## Diabetes Acute and Chronic Complications III

### P/FRI/31

### Atherosclerotic changes in Japanese patients with type 1 diabetes mellitus during adolescence

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**Objectives:** Diabetes itself is known as an independent risk factor for micro- and macro-angiopathy. However, only a few studies have examined the onset of cardiovascular complications in Japanese patients with type 1 diabetes mellitus (T1DM). In this study, we investigated atherosclerotic changes in Japanese patients with T1DM in terms of age or duration.
**Methods:** The subjects were 41 patients with prepubertal onset T1DM (17 males) and 26 non-obese non-diabetics as controls (group C: 13 males, 19.7 ± 0.6 year). The T1DM patients were divided into two groups according to Tanner stages (group A: stage 2 to 3; 11.8 ± 2.2 year and group B: stage 4 to 5: 18.2 ± 3.5 year). The obesity index was not significantly different between three groups. We examined parameters of early arteriosclerosis, such as blood pressure, blood flow-dependent vasodilative response (%FMD) and carotid artery intima media complex thickness (IMT), and blood parameters of glycemic and lipids metabolism.
**Results:** i) There was no significant difference in age at onset nor HbA1c between groups A and B. Thus, diabetic duration in group B is significantly longer than group A ($p < 0.0001$); ii) IMT values in groups A and B were 0.50 ± 0.08 mm and 0.52 ± 0.07 mm respectively, with significant differences in comparison with that of group C (0.45 ± 0.05 mm, $p < .05$ vs. group A, and $p < .005$ vs. group B); iii) %FMD value in group B (7.1 ± 3.2%) was significantly lower than those in groups A (10.6 ± 5.4%, $p < .05$) and C (12.0 ± 5.5%, $p < .005$); andiv) The atherosclerosis index (AI) in group B is significantly higher than in group A ($p < .05$). However we can not compare these AI with that in group C, since HDL-C level in T1DM is known to be higher than that in non-diabetics.
**Conclusion:** In non-obese Japanese T1DM patients, age and diabetic-duration dependent atherosclerotic change has already started during adolescence.

### P/FRI/32

### Tumor necrosis factor-alpha and interleukin-6 at early stage of celiac disease in type 1 diabetes mellitus children

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**Objective:** The aim of the study was to analyze whether increased levels of pro-inflammatory cytokines in the course of DM1 in children might play a role in the development of celiac disease in this particular group of patients.
**Patients and methods:** The study was conducted on a group of 223 children with long-standing DM1. In all the patients the following parameters were measured: HbA1c, C-reactive protein, 24 h urinary albumin secretion, levels of anti-gliadin antibodies (AGA) IgA and IgG, anti-endomysium (EmA) IgA and IgG antibodies, anti-tissue transglutaminase (tTG) IgA antibody and TNF-alpha and IL-6. Selected patients had jejunal biopsy performed.
**Results:** 21 (9.4%) out of 223 examined patients were diagnosed with celiac disease on the basis of positive result of jejunal biopsy. The children with long-standing DM1 and concomitant celiac disease, in relation to the DM1 patients without celiac disease, were characterized by statistically significant higher levels of HbA1c ($p < 0.001$), CRP ($p < 0.001$), higher 24 h urinary albumin secretion, elevated TNF-alpha ($p < 0.001$) and IL-6 ($p < 0.001$) as well as higher levels of the IgA-anti-tTG ($p < 0.001$), IgA-AGA ($p < 0.001$) and IgG-AGA ($p < 0.001$) antibodies. Additionally, significant positive correlation between HbA1c and IgA AGA ($R = 0.14$, $p = 0.036$) and IgA EmA ($R = 0.21$, $p = 0.001$) was found. There was also a statistically significant positive correlation between IgA tTG and serum TNF-$\alpha$ ($R = 0.28$, $p = 0.026$) and IgG AGA and serum IL-6 ($R = 0.31$, $p = 0.023$).
**Conclusions:** Persistent inadequate metabolic compliance and permanent elevated level of TNF-alpha and IL-6 in the course of DM1 in children might influence the prevalence of celiac disease in those patients.

### P/FRI/33

### The possible role of glycemic variations to sleep disorders in children with insulin dependent diabetes mellitus – preliminary data

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**Objectives:** We investigated whether diabetic children with poorly or good controlled diabetes have respiratory dysfunctions during sleep and if so, whether these abnormal respiratory patterns during sleep are related to the duration of diabetes and glycemic control.
**Methods:** At the end of our study we have 20 children with IDDM (age range 10–16 years). All children had normal growth (average BMI 20). The duration of disease ranges from 1 to 12 years. All patients were insulin-dependent at diagnosis. No drugs were used to induce sleep. All patients receive MDI therapy (long-acting insulin analogue based). We divided our cohort into two groups according to HbA1c:10 with ≤ 7.5% (av6.4%), 10 with ≥ 7.6% (av9.3%). None of the children had neurological or vascular diabetes complications. Polysomnography: All patients underwent a polysomnographic study (multichannel poligraph, VitalNight8, VitalAire Italia) overnight (from 23.00p.m. to 07.00 a.m.). The following tests were recorded: air flow triply monitored with a nasal cannula; snoring was monitored with a microphone sensor; SaO2 was assesed by pulse oximetry with simultaneous recording of the pulse wavefrom; thoracoabdominal excursions by inductance plethismography; movement of both chest and body positions were also monitored with body position sensor. Metabolic control: The glycemic profile of patients has been valued trough the use of glycemic holter (CGMS MEDTRONIC), blood samples were collected for HbA1c (DCA 2000 + Bayer).
**Results:** The data that we present concerns the first six children tested (three with good HbA1c and three poor). Overnight polysomnograms shown abnormal AHI > 3 in a boy having no obstruction in air ways and good-controlled diabetes, but 12 years duration of diabetes.The abnormal diagnostic for children is AHI > 1/h. OSAS in children is classified as mild (1 > AHI < 5/h) moderate (5 > AHI < 9/h) severe (AHI > 10/h).
**Conclusions:** Our early data indicate a possible correlation between IDDM and sleep-disordered breathing.

