conducted between November 2008 and March 2009. Patients filled out the Child Depression Inventory (CDI). A score ≥ 16 is indicative of clinically relevant depressive symptoms. Demographics, most recent HbA1c and history and appreciation of psychological care received were assessed as well.
Results: 230 adolescents (160 girls) completed the web survey. Mean age was 15.5 ± 2.2 years; mean diabetes duration 9.5 ± 4.4 years; mean HbA1c 8.1 ± 1.6%. Mean CDI score was 9.3 ± 7.6; girls reporting more depressive symptoms than boys ($P = 0.003$). Overall 16.5% had elevated depressive symptoms (CDI ≥ 16). Youth in poorer glycemic control (HbA1c > 7.5) reported more depressive symptoms relative to those in better glycemic control (HbA1c ≤ 7.5) ($P = 0.001$). Overall 44% (102/230) reported a history of psychological care, of whom 21 (21%) were currently under treatment. Of those with elevated depressive symptoms, 25% received psychological help, 16% wished to see a psychologist and 59% thought professional support was not necessary. seven

children (3%) expressed suicidal intention, but only two received psychological care. Of the 102 children who (ever) received psychological care, just over half (53%) considered the received counselling helpful.

Conclusions: Depressive symptoms are common among Dutch youth with diabetes, especially in girls and youth with higher HbA1c values. Of those with a likely depression, only 25% received psychological care, underscoring the need to improve recognition and adequate referral to mental health services.

O/3/WED/06

Metabolic control in italian children with type 1 diabetes: is it changing during the years? preliminary results of vikids study

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In 2001, Vanelli and co-workers performed a survey on 3596 children with type 1 diabetes (T1D) from Italian paediatric centres reporting an average HbA1c of 8,87% (95%CI: 8,81–8,93). VIPKIDS (eValuation of Insulin Pump treatment in Kids) is an on-going multi-centre, cross-sectional study, involving 14 Italian paediatric centres widespread all over the Country, started February 2008. The objectives were to compare quality of life (QOL), metabolic control, and the impact of diabetes on parents of children in a real life setting.

Aim: In this report, we describe the metabolic control of a cohort of Italian children with T1D treated with MDI or CSII.

Methods: During a 12 months period, we recruited consecutively 792 subjects with T1D, aged less than 18 years. A written informed consent for QOL questionnaires and blood sample was requested. A physician recorded personal and clinical data. The blood samples were analysed centrally for HbA1c. Intra- and inter-centres HbA1c variability were evaluated by coefficient of variation (CV) and 95% confidence intervals (95% CI); mean and 95% CI of HbA1c were compared according to the type of treatment.

Results: The HbA1c grand mean was 8.1% (DS = 1.1%). In more than half of the children (52%) HbA1c was ≤ 8.0%; HbA1c 25° percentile and 75° percentile were 7.4% and 8.7% respectively. No significant differences of HbA1c means between children treated with MDI (8.2%; 95%CI: 8.0–8.3) and CSII (8.0%; 95%CI: 7.9–08.2) were observed. All centres showed an intra-centres HbA1c variability ≤ 17% (range 8.8–16.8); no significant differences of the inter-centres HbA1c variability were reported.

Conclusions: Comparing with the previous report, VIPKIDS seems to show an improvement of the metabolic control in children treated by Italian paediatric centres. The insulin delivery system is not associated with the change of HbA1c levels. It remains to identify the main determinants of this improvements in order to move towards the HbA1c benchmark.

O/3/WED/07

Predictors of glycemic control in patients with type 1 diabetes switched to insulin pump therapy

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Objective: To identify variables that predict metabolic control in patients with type 1 diabetes (T1D) using continuous subcutaneous insulin infusion (CSII), in order to improve patient selection for this treatment.

Patients and Methods: The charts of 421 patients with T1D aged 2.6–39.8 years (median 19.38) who initiated CSII treatment in 1998–2007 at a tertiary medical center and used it for ≥ one year, were reviewed for background, disease-related, and treatment-related variables. At pump initiation, the mean age was 15.9 ± 7.2 years, and mean diabetes duration 6.4 ± 5.8 years. Mean time of CSII use was 4.1 ± 2.1 years. Good metabolic control was defined by HbA1c stratified by age (ADA and ISPAD target levels). Improvement in metabolic control was defined as a reduction of ≥0.5% in HbA1c from baseline and a decreased rate of severe hypoglycemic or diabetic ketoacidosis events.

Results: A significant sustained decrease in HbA1c (from 8.13 ± 1.29% to 7.53 ± 1.11%, $P = 0.003$) with CSII was found for an average of 6 years, without increased rate of hypoglycemia. Achievement of target HbA1c was significantly associated with the following parameters at CSII initiation: lower HbA1c ($p < 0.001$), younger age (< 12 years) and Tanner 1 pubertal stage (first 2 years; $p < 0.05$), shorter diabetes duration (first year; $p < 0.001$), and more frequent daily self blood glucose monitoring (SBGM) at CSII initiation (first 3 years; $p < 0.005$). Improved metabolic control was associated with a higher HbA1c at CSII initiation ($p < 0.001$).

Conclusions: Switching patients to CSII resulted in a sustained decrease in HbA1c and improved diabetes control in patients with high HbA1c. Young age, frequent SBGM, and lower HbA1c at insulin pump initiation were identified as predictors of good glycemic control with CSII in T1D patients.

O/3/WED/08

Afternoon exercise and overnight closed-loop (cl) insulin delivery in adolescents with type 1 diabetes (t1d)

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Objectives: We investigated the ability of overnight CL insulin delivery to prevent nocturnal hypoglycaemia following afternoon exercise in adolescents with T1D.

Methods: Nine post-pubertal subjects with T1D treated by CSII (M 3; age 14.4 ± 2.1 years; BMI 20.0 ± 2.9 kg/m^2; duration diabetes 5.8 ± 3.3 years; A1C 7.8 ± 1.0%; mean ± SD) were studied on two separate nights. Subjects received either overnight CL or CSII therapy in random order. On each occasion, subjects had a snack at 16:00 and exercised at 55% VO_2MAX from 18:00 for 40min. CL was performed between 20:00 and 08:00 the next day.

Subcutaneous (sc) continuous glucose monitoring data was fed into a model predictive controller (MPC) every 15 minutes, which calculated sc insulin infusion for manually adjusted insulin pump. On CSII night, subject's standard insulin pump settings were applied.