P/FRI/34

## Reversible hepatomegaly due to glycogen storage in adolescents with poorly controlled type 1 diabetes: a minimalist form of the Mauriac syndrome

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By improvement of insulin therapy the classical features of Mauriac syndrome i.e hepatomegaly, dwarfism, delayed sexual maturation and hyperlipidemia are reported only rarely today. But numerous case reports were published in the past on adolescents with poorly controlled diabetes mellitus type 1 (DM) and hepatomegaly due to glycogen storage. We report on three adolescents with DM: two females (15.3 and 14 years) and one male (15.7 years). The patients had poor control of DM over time and developed hepatomegaly with elevated transaminases and combined hyperlipidemia. With improved glycemic control by i.v/s.c. insulin therapy almost complete recovery occured within a short time. Serological examinations yielded negative results for infectious and metabolic diseases (hepatitis A, B, C, EBV, CMV, α1-antitrypsin deficiency, Wilson disease). Liver biopsies revealed glycogen deposits in the hepatocytes and mild steatosis. Classical glycogen storage diseases were excluded by measurement of activities of the correspondent enzymes and by mutation analysis of the glucose-6-phophatase-gene. The pathogenesis of hepatic glycogen storage in patients with unstable DM can be explained by an imbalance between glycogenesis and glycogenolysis: during hyperglycemia glucose enters -independently of insulin- the hepatocytes promoting glycogenesis, which is augmented further by administration of insulin. Simultaneously glycogenolysis is inhibited by the presence of glucose. Glycogen-induced hepatomegaly appears to be completely reversible in contrast to steatosis-induced hepatomegaly leading to fibrosis and even cirrhosis. Thus the differentiation between these two is important for the management and prognosis of these patients. The question remains why not all patients with poorly controlled DM develop abnormal glycogen storage in the liver. Therefore, further genetic analyses regarding the enzymes of glycogenesis and glycogenolysis are necessary to unravel this phenomenon in some patient.

P/FRI/35

## Antithrombogenic activity of vessel wall in children with type 1 diabetes mellitus

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**Objectives:** To study peculiarities of antithrombogenic activity of vessel wall in children with type 1 diabetes mellitus (T1DM).
**Methods:** Out of 100 children (40 boys, 60 girls) 3–16 years old. with T1DM were examined. The duration of the disease was: less than 1 year - in 17 patients (HbAc1 7.4 ± 0.3%) - group 1, from 1 to 5 years - in 48 patients (HbAc1 8.8 ± 1.2%) - group 2, more then 5 years - in 35 children (HbAc1 11.1 ± 2.1%) - group 3. Control group: 30 healthy children 3–16 years old. The indexes of tromboresistance of vessel wall (antiaggregating, anticoagulating, antifibrinolytic activity) measured by manjetic method. The indexes of trombocyte aggregation (degree, speed and time of aggregation) measured by laser method with different inductors (ADP, adrenalin, kollagen) were evaluated.
**Results:** Tromboresistance of vessel wall was normal in group 1 in comparance of control group ($p < 0.05$). Tromboresistance of vessel wall was decreased in group 2 ($p < 0.05$). Decrease of tromboresistance of vessel wall ($p < 0.001$) was found in patients of group 3 in comparance of control group.
**Conclusions:** Disorders of antithrombogenic activity of vessel wall in children with T1DM correlated with duration of the disease and may demand treatment with heparinoids.

P/FRI/36

## Endothelial function in children with type 1 diabetes mellitus: a longitudinal study

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**Background:** Patients with type 1 diabetes mellitus (T1DM) have an increased risk of vascular complications related to the duration of diabetes and the degree of glycemic control. Impaired flow-mediated dilation (FMD) has been used to evaluate the vascular function. Aim is to evaluate longitudinally changes of FMD in T1DM patients.
**Methods:** Thirty-two children (18 male, 14 female; 11.6 ± 3.33 year.) with T1DM (duration of disease 49.1 ± 39.5 months) entered the study. In all patients' lipid values, HbA1c and FMD were determined at the beginning and after 30.3 ± 7.42 months. Vascular function was assessed by measurement of endothelium-dependent vasodilatation of the brachial artery using a high-sensibility ultrasound system. FMD was expressed as percentage change of diameter following reactive hyperemia from baseline and normal values were considered > 7%.
**Results:** During the follow up HbA1c values (7.99 ± 1.06 vs. 8.12 ± 1.11%; $p = 0.28$) were unmodified. Conversely, at the end of the study, an impairment of FMD was demonstrated in 75% vs. 50% of children found at the start. However, mean values did not significantly change (6.41 ± 10.6 vs. 2.57 ± 9.01%; $p = 0.09$). No correlation was demonstrated between FMD and lipid profile, HbA1c or duration of the disease. At follow-up no difference was shown in FMD between children with HbA1c > 8% vs. < 8% (2.69 ± 8.55 vs. 2.33 ± 10.2%; $p = 0.91$), despite significantly difference in the months from diagnosis (91.6 ± 42.7 vs. 56.2 ± 26.1 months; $p = 0.01$). According to sex, no difference of age, months of disease, HbA1c and FMD was revealed, while longitudinally boys had significantly lower FMD than girls (- 0.95 ± 8.15 vs. 7.10 ± 8.19%; $p = 0.009$).
**Conclusion:** Our data show that after few years, patients with T1DM have a worse FMD not apparently related to glycemic control or to duration of T1DM. This difference, more evident in males, suggests that further studies are needed to better understand other factors involved in functional changes of endothelial dysfunction.

P/FRI/37

## Early signs of left ventricular dysfunction in adolescents with type 1 diabetes mellitus: the importance of impaired circadian modulation of blood pressure and heart rate

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**Introduction:** Diabetic cardiomyopathy is a well-defined complication of diabetes that occurs in the absence of ischemic heart disease

or hypertension and has been associated with autonomic dysfunction.
**Objectives:** Our aim was to evaluate diurnal BP fluctuations and autonomic function and their possible association with left ventricular function in adolescents with T1DM.
**Methods:** In 48 normotensive, normoalbuminuric diabetic adolescents, with a mean (± SD) age of 17.3 (± 4.1) years and diabetes duration of 8.5 (± 3.3) years, 24 h ambulatory BP and heart rate (HR) monitoring was performed. Left ventricular end-diastolic (EDDLV) and end-systolic diameters (ESDLV) were estimated by echocardiogram and left ventricular mass index (LVMI) was calculated.
**Results:** The patients were divided into two groups according to the absence of decrease (non-dippers) or the decrease (dippers) of nocturnal diastolic BP (DBP). The non-dippers presented, in comparison with the dippers, reduced mean HR during 24 h (79.6 vs. 84.0 beats/min, $p = 0.05$) and also during day-time (81.3 vs. 86.0 beats/min, $p = 0.05$). The non-dippers also presented greater ESDLV (28.7 vs. 25.9 mm, $p = 0.001$) and EDDLV (47.8 vs. 45.1 mm, $p = 0.040$) and greater LVMI (90.2 vs. 78.3 g/m$^2$, $p = 0.044$), in comparison with the dippers. During stepwise multiple regression, the most important factors affecting LVMI were meanHR (day): ($b = -0.40$, $p = 0.001$), HF variable of HRV ($b = 0.38$, $p = 0.016$) and HbA1c: ($b = 0.67$, $p = 0.001$).
**Conclusion:** A group of normotensive diabetic adolescents with abnormal nocturnal BP reduction and impaired HRV also had impaired left ventricular function. Our findings suggest that altered diurnal BP profile, as a result of autonomic dysfunction, may contribute to the development of left ventricular hypertrophy in patients with T1DM.

### P/FRI/38
### Homocysteine levels of children with type 1 diabetes mellitus

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**Introduction - aim:** Homocysteine is a sulphur amino acid with a free thiol group not available in dietary protein. High levels are strongly related to vascular disease which may develop in patients with IDDM. The purpose of the present study was to determine homocysteine levels of children with type 1 diabetes by comparing them to a control group as well as find how these might be related to disease duration and glycemic control (HbA1c).
**Patients - method:** Out of 17 children with type 1 diabetes mellitus comprised our study group. Their mean age and disease duration were 15 ± 6.46 and 6.32 ± 5.22 years (disease duration range 1–19 years), respectively. 17 normal children of similar age and sex served as our control group. Homocysteine levels were determined using high resolution liquid chromatography and expressed as μmol/l. The Pearson correlation coefficient, Mann-Whitney test and one way ANOVA were employed for comparative purposes.
**Results:** Homocysteine levels (6.02 ± 1.86 μmol/l) of children with type 1 diabetes were not significantly different from those of the control group (7.28 ± 1.72 μmol/l). When children were further divided into groups of adequate (HbA1c ≤ 8, n = 7, mean ± SD = 5.11 ± 1.03) and inadequate (HbA1c > 8, n = 10, mean ± SD = 6.33 ± 2.00) glycemic control and compared to normal controls (n = 17, mean ± SD = 7.28 ± 1.72), no significant differences in homocysteine levels were discovered between the three groups. However, a strong positive correlation ($r = 0.808$, $p = 0.001$) was identified between duration of the disease and homocysteine levels. No correlation ($r = 0.134$, $p = 0.567$) was found between glycemic control and homocysteine levels.
**Conclusion:** Hyperhomocysteinemia does not develop in children with type 1 diabetes. There is a tendency for levels to rise in relation to the duration of the disease but they never become abnormal. However, larger scale studies should be conducted to ascertain this.

### P/FRI/39
### Carotid intima media thickness (cIMT) of children with type 1 diabetes mellitus

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**Introduction - aim:** Cardiovascular disease and the development of coronary artery atherosclerosis hold a key role in increasing mortality among patients with diabetes. The aim of the present study was to determine the possible presence of subclinical atherosclerosis (evaluated as carotid intima media thickness (cIMT) in children with type 1 diabetes mellitus.
**Patients - methods:** Out of 12 children with a mean age of 15.87 ± 7.07 years who had type 1 diabetes mellitus participated in the study. Their average disease duration was 6.95 ± 5.29 years (range 2–18 years). Lipid profile and HbA1c were also assayed. 12 normal children of similar age and sex served as our control group. Carotid artery media thickness (cIMT) was measured using coloured Doppler ultrasound. Patients were being treated with three or more daily subcutaneous insulin injections. The Pearson correlation coefficient and Mann-Whitney tests were employed for purposes of comparison.
**Results:** The mean cIMT was significantly higher in diabetic children than controls (0.54 ± 0.08 mm vs. 0.42 ± 0.078, $p = 0.004$). However, cIMT was not found to positively correlate with either age($r = 0.430$, $p = 0.163$), duration of disease ($r = 0.387$, $p = 0.240$) and HbA1C ($r = 0.112$, $p = 0.728$). No correlation was also identified between the lipid profile and cIMT (TGs, $r = 0.260$ $p = 0.415$, LDL $r = 0.155$, $p = 0.631$, HDL $r = -0.150$, $p = 0.641$).
**Conclusion:** cIMT is definitely higher in diabetics than controls and can prove a very useful index in monitoring early vascular changes in certain high risk groups. This can help reduce cardiovascular events in those patients.