Results: CL increased time with sc glucose in target range 3.9 to 8.0 mM (84 ± 20 vs 40 ± 37% of time; p = 0.01) (Figure). One CSII study was stopped as plasma glucose < 2.0mM, whereas no hypoglycaemia occurred on CL nights. CL tended to reduce Kovatchev's Low BG Index (LBGI) (0.8 ± 0.7 vs 5.3 ± 8.0) although this failed to reach statistical significance.

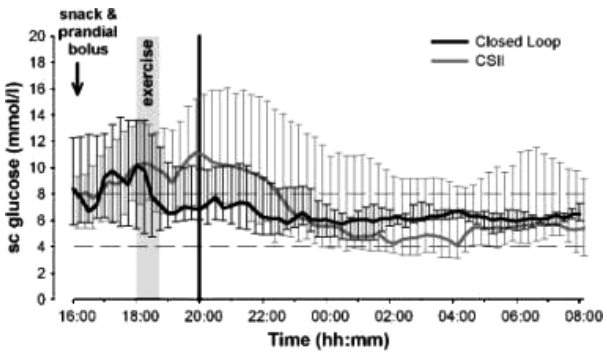

Figure 1. Median (IQR) sc glucose.

Conclusions: 12h overnight CL with MPC following afternoon exercise avoids hypoglycemia and increases time spent in target glucose range twofold.

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Oral Session IV: Diabetes Genetics, Immunology

O/4/FRI/01

Gad65 treatment of type 1 diabetic children and adolescents may act via a specific immunomodulatory effect

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Background: GAD_{65}-alum seems to preserve residual insulin secretion in children and adolescents with recent onset Type 1 diabetes (T1D). We intended to clarify the mechanisms of this effect by analyzing the immune responses.

Methods: Samples from T1D children who received 20μg rh-GAD_{65}-alum (n = 35) or placebo (n = 35) and a booster after 4 weeks were collected at baseline and at 1, 3, 9, 15, 21 and 30 months. Isolated PBMC were stained for flow cytometry with anti-CD4, CD25, CTLA-4, Neuropilin and FOXP3. At 21 months cells were cultured over-night with GAD_{65} before staining. After 72 hours stimulation, cytokines IL-5, -6, -10, -12, -13, -17, TNF- α, IFN- γ were analyzed by Luminex, FOXP3 by RT-PCR and serum GADA, IA-2A, tetanus toxoid and IgE by RIA.

Results: After one month GAD_{65} induced Th2 deviation (IL-5,-13) and FOXP3 ($p < 0.05$) in GAD-alum treated patients. At three and nine months, IL-17, TNF-α and IFN-γ ($p < 0.05$) were additionally induced and GADA increased to a maximum at 3 months and then decreased again ($p < 0.001$). At nine months also IL-10 was higher in GAD-alum group. At 21 months GAD_{65} induced $CD4+CD25^{high}FOXP3+$ cells ($p < 0.05$) while CD4 + CD25 + ($p < 0.005$) were reduced. No differences in IA-2A, tetanus antibody or IgE were observed.

Conclusions: GAD-alum induced long-lasting specific T and B cell memory, and a specific T cell population characterized by early Th2 and regulatory immune responses that increased over time, in parallel to reduction of the inflammatory process. These changes of the autoimmune process may be one explanation of the GAD_{65}-alum effect on residual insulin secretion.

O/4/FRI/02

Discordance for diabetes mellitus in monozygotic twin boys with ipex syndrome

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IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome is a rare disorder caused by mutations in the FOXP3 gene that result in defective development of CD4 + CD25 + regulatory T cells. Patients may manifest several autoimmune disorders including type 1 diabetes, entheropathy, dermatitis, thyroiditis, hemolytic anemia, membranous nephropathy and recurrent infections.

Objective: To demonstrate a new mutation in FOXP3 gene in identical Brazilian twin brothers with IPEX syndrome and discordant phenotypes.

Subjects and Methods: The boys were born from unrelated healthy parents after an uneventful pregnancy. Twin 1 presented bronchiolitis at 2 months, recurrent respiratory infections, type 1 DM with ketoacidosis at 6 months, membranous glomerulonephritis diagnosed at 9 months of age. Failure to thrive and periods of watery diarrhea were maintained despite dietary changes. Laboratory work-up showed altered liver enzymes, positive anti-liver microsomal antibodies, positive anti-TPO anti-Tg andanti-insulin antibodies; upper endoscopy revealed eosinophilic esophagitis. **Twin 2** presented 3 pneumonia episodes needing hospitalization, the first one with 15 days of life, chronic diarrhea with failure to thrive and membranous glomerulonephritis. Auto-antibodies (RF, anti-TPO, anti-TGB, anti-insulin) were present but diabetes was not manifested until he was 15 months old and died after another severe respiratory infection. High serum levels of total IgE and specific IgE for cow' milk protein were detected in both patients.

Results: Flow cytometry analysis showed low expression of FoxP3 and molecular research showed a change in splicing site located immediately after the exon 1 (IVS1 210 + 1G > A), a novel mutation.

Conclusion: IPEX syndrome is a cause of monogenic diabetes and perhaps exposure to different environmental factors in addition to genetic causes could explain the discordant phenotype for diabetes in these patients.

O/4/FRI/03

Polymorphism c1858t in the protein tyrosine phosphatase non-receptor type 22 gene is not associated with joint susceptibility for type 1 diabetes and hashimoto's thyroiditis in the young

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Objectives: Polymorphism C1858T in the protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene was, in adults, recently associated with joint susceptibility for type 1 diabetes (T1D) and autoimmune thyroid disease (AITD) - a mixed group of Hashimoto's thyroiditis (HT) and Graves disease (GD) subjects. Aim of the study was to determine whether this polymorphism is associated with joint susceptibility for T1D and HT in the young.
Methods: Seventy-five subjects with T1D and HT (age 20.5 ± 0.6; years ± SE) and 110 subjects with T1D (age 20.9 ± 0.5; years ± SE) were studied. Male to female ratio was equal in both groups. HT was determined according to the clinical, biochemical and ultrasonographic criteria. SNP C1858T in PTPN22 gene was determined by TaqMan SNP method. Genotype and allele frequencies were compared between groups using Chi-Square test. We were able to exclude a medium size effect of the investigated SNP (Power (1 - β) = 95%, effect size = 0.3, P = 0.05).
Results: No association between the two study groups was found regarding allele frequencies and genotype distribution for SNP C1858T, as presented in the table.