## Type 2 Diabetes, Diabetes and Obesity II

### P/FRI/40
### Adipo-insular interplay at OGTT in obese children

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**Objectives:** The mile stone disorders in childhood and adolescence obesity are: changed secretion of adipokines and insulin resistance. Their short time interplay in OGTT has not been described in children yet.
**Methods:** A total of 102 children (31 Tanner stage I, 71 puberty stages II-V; age 12.6 ± 3.3) were involved into the study. Normal weight 26 children had BMI-SDS ≤ 1.0; 17 overweight had SDS 1.1–2.0; 37 moderately obese with SDS 2.1–4.0 and 22 severely obese SDS ≥ 4.1. OGTT with insulin, adiponectin, resistin measures were performed.
**Results:** Adiponectin serum concentrations (ADQ mean ± SD; μg/ml) decreased during OGTT. Significant differences in 0' vs.120' of the test were observed in obese patients: controls 10.78 ± 6.00

vs. 7.49 ± 10.29; overweight 7.41 ± 5.91 vs. 4.84 ± 4.03, in moderately 7.25 ± 4.07 vs. 3.29 ± 2.12 ($p < 0.0001$) and severely obese 7.48 ± 4.12 vs. 3.11 ± 1.92 ($p < 0.0001$). Resistin (RES mean ± SD; μg/mL) had the same trend but without significant differences 0'vs.120': controls 9.83 ± 7.40 vs. 4.63 ± 0.93; overweight 11.14 ± 9.56 vs. 5.32 ± 0.61; moderately 11.96 ± 12.16 vs. 5.53 ± 2.03 and severely obese 14.33 ± 22.76 vs. 6.04 ± 4.19. RES values at 0' and 120' correlated in controls ($r + .884$; $p < .004$) and obese children ($r + .699$; $p < .036$). ADQ: RES ratio was lowered in both obese groups: 0.59 ± 0.44 ($p < .007$) or 0.52 ± 0.43 ($p < .048$) at 0' and 0.59 ± 0.43 ($p < .027$) or 0.49 ± 0.34 ($p < .042$) at 120'; if compare to controls: 1.08 ± 0.69 (0') and 1.68 ± 1.52 (120'). There were found ADQ (from $p < .004$ to $p < .03$) and ADQ: RES ($p < .01$) negative correlations at 0' & 120' to body mass, BMI and BMI-SDS. RES alone didn't correlate with mentioned anthropometric parameters.

**Conclusions:** Abrupt fall down of adiponectin blood level and its diminished ratio to resistin in course of OGTT are aggravated with obesity. The possible causative relations between hyperinsulinemia and/or hyperglycemia and these adiponectin changes should be considered in obese children at risk of type 2 diabetes.(Supported by MNiSW 2 P05E 064 30).

## P/FRI/41

## Progressive β-cell dysfunction in obese children

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**Objectives:** Insulin (INS) resistance and β -cell function decline are the major risk factors of type 2 diabetes in childhood obesity. The aim of study was to evaluate β -cell function in obese children in relation to disease advancement.

**Methods:** Study comprised 398 children (incl. 50 controls) of both genders; mean age of 12.3 ± 1.2. OGTT with INS (C-peptide, proinsulin and amylin are not presented in abstract) measures was performed in all; IVGTT was applied in 157 children. Patients were ordered by BMI-SDS: controls SDS ≤ 1.0, overweight SDS 1.1–2.0, moderately SDS 2.1–4.0 and severely obese SDS > 4.0. They were divided as follows: with (+ IR) or without (non-IR) insulin resistance; with combined glucose intolerance (IFG/IGT) or with normal tolerance (NGT).

**Results:** Out of 140 children appeared non-IR and 208 + IR (58%); 308 presented NGT and 40 IFG/IGT (11.5%). BMI-SDS correlated with 0' and 120' INS ($p < 0.0001$), HOMA-IR ($p < 0.0001$), WBISI (Whole Body Insulin Sensitivity Index) (negative, $p < 0.0001$) and QIUCKI (negative, $p < 0.0001$). BMI-SDS did not correlate with 0' and 120' glycemia. (+IR) and IFG/IGT correlated to 0' and 120' INS ($p < 0.0001$ for all) and to 0' and 120' glycemia ($p < .01$ to $p < 0.0001$), HOMA-IR ($p < 0.03$ to $p < 0.0001$), WBISI (neg. $p < 0.0001$) and QIUCKI (neg. $p < 0.0001$). IVGTT was essential for the study: mean INS in 0–15 min. increased with BMI-SDS ($p < 0.01$), but IFG/IGT patients demonstrated reduced response during first 3 and 5 min. of the test in comparison to NGT ($p < 0.04$). This original finding pointed to the failure of the first phase of insulin secretion in children with combined glucose intolerance (IFG/IGT).

**Conclusions:** i) The childhood obesity influences β -cell function even at the moderate degree of disease and the fasting and/or glucose induced hyperinsulinemia expresses their most frequent disorder; and ii) The earliest phase of insulin secretion in obese children is failing together with appearance of the impaired glucose tolerance.(Supported by MNiSW 2 P05E 064 30).

## P/FRI/42

## Elevated R-HOMA in obese children and adolescents with regard to their migration background

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**Objective:** Elevation of R-HOMA is known as an important risk factor in metabolic syndrome. Ethnical subgroups (Pima-Indians, Afro-Americans) are risk-groups for R-HOMA-elevation and metabolic syndrome compared to white population. We investigate if children with a Turkish/Near East (TNE) vs. a German background should be seen as a high risk group regarding R-HOMA-levels.

**Methods:** In the paediatric obesity centre at the Charité Children's hospital data about migration background and R-HOMA levels were available in 866 patients, 598 (69%) of them were Germans. From 407 boys 127 (31.2%) and 141 (30.6%) out of 460 girls were TNE. We used R-HOMA reference values by Allard (2003), BMI-SDS was based on reference values by Kromeyer-Hauschild (2001). Statistical analysis was performed with SPSS 13.0 using $CHI^2$ and Mann-Whitney-U-Test.

**Results:** TNE-patient group shows significantly more often a pathological elevation of R-HOMA compared to Germans. This is also significant for boys. After stratification for BMI-SDS we find a significant higher median R-HOMA for TNE patients who are overweight (BMI-SDS < 2) or obese (BMI-SDS 2–2.5). In extremely obese German and TNE-patients (BMI–SDS > 2.5) we do not see any difference in their median R-HOMA.

**Conclusions:** TNE-patients, especially boys, are more likely to have pathological R-HOMA-levels. Extremely obese patients have a high risk for R-HOMA-elevation independently from their migration background. Overweight and obese patients with TNE-background however have significantly more frequent higher R-HOMA levels. Therefore preventive strategies should turn their special effort to TNE-patients as a high risk group before getting extremely obese.

## P/FRI/43

## Body mass index, waist circumference, which is a better predictor of metabolic syndrome?

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**Objective:** To determine in children the association between waist circumference (WC), body mass index (BMI) and insulin resistance determined by homeostasis modeling (HOMA-IR) and components of the metabolic syndrome, including lipid profile and blood pressure (BP).

**Methods:** A total of 279 subjects (184 boys) aged 6 to 18 years and matched for sex and age underwent anthropometric measurements; 140 were obese; 33, overweight; and 106, nonobese. BMI, WC, BP, and Tanner stage were determined. An oral glucose tolerance test, lipid profile, and insulin assays were performed. Overweight and obese were defined according to BMI reference norm of Group of China Obesity Task Force.

**Results:** In total population, there were positive correlation ($P < 0.01$) between WC, BMI and systolic blood pressure ($r = 0.586$, 0.596), diastolic blood pressure($r = 0.557$, 0.567), triglyceride($r = 0.438$, 0.444), cholesterol($r = 0.170$, 0.170), fasting blood glucose($r = 0.147$, 0.152) and HOMA-IR($r = 0.717$, 0.709) respectively, negative correlation between WC, BMI and high-density lipoprotein cholesterol ($r = - 0.363$, −0.340). In control group, multiple linear regression analysis

indicated that WC (β coefficient = 2.169) and triglyceride (β coefficient = 0.429) were predictors of HOMA-IR, but in overweight and obese group, BMI (β coefficient = 0.356) and triglyceride (β coefficient = 0.886) were predictors of HOMA-IR.
**Conclusions:** BMI maybe a useful tool to determine overweight/obese children and adolescents at high risk for MS.

## P/FRI/44

## Are IVF children more prone to metabolic syndrome?

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Assisted reproduction techniques are commonly used worldwide. Mothers of children conceived with IVF experience stress, which has been associated with a smaller birth weight (BW) and a higher risk of occurrence of the metabolic syndrome in the offspring. Also, these children have a considerably higher risk of being born prematurely and with a lower BW than naturally conceived ones. The aim was to study the metabolic profile of children born after IVF and to determine the incidence of the metabolic syndrome in this population.
**Methods:** A total of 106 children born after IVF (48 boys-58 girls) and 68 controls born after normal conception (33 boys-35 girls), ages 4–14 years, were studied. All children had their height, weight, BMI, waist/hip ratio (W/H), Tanner stage, and blood pressure (BP) recorded. Morning blood was drawn after 12 h of fasting and glucose, insulin, triglycerides, total cholesterol, HDL, LDL, and uric acid were determined and fasting glucose/insulin ratio (FGIR) was calculated. As criteria for the metabolic syndrome we used. i) BMI > 95th centile; ii) Triglycerides > 95th centile; iii) HDL < 5th centile; iv) Systolic or diastolic BP > 95th centile for the age and gender of Greek children; and v) FGIR < 7. Children fulfilling three criteria were considered to have the metabolic syndrome.
**Results:** Children born after IVF had significantly higher systolic ($p < 0.001$) and diastolic BP ($p = 0.002$) and serum triglycerides ($p = 0.01$) than the controls, but values were within the normal range. There were no statistically significant differences in BMI, fasting glucose, insulin, FGIR, total cholesterol, HDL, LDL, or uric acid. Also, there was no statistically significant difference in the frequency of the metabolic syndrome or in the number of criteria fulfilled per child between the two groups. The increase of blood pressure and triglyceride concentrations, which are early markers of the metabolic syndrome, in the IVF children, should raise the suspicion of an early occurrence of this state in this population.