Alleles	C	T	
T1D+HT (n = 75)	86.0%	14.0%	
T1D (n = 110)	80.0%	20.0%	
Chi-Square		2.217	
P		n.s.	
Genotypes	CC	CT	TT
T1D+HT (n = 75)	72.0%	28.0%	0.0%
T1D (n = 110)	62.7%	34.5%	2.7%
Chi-Square			3.221
P			n.s.

[Allele frequencies and genotype distribution]

Conclusion: SNP C1858T in PTPN22 gene wasn't associated with the joint susceptibility for T1D and HT in the young. This is in disagreement with the recent study in adults where C1858T was associated with an increased joint susceptibility for T1D and AITD (a mixed group of HT and GD subjects).

O/4/FRI/04

Ctla-4 +49 a/g gene polymorphisms modify the risk for autoimmune thyroid disease in children with diabetes mellitus type 1

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Objectives: Type 1 diabetes mellitus (T1DM) and autoimmune thyroid disease (AITD) are the most common autoimmune endocrine disorders. Epidemiological data suggest common genetic risk factors involved in their pathogenesis. An immune regulatory gene, cytotoxic T-lymphocyte antigen 4 (CTLA-4), is considered to contribute to the susceptibility to both diseases. The aim of our study was to assess the contribution of polymorphisms of the exon 1 of the CTLA-4 +49 A/G gene to AITD susceptibility among children with T1DM.
Methods: To this purpose, polymorphisms of the exon 1 of the CTLA-4 +49 A/G gene were determined by group-specific polymerase chain reaction amplification (PCR) method based on time-resolved fluorometry (TRF) technique, in 18 patients with T1DM and AITD, aged 11.07 ± 3.42 years, as well as to 100 patients with T1DM without AITD, age and sex matched. In our study group, T1DM was diagnosed at an age of 7.85 ± 1.98 years and AITD at an age of 8.92 ± 2.21years. AITD was diagnosed through positive antithyroid antibody testing and ultrasound findings suggestive of the disease (heterogenity and hypertrophy of the gland). The TSH levels at diagnosis were 5.11 ± 2.25 μIU/ml and the exogenous thyroxine requirements at last examination were 1.6μg/kgr/day.
Results: In our study, the incidence of CTLA-4 +49 AG and GG genotypes was significantly higher in children with T1DM and AITD compared to those without AITD($p < 0.05$, OR = 3,95 and $p = 0.003$, OR = 6,43 respectively). Furthermore, the G allele increases significantly the risk for AITD in children with T1DM ($P < 0,001$, OR = 8,45).
Conclusions: Our results suggest that the CTLA-4 +49 A/G gene polymorphisms modify the risk for AITD in children with T1DM.

O/4/FRI/05

Abnormal interleukin-1 (il-1) signalling characterizes monocytes from humans and mice at risk of and with type 1 diabetes (t1dm)

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Objectives: Splenocytes of non-obese (NOD) mice (model of T1DM) secrete high IL-1 levels prior to diabetes. IL-1 is over-expressed in peripheral blood mononuclear cells (PBMC) of T1DM subjects. Incubation of healthy PBMC with T1DM serum causes a gene signature associated with IL-1 over-expression. Our aims were to: In NOD mice, determine when IL-1 secretion occurred, from which cells, and possible drivers of IL-1 expression; in T1DM subjects, determine whether PBMC express an IL-1 associated gene signature constitutively.
Methods: We analysed splenocyte supernatants from NOD mice stimulated with anti-CD3 4 weekly from weaning until diabetes onset. We characterised splenocytes and islet infiltrating cells for IL-1. NOD mice IL-1 secretion was compared to NOD.I-A^k congenic mice which do not express NOD MHC class II proinsulin antigen restriction element I-A^{g7} and to CD11c pro-insulin NOD mice (tolerant to pro-insulin, no diabetes). We examined microarrays of PBMC for constitutive expression of inflammatory genes in 6 T1DM subjects and 6 controls.
Results: IL-1 secretion by NOD splenocytes was increased between 6 - 16 wk (peak 12 wk) at the onset of insulitis, prior to diabetes. IL-1 was produced by monocytes and dendritic cells in the islet and by splenic T cells. IL-1 production by NOD mice splenocytes was increased when compared to NOD.I-A^k congenic and CD11c pro-insulin NOD mice (356 ± 6 vs 13 ± 2 pg/ml, $P < 0.001$). In T1DM subjects, 2 subjects had PBMC displaying a gene signature associated with constitutive IL-1 over-expression, 3 had IL-1

under-expression and one displayed a gene signature resembling controls.

Conclusions: In NOD mice, IL-1 over-production is driven by auto-antigen presentation and is associated with the development of insulitis. In T1DM subjects our data suggest abnormal IL-1 signalling. Studies on the relationship of IL-1 signalling and genetic background, environmental factors and clinical features at onset of T1DM are needed.

O/4/FRI/06

Lymphocyte apoptosis in the pathogenesis of type 1 diabetes mellitus

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Background: There is an emerging evidence that T cell-induced apoptosis is a dominant effector mechanism in type1 diabetes mellitus.

Aim: The study investigates the spontaneous lymphocyte apoptosis via CD95 molecule expression to demonstrate activation induced cell death in children with high risk of type1 diabetes mellitus and in type 1 diabetics under insulin therapy.

Methods: The study comprised 90 children and adolescents, divided into 3 groups. Group(1); comprised 40 type1 diabetics, their age ranged between 8–17 years and disease duration between 2–12 years.

Group(2); included 30 euglycemic subjects who were first degree relatives of type1 diabetics with normal fasting blood glucose and positive first phase insulin release and/or positive islet cell or glutamic acid decarboxlyase antibodies (prediabetics).

Group(3); 20 healthy, age and sex matched subjects with no clinical or laboratory signs or family history of type1diabetes. Patients were subjected to history taking and clinical examination. Study measurements included; random blood glucose, glycosylated hemoglobin, urinary microalbumin and flow cytometric assessment of apoptosis by measuring CD95 percentage expression on CD3 lymphocytes.

Results: The percentage of CD95 positive lymphocyte was significantly higher in prediabetics than in type1 diabetics and controls($P < 0.001$). CD3 positive lymphocytes were significantly lower in prediabetics than type1 diabetics and controls($P < 0.001$). The percentage of CD95 could not be correlated with age,insulin dose and random blood suger but glycated hemoglobin was positively correlated with both CD3 lymphocytes and CD95% expression. Complicated type 1 diabetics showed higher CD95% expression compared to non-complicated pateints.

Conclusion: Peripheral blood lymphocytes with CD95 antigen expression are increased in prediabetics. As CD95 is an important receptor for activation-induced cell death, CD95 mediated apoptosis could play a potential role in the pathogenesis of type1 diabetes mellitus.