## P/FRI/45

## The role of premorbid factors and character of feeding in the formation of metabolic syndrome in children

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Children and adolescents with obesity are representing the group-of risk of forming metabolic syndrome (MS). There is little information about the influence of premorbid factors, character of early postnatal feeding on forming MS.
**Aim:** To study frequency of MS in children and adolescents with obesity; to determine main features of early postnatal feeding, the influence of hereditary predisposition on severity and times of forming MS.
**Patients and methods:** A total of 100 children and adolescents with obesity (49 girls) 6–17 years old were examined. Insulin resistance was diagnosed according to HOMA. Data of anamnesis were investigated: heredity, course of ante- and perinatal periods, character of early postnatal feeding. Control group - 30 healthy children with normal BMI.
**Results:** Peripheral insulin resistance was diagnosed in 53% of children with obesity. Children with MS have higher frequency of hereditary predisposition of obesity and diseases, associated with it (diabetes mellitus type 2, coronary heart diseases, arterial hypertension, and atherosclerosis) then healthy children ($p < 0.05$). If there is corresponding hereditary anamnesis, then MS is registered in 90% of cases, and it forms in younger ages. Children without hereditary predisposition have this pathology in 10% of cases. Disorders of perinatal period in patients with MS are founded more often then in group of control ($p < 0.05$): gestosis of pregnancy (49%), noncarrying of pregnancy (37%), operative method of delivery (28.7%), asphyxia in delivery (17%). Breast feeding had 40% of children with MS, in control group - 74%. Bottle feeding with non-adapted milk formulas and undiluted cow milk had 51% of children with MS. These indexes are higher than in control group ($p < 0.01$). Defects of nutrition (early given cereal porridges, overfeeding, and misuse of carbohydrated products) in early postnatal period was established in 47% of patients, that is two-fold than in control group.

## P/FRI/46

## An impaired vascular endothelial function is detectable in obese adolescents

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Obesity is generally accepted as a risk factor for atherosclerosis and in adulthood is combined with endothelial activation. In this study we investigate the degree of endothelial activation in obese adolescents and determine the relationship between the markers of endothelial activation, inflammation, and cardiovascular risk factors.
**Methods:** A total of 99 obese ($14.3 \pm 1.8$ year) and 30 matched nonobese children were studied. Fasting levels of soluble (s) intercellular adhesion molecule-1 (ICAM-1) and E-selectin, as indices of endothelial activation, were assessed in both groups. Moreover: adiponectin, resistin, total, HDL and LDL cholesterol, triglycerides, OGTT with plasma glucose and insulin, HbA1c were determined. Insulin resistance was assessed by the homeostasis model. Blood pressure and anthropometric measurements were obtained.
**Results:** Significantly higher serum concentrations of sICAM-1 and sE-selectin were observed in obese patients. HOMA IR correlated significantly with sICAM-1 and adiponectin. Serum concentrations of soluble adhesion molecules were not significantly influenced by adiponectin and resistin levels, hypertension, hyperglycemia or dyslipidemia.
**Conclusions:** Endothelial dysfunction is present in obese children and is mainly associated with insulin resistance as well as BMI.

P/FRI/47

### Prevalence of impaired glucose tolerance and fasting hyperinsulinemia among obese adolescents

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The prevalence of obesity and type 2 diabetes (T2DM) in adolescents is increasing.

**Objective:** To determine the prevalence of impaired glucose tolerance (IGT) and fasting hyperinsulinemia (FH) in a sample of obese adolescents in Cyprus.

**Methods:** Preliminary data from the first 72 obese adolescents (classified using the IOTF definition) enrolled in a prospective study are presented. Another 22 overweight and 19 normal-weight subjects were included as controls. All adolescents underwent a 2-h oral glucose-tolerance test. Fasting glucose and insulin levels as well as glucose 2 h post-load were determined. Family history for type 2 diabetes was determined. HOMA-IR was calculated as an index of insulin resistance.

**Results:** No subject was diagnosed with T2DM or impaired fasting tolerance (i.e. fasting serum glucose > 100 mg/dl and < 126 mg/dl). Impaired glucose tolerance was detected in only 2 subjects (1.8%, both males), but FH (cutoff of 15 $\mu$IU/ml) was detected in 30.1% of all subjects (n = 34). Eighty eight percent of subjects with FH were obese, but only 34% reported a family history for T2DM. Obese children had significantly higher levels of HOMA-IR compared with normal weight children in age adjusted comparisons (mean HOMA-IR 3.43 [95% CI 2.82–4.05] vs. 1.68 [0.48–2.87], respectively). There was no difference, however, in HOMA-IR levels among children with and without positive family history for T2DM. The OR (95% CI) for FH was 15.4 (1.69–139.0) p = 0.015 in obese subjects compared with normal weight subjects after adjustment for age and tanner stage. On the contrary, family history for T2DM did not predict increased risk for FH.

**Conclusions:** These preliminary data suggest that IGT is rare among obese Greek Cypriot adolescents, but FH appears to be more common. Obesity, but not family history for T2DM, is associated with increased risk for FH.

P/FRI/48

### Antioxidation activity and lipid peroxidation in children with insulin resistance

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Childhood obesity increases the risk of potentially fatal health problems in adulthood, such as type 2 diabetes mellitus, hypertension, cardiovascular disease, sleep apnea. Metabolic disorders in obesity seemed to be connected with disturbances of lipid peroxidation.

**Objective:** To investigate antioxidation activity and lipid peroxidation level in children with obesity and insulin resistance. Patients and methods: 30 obese children with insulin resistance (BMI > 95") 6–17 years old were investigated (12.7 - mean age). Insulin resistance was diagnosed according to HOMA. BMI, WC, Fat Mass (FM% by BIA) were measured. Control group - 20 healthy children with normal BMI. Serum concentrations of malonic dialdehyde (MDA) - the product of lipid peroxidation (LPO) and superoxiddismutase activity (SOD) were estimated.