O/4/FRI/07

Abnormal relb signalling characterizes monocytes from individuals at risk of type 1 diabetes (t1dm)

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Objectives: NF-kappa B is a transcription factor family involved in two pathways: Classical (RelA transcriptional activity) controls innate immunity and cell survival genes; Alternate (RelB transcriptional activity) controls dendritic cell (DC) and thymic function for immune tolerance, chemokine production and represses IL-1. In T1DM subjects, NF-kappa B activity of peripheral blood (DC) and monocytes (PBMC) is suppressed in response to lipopolysaccharide (LPS). We aimed to investigate NF-kappa B signalling in siblings at risk of T1DM and the underlying mechanisms. We hypothesized that low NF-kappa B transcriptional activity predisposes to T1D.

Methods: RelA and RelB nuclear binding activity were measured in 2 ml whole blood by ELISA before and after incubation with LPS. Families were HLA-typed and heritability was assessed as a quantitative variable using the 'SOLAR' program. Cell lysates were immunoprecipitated with RelA and immunoblotted with RelB then quantitated by densitometry.

Results: In PBMC, constitutive RelB nuclear activity was 2–5 fold higher in T1DM subjects and in islet-AB+ siblings than controls ($P < 0.001$). After LPS, RelA nuclear activity was reduced relative to untreated PBMC: 0.7 ± 0.1 fold in T1DM subjects, 0.6 ± 0.1 in AB+ siblings and 1.7 fold ± 0.4 in controls ($P < 0.001$). RelA was < 0.6 after LPS in 13% of AB- siblings. In family studies the NF-kappa B phenotype was not heritable. LPS-induced RelA/RelB heterodimer formation, as demonstrated by immunoprecipitation, correlated with constitutive levels of RelB.

Conclusions: Our data suggest environmental factor(s) promote constitutive activation of RelB in T1DM subjects or those at risk. When induced by LPS to hetero-dimerize with RelA, RelB forms an inactive complex, preventing further RelA activation. The consequences of this for DC will include excess IL-1 production, poor cell viability, and reduced T cell function. This RelB/RelA phenotype may be an early T1DM susceptibility biomarker.

O/4/FRI/08

Increased insulin resistance and oxidative stress in obese and non-obese pre-pubertal children born small and large for gestational age

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Objectives: Birth weight (BW) and obesity are associated with an increased risk of adult diseases. Insulin resistance (IR) seems to play a key role in small (SGA) and large (LGA) for gestational age children, whereas no data on oxidative stress are available. The aim was to evaluate the effect of BW and obesity on oxidative stress and IR in pre-pubertal SGA and LGA than appropriate for gestational age (AGA) children.

Methods: We performed a cross-sectional study comparing oxidative stress and IR in 103 children divided into six groups according to BW (26 SGA, 15 AGA, 16 LGA normal-weight children) and obesity (15 SGA, 15 AGA, 16 LGA obese children). Infants born from mothers with gestational diabetes mellitus, hypertension, obesity were excluded. Indexes of IR (homeostasis model assessment, glucose to insulin ratio) and marker of oxidative stress (urinary isoprostanes) were evaluated.

Results: Homeostasis model assessment was higher in both normal-weight SGA and LGA than in normal-weight AGA children (all $P \leq 0.02$). Furthermore, a difference was detected between obese SGA and obese LGA subjects than normal-weight SGA (all $P \leq 0.0007$) and LGA children (all $P \leq 0.01$), respectively. Glucose to insulin ratio was lower in the three obese groups than normal-weight AGA (all $P \leq 0.009$) and normal-weight SGA children (all $P \leq 0.02$). Furhermore, a difference was detected between obese SGA and obese LGA compared to normal-weight LGA subjects (all $P \leq 0.0002$). Isoprostanes levels were higher in both normal-weight SGA and LGA than in normal-weight AGA children (all $P \leq 0.002$). Moreover, both obese SGA and LGA

showed higher levels than obese AGA subjects (all $P \leq 0.01$) and in comparison to the three normal-weight groups (all $P \leq 0.04$).
Conclusions: Increased IR and oxidative stress are already present in pre-pubertal normal-weight SGA and LGA children with a continuous alteration in relation to obesity, suggesting that BW and adiposity represent two independent risk factors for degenerative diseases.

Oral Session V: Monogenic Diabetes and Novel Treatment

O/5/FRI/01

The identification of monogenic diabetes in a norwegian population-based childhood diabetes registry has implications for treatment

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Objectives: The prevalence of monogenic diabetes is probably 2–3% of all types of diabetes. Our aim was to investigate the incidence of monogenic diabetes in childhood diabetes based on the Norwegian Childhood Diabetes Registry. Moreover, for cases positive for mutations in *KCNJ11* or *ABCC8*, we aimed to switch treatment from insulin to sulfonylurea.
Methods: The screening was based on 1601 cases consecutively included between 2002 and 2008. Clinical data, family history, age at diagnoses, treatment, GAD and IA-2 antibody status, were evaluated and a monogenic cause was suspected if: 1) Age was under 12 months, 2) There was a positive family history of monogenic diabetes, 3) Negative antibody status. If age under 12 months, we screened *KCNJ11*, *ABCC8* and *INS*. Otherwise, we screened *HNF1A*, *HNF4A*, *INS* or *CEL*.
Results: In total, 27 cases (1.7%) were selected for screening. Of these, 14 (0.9%) had a pathogenic mutation in either of the genes screened. Five subjects (0.3%) were below 12 months of age. Four cases (0.2%) had a mutation in *KCNJ11* while none were positive for *ABCC8*. All four cases were successfully switched from insulin to sulfonylurea. HbA1c prior to sulfonylurea was mean 8.0% and after mean 45 months on sulfonylurea it was 6.5%. Of the 22 subjects with age above 12 months of age, we found pathogenic mutations in *HNF1A* (7 cases), *INS* (1 case), *ABCC8* (1 case) and *CEL* (1 case).
Conclusions: In the population-based Norwegian Childhood Diabetes registry, we find that the incidence of monogenic diabetes is at least 1.9%. *HNF1A*-diabetes is most common. Mutations in *KCNJ11* were 0.4% of the cases, and all were successfully treated with sulfonylurea. Screening for monogenic diabetes in childhood diabetes is important, not only for a precise diagnosis, but also for choice of treatment.

O/5/FRI/02

Parental consanguinity strongly influences genetic aetiology in permanent neonatal diabetes

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Objectives: Defining the genetic aetiology of permanent neonatal diabetes (PNDM) is important to guide both clinical management and genetic counseling. Activating mutations in either of the two genes encoding the ATP-sensitive (K_{ATP}) potassium channel, *KCNJ11* and *ABCC8*, are the most common genetic cause of PNDM, followed by mutations in the preproinsulin gene (*INS*). Many other genetic subtypes have been described but their prevalence is unknown. As both dominantly and recessively acting mutations have been identified we aimed to explore the usefulness of self-reported parental consanguinity as a clinical criterion to prioritise genetic testing in patients with PNDM.
Methods: We studied a consecutive international series of 448 PNDM patients. Parental consanguinity was reported for 66 probands (15%). *KCNJ11*, *ABCC8* and *INS* were sequenced in all patients. Further genetic investigation depended on the phenotype. In patients with isolated PNDM, *GCK* was sequenced. In patients with syndromic PNDM other genes were tested depending on the additional clinical features.
Results: Mutations were identified in 270 patients (60%), with no difference between inbred and outbred probands ($p = 0.8$). Mutations in *KCNJ11*, *ABCC8* and *INS* were the three most common genetic causes of PNDM in non-consanguineous families (33%, 11%, and 10% respectively). However, presence of consanguinity was associated with a completely different genetic profile, *EIF2AK3* being the most common genetic cause of PNDM (23%), followed by recessive *INS* (14%), *GCK* (11%), and *ABCC8* (6%) mutations. K_{ATP} mutations accounted for 44% of non-consanguineous probands but only 9% of consanguineous cases ($p = 8 \times 10^{-8}$).
Conclusions: A genetic diagnosis is possible for at least 60% of patients with PNDM. Parental consanguinity determines the order in which genetic testing should be performed. K_{ATP} mutations and hence chances of treatment with oral sulphonylureas are much less frequent in consanguineous probands.

O/5/FRI/03

Genotypic heterogeneity and clinical phenotype in neonatal diabetes mellitus: a review of the single centre experience 1998–2008

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Objective: Neonatal diabetes mellitus (NDM) is a rare disorder with an incidence of 1 in 500 000 live births. It could be transient or permanent (proportion is 1:1). While TNDM is associated with abnormalities involving chromosome 6, the commonest causes of PNDM are mutations in KCNJ1, ABCC8 and insulin (INS) gene. We aimed to determine genetics and clinical phenotype in cohort of patients with NDM whose diagnosis was established in our center over the last 10 years.
Methods: We have evaluated four patients with clinical diagnosis of NDM. UPD6 analysis was carried out in two patients who had TNDM, and KCNJ1, ABCC8 and INS genes were sequenced in the patients with suspected permanent forms of NDM.
Results: The diagnosis of NDM was established in four children (two with TNDM). Age at presentation was 5 days and 10 days in group with TNDM. In group with PNDM, one child presented at 13 days and another at 4.5 months. Birth weight ranged from 2000 to 3200 g and length from 45 to 49 cm. Ketoacidosis was present only in patients with PNDM. Dose of insulin ranged from 1.7 to 3.5 U/kg/day. TNDM lasted 2 months in one and 6.5 months in another patient. Paternal UPD6 was established in both children with TNDM. In one patient with PNDM, heterozygous mutation of *INS* gene (C96Y/N) was identified. In the other patient with PNDM, no mutation was established yet.
Conclusions: Although rare, NDM must be considered in each newborn with hyperglycemia. Molecular genetic analysis is

important for prediction of the outcome of NDM and for informed genetic counseling. As the "transient" form of the disease is probably a permanent β cell defect, these patients should be closely followed. Particular attention should be paid to glucose homeostasis at the time of puberty.

O/5/FRI/04

Hepatocyte nuclear factor 1α and 4α mutation occurring simultaneously in a two sisters with maturity-onset diabetes of the young

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Objectives: Maturity-onset diabetes of the young (MODY) is characterized by early onset, an autosomal dominant mode of inheritance, a primary defect in the function of the ß-cells of the pancreas and is most frequently due to a mutation in the glycolytic enzyme glucokinase (associated with MODY-2) or hepatocyte nuclear factor (HNF)1α (associated with MODY-3) genes, followed by mutations in the HNF-4α gene (associated with MODY-1).

Case report: An 8-year old girl (proband) was referred to our outpatient clinic with hyperglycemia (12 mmol/l). Family history revealed diabetes at young age (father of proband).Two cousins are treated for diabetes. No details are available.Immunological investigations for type 1 diabetes was negative in the proband. DNA analysis revealed: two new mutations in this girl: For the HNF 1α gene: c.335C > T p.Pro112Leu and for the HNF4α gene: c.625C > T p.His218Tyr. Insulin treatment was changed to sylfonylurea. Her sister (6 yrs) proved to have an elevated blood sugar (21 mmol/L) at routine examination. DNA analysis revealed the same mutations.

Results: On insulin treatment HbA1c was 6.9% and 8.1% changed to 6.3% and 6.6% respectively. On sulfonylurea treatment HbA1c was 6.2 and 6.8% respectively. Postprandial rises in Glucose were monitored were less on sulfonylurea than on MDI.

Discussion: In two girls two mutations found for HNF 1α and HNF4α gene were found simultaneously. Insulin treatment was changed to sulfonylurea with good result on blood sugar variations and (nearly) normalisation of HbA1c. No extra pre-prandial short acting insulin is necessary so far.

Conclusions: We report two female siblings in one family carrying both a new mutation of HNF-1α gene and HNF-3α gene simultaneously. The exact contribution of each substitution to the phenotype of our subjects remains to be further elucidated.

O/5/FRI/05

Age-different response to sulfonylurea in mother and daughter with permanent neonatal diabetes mellitus carrying the same kcnj11 activating mutation of kir 6.2 subunit

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Objectives: Heterozygous activating mutations in KCNJ11, encoding the KIR 6.2 subunit of the ATP-sensitive potassium (K_{ATP}) channel, cause up to 60% of cases of permanent neonatal diabetes mellitus (PNDM). Diabetes results from impaired insulin secretion caused by a failure of the β-cell K_{ATP} channel to close. Sulfonylureas (SU) close the K_{ATP} channel and represent the best therapeutic option for KIR 6.2 mutant patients. Two patients (mother and daughter), aged 36 and 8 year, were affected by insulin-treated PNDM. C-peptide levels were undetectable; pancreas morphology evaluated by ultrasound and NMR was normal; mean insulin requirement with basal-bolus regimen was about 0.4–0.7 U/kg/day. Metabolic control was unsatisfactory. Neurologic history was uneventful.