**Results:** Significant decrease of SOD levels were revealed in obese children with insulin resistance in comparance with controls (1.71 ± 1.36 units/ml and 5.88 ± 1.08 units/ml, respectively, p < 0.001). MDA was slightly increased in obese children. MDA positively correlated with BMI (r = 0.32), insulin (r = 0.39) and HOMA index (r = 0.46); SOD negatively correlated with serum insulin (−0.36). Due to the decrease of antioxidation potential, some patients (14) were treated with complex of vitamins A, E, C and selenium together with diet (after informed consent signed). All measurements were repeated after 3 months of treatment, and also in 16 obese children with diet only (informed consent). Significant elevation of SOD level (1.99 ± 1.02 units/ml, 3.05 ± 1.52, p = 0.035) and decrease of MDA (1.9 ± 1.03 mcmol/L, 1.12 ± 0.65, p = 0.027) parallel to decrease of FM% were revealed after treatment. No significant changes were found in BMI, WC, and HOMA as well as in children with diet only. No changes in FM%, MDA and SOD were registered in diet group.

**Conclusion:** Children with obesity present disorders of LPO and antioxidation activity. Antioxidant complex of vitamins is an effective tool for correction.

## Epidemiology of Diabetes

P/FRI/49

### Association between type 1 diabetes and perinatal factors – Catalonia study

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**Introduction:** The age of onset of type 1 diabetes (DM1) is decreasing progressively. It has lead to the search for causal environmental factors operating very early in life.

**Aims:** To identify perinatal risk factors associated with the development of DM1 and to investigate if the effects of these factors differed between early and late childhood onset disease.

**Methods:** Inclusion criteria: Children under 10 years of age with DM1 diagnosed in Catalonia and born between 1993 and 2003. Data sources: Catalonian registry of incidence of DM1.Variables studied: sex, birth weight, age of onset of DM1, maternal age, type of feed, type of labour, birth order and multiple births. Cases and controls were individually and randomly matched by year of birth from the total number of births in Catalonia, 660 611; ratio1:4. Statistical analyses: Bivariate and multivariate analysis. Odds ratios and 95% confidence intervals.

**Result:** A total of 1530 infants were analysed (306 DM1 cases; 1224 control subjects) by possible perinatal risk factors associated with DM1.

| | | Cases | Control | BIVARIATE ANALYSIS | | | MULTIVARIATE | |
|---|---|---|---|---|---|---|---|---|
| | | N (%) | N (%) | P | OR | IC | OR | IC |
| Sex | Boys | 160 (52,3) | 632 (51,7) | 0,86 | 1,02 | (0,79 ; 1,31) | 0,98 | (0,75 ; 1,26) |
| | Girls | 146 (47,7) | 589 (48,2) | | | | | |
| Birth Weight | Normal birth weight | 340 (78,4) | 1066 (86,9) | 0,00* | 1,00 | | 1,00 | |
| | Small gestat. age SGA | 19 (5,9) | 80 (6,5) | | 1,02 | (0,60 ; 1,73) | 1,12 | (0,65 ; 1,93) |
| | Large gestat. age LGA | 46 (15,7) | 56 (4,6) | | 3,88* | (2,57 ; 5,85) | 3,91* | (2,58 ; 6,93) |
| Maternal age | ≤ 35 years | 276 (91,4) | 1076 (89,7) | 0,39 | 0,82 | (0,52 ; 1,28) | 0,81 | (0,51 ; 1,27) |
| | > 35 years | 26 (8,6) | 123 (10,3) | | | | | |
| Delivery type | Normal labour | 168 (56,6) | 701 (57,3) | 0,45 | 1,10 | (0,85 ; 1,41) | 1,02 | (0,79 ; 1,33) |
| | Difficult labour | 129 (43,4) | 523 (42,7) | | | | | |
| Type of feed | Breast-feeding | 245 (80,1) | 961 (78,5) | 0,55 | 0,90 | (0,66 ; 1,24) | 0,81 | (0,60 ; 1,16) |
| | Artificial | 61 (19,9) | 263 (21,5) | | | | | |

*Statistically significant

[*Perinatal risk factors associated with DM1*]

Data was analysed in age ranges of greater or less than 5 years at diagnosis of DM1.There is association between being LGA and DM1 (p < 0,005). The estimated risk of developing DM1 was more than tripled for children with LGA; OR = 3.88; IC95% (2.57–5.85).

**Conclusions:** Only being born LGA was significantly associated with developing DM1. However, this association was not

influenced by sex nor was there an association between LGA and the age on onset of DM1.

## P/FRI/50

### Common childhood vaccinations and the risk for type 1 diabetes – an ecological study in Germany

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**Objectives:** Childhood vaccinations have been discussed to be associated with an increased risk of type 1 diabetes. Aim was to analyse associations between the incidence of childhood type 1 diabetes and the vaccination coverage in children in an ecological study.

**Methods:** The ecological study is based on aggregated data at the district level of the federal state of North Rhine-Westphalia (NRW). Incidence data of type 1 diabetes in children under 15 years for 1996–2002 were taken from the diabetes register of NRW (completeness of ascertainment 97%). Data on coverage of common vaccinations among 5–6 year-old first graders at the compulsory school entrance examination based on vaccination booklets were obtained for 52 out of 54 districts for 1995–2000 from the Institute of Public Health of NRW and local health authorities. Data were analysed by Poisson regression adjusting for overdispersion and socio-economic indicators (data from official statistics).

**Results:** No significant associations could be detected between vaccination coverage and type 1 diabetes incidence in children below 5 years ($p > 0.2$). Relative risks (RR, (95%-CI)) for type 1 diabetes per 5% increase in vaccination coverage of the different vaccinations varied between 0.74 (0.46–1.18) for tetanus and 1.03 (0.91–1.16) for measles vaccination. Vaccination coverage for rubella (RR: 1.02 (1.00–1.05), $p = 0.035$) and pertussis (RR: 1.02 (1.00–1.04), $p = 0.086$) were positively associated with the diabetes incidence in children under 15 years in simple Poisson regression. However, when adjusting for the proportion of non-German nationals and population income these associations were no longer present.