Methods: Both patients were carrying the heterozygous mutation in KCNJ11 c.601 C > T; p.R201C detected by PCR and were admitted to switch from s.c. insulin to oral Glibenclamide 3 times a day.

Results: In the girl, initial SU dose (given as oral suspension) was 0.08 mg/kg/day and increased up to 0.27 mg/kg/day. Insulin independance was achieved within 4 days. C-peptide levels gradually increased and a dramatic improvement of glucose profile was reported. Fructosamine levels decreased from 416 μmol/l up to 354 μmol/l within 2 weeks. On the contrary, the mother showed an unsuccessful switching, with no improvement in glycemic control even with a daily SU dose up to 50 mg. Due to persistent hyperglycemia and blood and urine ketone bodies positivity, s.c. insulin was replaced.

Conclusions: We report the different response to SU in 2 consanguineous patients with the same mutation. Therefore, mutation type seems not to be the limiting factor in successful transfer to SU. Diabetes duration and/or disturbed metabolism of β-cells due to gain-of-function mutations in KIR 6.2 may have an additional impact. Early genetic diagnosis in PNDM is mandatory, for the best therapeutic choice and for patients' quality of life.

O/5/FRI/06

Gad_{65} treatment induces high gada but no changes in epitopes or adverse signs/symptoms in type 1 diabetic children

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Background: GAD_{65} treatment (Diamyd) has shown to preserve residual insulin secretion in children and adolescents with recent onset Type 1 diabetes (T1D) and also an increase of GAD autoantibodies (GADA). High GADA may be associated to risks for neurological adverse events and we have therefore made a clinical follow-up of patients 4 years after GAD_{65} -treatment, as well as studied GADA and its binding in more detail.

Methods: 70 Type 1 diabetic patients (10–18 years old) with diagnosis within the previous 18 months were included in a double-blind, randomised, controlled trial receiving a primary injection on day 1 of 20 μg recombinant human GAD_{65}-alum (n = 35) or placebo (n = 35) and a booster dose after 4 weeks. Blood samples were collected before the first injection and after 1, 3, 9, 15, 21, 30 months. The serum levels and the epitope binding pattern of GADA were analysed. A 48 months follow-up is on-going.

Results: There were no clinical adverse events after 30 months, and none is seen so far in the 48 month follow-up. Patients receiving GAD_{65}-alum or placebo had similar levels of GADA at

baseline, but GADA were higher in GAD_{65}-alum treated patients after 3 months ($P = 0.001$), and remained so still after 30 months ($P < 0.05$). There were no differences in the binding pattern of GADA to a number of selected epitopes of GAD. High GADA, seen in both groups, were not related to any signs of neurological or other clinical adverse events. Analyses of enzymatic inhibition, anti-idiotypic antibodies and subclasses of GADA are ongoing.
Conclusions: The effect of GAD_{65}- treatment on the humoral response was antigen specific and induced a long lasting specific B cell memory, without inducing epitope spreading. So far there are still after 48 months no treatment-related adverse events.

O/5/FRI/07

Integrated real-time continuous glucose monitoring/ insulin pump system (prt) usefulness in 122 children with type 1 diabetes. a 3-year follow-up study

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Objectives: Real-time continuous glucose monitoring and the insulin pump have been combined into the sensor-augmented pump system (PRT) (Medtronic MiniMed, Sesto San Giovanni, Italy). The objective of the study was to evaluate the clinical effectiveness and safety of PRT in a large series of children with type 1 diabetes using insulin pump therapy.
Methods: This is a multicenter observational study. A questionnaire was sent to all paediatric diabetologic centres in Italy (n = 65); data was analyzed only regarding patients aged 18 or less and using PRT for 6 months or more.
Results: A total of 48 centres (73.85%) answered the questionnaire. The total number of patients with type 1 diabetes followed by the centres is 12.549, of whom 1437 (11.4%) have been using insulin pump therapy for more than 6 months. Of all patients using an insulin pump, 129 have been using PRT for at least 6 months, with a mean follow-up of 1.4 ± 0.7 yrs (range 0.5–3 yrs). Their age was 13.5 ± 3.8 yrs, with disease duration of: 6.3 ± 3.4 yrs). After 0.5–3 yrs of using PRT, HbA1c showed a significant improvement (8 ± 1.5 versus 7.4 ± 0.8%, $P = 0.002$). Insulin requirement showed a significant decrease (0.88 ± 0.25 versus 0.79 ± 0.23 U/kg/day, $P = 0.003$). BMI did not change during the observational period. Mean usage of PRT per month was 8.1 day/month and any significant correlation between sensor use and HbA1c has been observed ($r^2 = 0.0005$, $P = 0.239$). No DKA was observed during the follow-up, while episodes of severe hypoglycemia significantly decreased ($P = 0.04$).
Conclusion: The increased availability of continuous glucose sensors is likely to have a significant impact on pediatric diabetes therapy and education in the near future. Selection of patients capable and motivated to use sensor-augmented pump with proper age-appropriate education could be the key factors for the long-term success of these new technological advances in diabetes therapy as we have seen in our large group of children using PRT.

O/5/FRI/08

Children, adolescents and young adults with type 1 diabetes who discontinue insulin pump therapy: prevalence and characteristics

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The Initiation and management of continuous subcutaneous insulin infusion (CSII) therapy in type 1 diabetes patients requires a multidisciplinary experienced team. This study was prompted by the high discontinuation rates for CSII quoted in the literature (18–49%).
Aim: To characterize patients discontinuing CSII therapy in our tertiary medical center and determine the dropout rate.
Patients and methods: Medical charts of 459 type 1 diabetes patients (1.8–33 years, median 15) who initiated CSII therapy from 1998–2006 were reviewed. Fifty-nine patients discontinued CSII treatment (12.7%). Included in the study were 44 patients (9.5%), who discontinued CSII at least 3 months after initiation. The study group was compared to 93 randomly assigned CSII treated controls. Follow-up duration since CSII initiation was 4.3 ± 1.9 years.
Results: The dropout group had a significantly higher proportion of female patients than the control group (77% versus 57%, $P = 0.024$). Comparable findings were noted for other background factors: rate of familial cases; confidentiality; ethnicity; age at diagnosis, pubertal stage and duration of diabetes at CSII initiation; height-SDS, weight-SDS, BMI-SDS; and rate of hypoglycemic and DKA episodes. There were no between-group differences in number of daily insulin injections and blood glucose measurements before CSII treatment. At CSII initiation, HbA1c was significantly higher in the dropout group than the controls (8.57 ± 1.29% versus 8.09 ± 1.28% $P = 0.04$).This difference was maintained at the last follow-up.
Conclusions: The CSII dropout rate for children and young adults in our center is lower than reported. Female gender and poor metabolic control are associated with a higher risk of CSII dropout.

Oral Session VI: Diabetes Project in Developing Country

O/6/FRI/01

Wound care in cameroon

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Background: Most health Units in Cameroon like in any developing country lack modern products for health management. There are neither podiatrists, foot nor wound care specialist centers; yet people with diabetes are highly susceptible to ulcerations especially of feet. Cameroon has about 17 millions inhabitants, yet no known single podiatrist in any of the hospitals.
Method: Assessing the care of diabetics with ulcers especially foot ulcers in Cameroon clinics and hospitals; applying personal assessment with 10 years of working experience with 2 nationally renowned Baptist hospitals as well as visits to other hospitals like the Shisong general hospital alongside many clinics and now Divine Providence Low Cost Clinic (DIPROLOCC) where I am working.

Result: Available wound care products range from povidone, sterile gauze, chlohexidine, hypochlorite solution, normal saline, silvadine and neomycin. The leading products of silver nitrate, alginate, collagen…are not available perhaps due to cost or custom policies. The common, efficient, cheapest and most available product for these ulcers is honey from special wild bees that swarm called *Apis mellifera*, produced locally. Vascular assessment and foot exams are very rare even in the diabetes clinics and there are no wound care specialists.

Conclusion: Diabetes is gradually acknowledged as a global epidemic and the situation is worst with developing nations due to lack of expertise. Poverty hinders training of interested health care professionals yet there are no such training facilities. There is a great need for umbrella organizations like IDF, WDF and importantly ISPAD who have realized this burden. Expertise gotten from such training will enhance diabetes programs which with good compliance, will greatly cut down complications especially of the foot.

O/6/FRI/02

Glycaemic control in kenyan children and adolescents with type 1 diabetes mellitus

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Type 1 Diabetes mellitus (T1DM) is the most common endocrine-metabolic disorder in children and adolescents worldwide. While data about prevalence, treatment and complications are recorded in many countries, few data exist for Sub-Saharian Africa. The aim of this study was to determine the degree of control in all patients with T1DM aged 1- 19 years referred over a 6 month period in 3 outpatient Kenyan clinics. It also sought to determine how control was influenced by various patient and treatment parameters.

Eighty two children and adolescents with T1DM were recruited and included in the study. Clinical history regarding duration of illness, type and dose of insulin, and recent symptoms of hypo/hyperglycaemia were recorded. Blood was tested for Glucose and HbA1c and urine for ketones.

Data were analysed using the Statistical Package for social sciences (SPSS version 11.0) comparison of means was used for continuous data and chi-square was performed for discrete variables. HbA1c of 8.0% and below was defined as the cut off for good control.

The median HbA1c for the study population was 11.1%. Overall, only 28% of patients had good glycaemic control as defined in this study (72% had poor control). In determining the degree of metabolic control no statistically significant differences were shown for sex, residence, primary care givers, family history of T1DM, insulin formulation, use of refined sugar, age at diagnosis, duration of illness, type of insulin used, dosing regimen. Only age above 12 years was significantly associated with poor control ($P < 0.001$).

These findings are important because they confirm our fears that African children and adolescents with T1DM are poorly controlled and that adolescents are particularly at high risk of poor control. These data have to push all people involved in diabetes care to make possible for T1DM children and adolescents in Kenya to receive more aggressive management and follow-up than is currently being provided.

O/6/FRI/03

Type 1 diabetes in "*have not*" children in India - project "disha" and the free "insulin life line" program in the state of Karnataka, India: pseudoaltruism or real justice?

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The life of children and youth with diabetes in India, especially from the poorer sections of society is full of unique additional struggles and hopelessness:

1. ''Death before diagnosis'' - lack of awareness and diagnostic facilities, especially in rural areas;
2. Unaffordability of insulin and medical care;
3. Discrimination in education, future employment and family life
4. Non-existent governmental programs.

Since 1994, in a small attempt to improve this grave situation, Samatvam Trust - Jnana Sanjeevini Medical Center, has tried to support 500 children through charity Project DISHA and Insulin Lifeline Program. The activities include: FREE Childhood Diabetes Clinic - 1st Sunday of every month, provision of FREE insulin and syringes, health education and counseling, social support - ''Adopt a child'', patient-parent support groups, residential health camps etc. Currently ˜200 children are actively attending the clinic. FREE insulin for this program has been procured through diverse sources: bulk purchased at discounted rates; pharmaceutical industry 'social' programs - often erratic and unfortunately business linked; short expiry and left over insulins from industry and hospitals; participation in limited time bound clinical trials; samples gifted by good samaritans, etc. During extreme scarcity of insulin stocks in the program, we were forced to implement rationing and reservation towards children of the lowest poverty rank order, even among the poor. SHBGM has been an unavailable luxury till recently (now 6–10 blood glucose strips provided/child/month); HbA1c unaffordable; TSH measured only on strong clinical suspicion.

Distressingly, self realizing the grossly suboptimal care these youngsters are receiving, we often question ourselves whether we are justified in prolonging the misery of these children, just to let them succumb helplessly few years later (infections, hypoglycemia, DKA, renal failure), and disappear from this rather cruel and uncaring world?

O/6/FRI/04

Access to insulin for children with type 1 diabetes: a global perspective

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Background: Type 1 diabetes (T1D) is a life-threatening auto-immune disease and one of the most common chronic illnesses of childhood (Ryden, Nevander, Johnson et al., 1994; Graue, Wentzel-Larsen, Hanestad, Batsvik, & Sovik, 2003). T1D requires intensive management with either multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII).

Problem: Despite insulin being available in the developed world for almost 80 years it still fails to reach those in the developing world (Beran, 2005). Without appropriate access to insulin, children with T1D in developing countries face increased morbidity and mortality.

Examples: Reduced access to insulin in Latin America, Africa and India may be explained by: (1) a lack of fairly distributed healthcare, (2) inequitable distribution of power resources, and (3) pharmaceutical policies which attempt to improve access to medications meet with resistance from influential countries.
Conclusion: It is necessary to coordinate the efforts of interest groups working towards improving access to insulin in developing countries and compelling more powerful groups to provide insulin at reasonable costs. Thus, ensuring attainment of the highest standard of health, one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition (World Health Organization [WHO], 1946).

O/6/FRI/05

The case of the missing girls: low female: male ratio in youth with diabetes in North India

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This multicentric, noninterventional, observational study carried out at five major centres in north India has studied the gender ratio in youth with diabetes. In the hinterland states, the female: male ratio is very poor. Data from a 2 year OPD registry at Bharti Hospital, Karnal, in Haryana state, reveals striking findings. The female: male ratio in the < 30 years age group is 75:132 (57:100) for people with diabetes presenting to the OPD. In the < 15 years age group, the gender ratio is 100:100, but in patients aged 15 to 30 years, it drop to an amazing 48:105 (46:100).This means that 54 girls are lost to follow up for every 100 boys attending the OPD.
In the Diabetes, Obesity and Thyroid Centre, Gwalior, Madhya Pradesh, the type 1 diabetes female: male ratio is 1:2 (8;16) in the 0–30 year group. An exactly similar ratio is reported by the Diabetes and Endocrine Centre at Amritsar, Punjab (25:50).
In the metro cities, however, an equal gender ratio is reported. At the North Delhi Diabetes Center, equal number of girls and boys below 15 years seek treatment for diabetes (20.each). In the 15–30 years group, the ratio is 26 girls to 24 boys. At the Hormone Care and Research Center in Ghaziabad, in the National Capital Region, too, no gender differences were noted (56 females, 59 males). Diabetes workers mention the reasons for this as social gender bias, which lead to less medical care,and less nutrition for girls with diabetes. This paper highlights the social and medical factors which contribute to discrimination against girls with diabetes.

O/6/FRI/06

Evaluation of microalbuminuria in children with type 1 diabetes mellitus

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Objective: Diabetic nephropathy is one of the major complications and a leading cause of mortality and morbidity in diabetes mellitus. Microalbuminuria is the earliest sign of diabetic nephropathy and it is highly related to glycemic control. Progression of diabetic nephropathy is mostly asymptomatic until advanced stages of renal failure. In this study micro-albuminuria and its correlation with duration of diabetes and quality of diabetes control (HbA 1 c level) is evaluated in 50 children with type 1 diabetes mellitus.
Material & Methods: Fifty children 4 to 6 years following the onset of type 1 diabetes, below 20 years of age, were enrolled in this study. Twenty four hrs urine was checked twice within 3 to 6 months period for microalbuminuria by nephelometry method and values > 30 mg/24hrs were considered abnormal. Also HbA 1 c level and FBS level assessed simultaneously.
Findings: Fifty children, 4 to 19 years old with mean age of 14.54 ± 3.62 years, 28 (56%) males completed the study. Nineteen (38%), 14 (28%) and 17 (34%) children enrolled in this study 4, 5, 6 years after the onset of their diabetes respectively. At 1 st evaluation microalbuminuria was detected in 5 (26.3%), 4 (28.6%) and 6 (35.3%) children, 4, 5, 6 years after diabetes respectively. At 2nd evaluation these values were 4 (21.1%), 6 (42.9%) and 7 (41.2%) respectively. There was no significant correlation between HbA 1 c level, FBS level, and mean FBS level during the years of diabetes in microalbuminuric and non-microalbuminuric children.
Conclusion: Microalbuminuria was detected in children even 4 years after the onset of diabetes and its frequency increased in children with five and 6 years of diabetes. We recommend earlier than usual recommendations for microalbuminuria screening in diabetic children.

O/6/FRI/07

Management of diabetes in children and adolescents attending the diabetic clinic at mulago hospital

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Background: Diabetes is said to be on the increase in Uganda due to changes in life style, HIV AIDS and other diseases hence the need for aggressive management and care. We report high average random blood sugar levels in children and adolescents attending the diabetic clinic at Mulago Hospital, in Kampala.
Objective: We aimed to review the management of patients who are being treated for diabetes mellitus in the children's diabetic clinic at Mulago Hospital.
Methods: A cross sectional survey was used to assess 59 children who are registered and attend the children's diabetic clinic at Mulago Hospital. Abstracted data from records included; weights, heights, random blood sugar levels, insulin doses dispensed and or missed and analysis was done using the Statsdirect computer program.
Results: The average age of patients was 15.2 years with a range of 3.5 to 20 years. The average Body mass Index -BMI was 18.2 kg/m2 ranging from 10.6 to 34.5 kg/m2. Most children had high random blood sugar levels with an average of 286.3mg/dl. The average insulin dose per patient per day was 46.1 IU indicating a high dose of 2.5 IU per kg/m2/day. Thirty nine (39, 66%) children missed an insulin dose over the one year review period but only eight reported a sick episode. Causes for missing insulin dose included lack of transport to collect insulin or meals before the doses.
Conclusions: Diabetic children at Mulago hospital receive high doses of insulin but have high random blood sugar levels indicating poor glycaemic control. Most missed doses due to social and financial reasons.

O/6/FRI/08

Bridging gaps for paediatric diabetics community: ngo initiatives in developing countries

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Issues: Diabetes in children's brings mental depression in family. Focused treatment for pediatric age-group unavailable in developing-countries. 26% of diagnosed diabetics are children's. Adequately trained physicians/Nurses provide continuity of care, relief from depression, smooth treatment. Qualitative collaborative relationship makes diabetics life bearable. Our NGO-project highlights significance of relationship between nurses and diabetic-children in community clinic setup of rural India. Retrospective analysis of past studies shows—counselling improves QOL, attitude towards diabetes.

Aims: To describe care issues in diabetic-children's. Observe/modify nature of relationship between nurse and child. Evolve comprehensive treatment plan.

Methods: A retrospective analysis of data base from 7 rural health-clinics. Specialized therapy/support to pediatric-age-group not available at any centre. Total 117 children's [4–13 years] diagnosed with diabetes. 23 had additional endocrine/metabolic problems. Nursing care analyzed. No specialized trained personal in rural/tribal India. Opinion/needs from patients families collected on feedback questionnaire. Trained 10 nurses & 2 physicians for handling pediatric cases [4 wks training].

Results: Out of 117, 41 discontinued Rx due to improper counseling/guidance. 3 died. Patient/family's feedback highlights: Better access to newer insulins, psychosocial support, follow-up-plan. Nurses/physician be sensitized in pediatric care-issues. Main issues of concern: [1] coping with their feelings. [2] Initial impact of diagnosis and a search for solution? Expectations for future life [3] Concerns of RX cost [4] Availability of proper follow-up centers

Conclusion: Multifaceted Relationship between physician/nurse and Diabetic-child crucial. This provides better continuity of treatment. We show concerns/difficulties while working in Asian set-up to international experts at ISPAD-congress.