**Conclusions:** Regional differences in the vaccination coverage in children did not explain the spatial variation of type 1 diabetes incidence. Although ecological bias cannot completely be ruled out, these results do not support the hypothesis that common childhood vaccinations increase the risk for type 1 diabetes.

## P/FRI/51

### National registers; Do they improve care?

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**Objectives:** In 1996, the Danish Register for Childhood Diabetes was initiated. This is the first register where incidence data, clinical data and biological material are collected on a national basis. National registers are difficult to finance since they are the step before research, they collect an enormous amount of data, but research question aren't posed necessarily at initiation. The question is, can the costs associated with running a national register be justified by the corresponding increase in health and derived benefits in quality of care?

**Methods:** The Danish Register for Childhood Diabetes includes patients aged 0–18 years. The yearly collected data include HbA1c. At the age 9, 12, 15 and 18 years all patients are screened for micro-vascular complications in eyes, kidneys and nerves. Ascertainment is estimated using capture-recapture. Central measured HbA1c was included as the response variable in a linear mixed model.

**Results:** The ascertainment in the register is above 99%. The incidence has increased with more than 3% per year from 1996–2005. Since the initiation of the register the mean HbA1c is reduced with more than 10%. In the same period the number of severe glycemic events has not increased. In 2006, five out of the 19 centers had a mean HbA1c of less than 8%. The percentage of children with HbA1c above 9% has fallen from 35% in 2000 to 18% in 2006. Of 1899 children screened, 29 (1.5%) had retinopathy. A number of 1662 children were all-together screened 2345 times for albuminuria and 38 (2.3%) of these were positive.

**Conclusions:** The costs of running this national register in Denmark in the year 2006 were 500.000 dkr. According to the results of the DCCT study, a decrease of 10% in HbA1c may lead to a reduction in retinopathy of 43% and a reduction in microalbuminuria of 25%. Compared to the prevalence of retinopathy and microalbuminuria from previous studies, the improved metabolic control has already led to a decrease in late diabetic complications.

## P/FRI/52

### Incidence of type 1 diabetes, MODY and type 2 diabetes in children aged less than 15 years and clinical characteristics of type 1 diabetes at the time of diagnosis: Data from the Childhood Diabetes Registry in Saxony, Germany

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**Objectives:** International studies have reported increases in incidence of childhood diabetes over the last decades. Aim of the Childhood Diabetes Registry in Saxony was to determine the incidence and clinical and metabolic characteristics of childhood diabetes in a defined population in Germany.

**Methods:** New cases of diabetes in children aged less than 15 years were registered prospectively from 1999 to 2006 in Saxony, Germany. Birth date, birth weight, gender, family history, date of diagnosis, clinical and laboratory parameters were obtained from all children's hospitals. Reported cases were ascertained by public health departments as an independent data source and verified using the capture-recapture method.

**Results:** A total of 603 patients with newly diagnosed diabetes were registered in Saxony, 94.3% of them were classified as having type 1 diabetes, 0.7% had type 2 diabetes and 3.0% had maturity onset diabetes of the young (MODY). Incidence of type 1 diabetes was estimated at 16.1 per 100 000 per year. The completeness of ascertainment calculated applying the capture-recapture method was 93.6%. At the time of diagnosis, 26.4% of children with type 1 diabetes had ketoacidosis, 2% were unconscious and 0.2% had cerebral edema. In autumn significant lower pH at the time of diagnosis was reported ($P < 0.05$).

**Conclusion:** The registry provides important data about epidemiology of diabetes in children in a defined population. Incidence of type 1 diabetes is higher than other incidence rates reported before in Germany. Further longitudinal studies will provide data for public health medicine and quality management in the future.

## P/FRI/53

## Incidence of type 1 diabetes mellitus in children's population in Russian Federation during 2001–2005

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**Introduction:** The incidence of type 1 diabetes mellitus (T1DM) annually increases in children's population in Russian Federation (RF). The territory of RF is large and subdivided into seven Federal districts (FD), located in various geographically defined areas: Northwest, Central, Volga, Southern, Urals, Siberia and Far East.
**Aim:** To estimate the incidence of DM1 among the children's population of RF during 2001–2004 years.
**Methods:** The information was received from national Register of DM and annual statistical reports from endocrinologists. The incidence was calculated on 100,000, the children's population. The confidential interval was 95%. The age standardized incidence was obtained using the direct method with a standard population consisting of equal members of children in each of three subgroups (0–4, 5–9, 10–14 years of age).
**Results:** On 01.01.2006, 16,097 children with T1DM were registered, 2533 of them were newly diagnosed. During the year 2001–2005, an average incidence of T1DM among children in RF was 10.1/100,000 (95% CI: 8.7–11.0), age standardized incidence was 10.3/100,000 (95% CI: 8.4–11.3). An incidence has been increased with age and was the greatest in 10–14 years age group (13.5/100,000). Significant distinctions in incidence were marked between FD. The highest incidence was constantly registered in northwest FD. It has reached 15.1/100,000 in the year 2004. Incidence rates were considerably below in Siberia and Far East FD: 7.2/100,000 and 7.7/100,000 accordingly. The annual incidence gain in Far East district was 99.5% in the year 2005. An incidence was similar to an average level in RF in Central, Volga and Urals FD. In South FD an incidence was in the middle between incidence levels in Central and Siberia FD: 8.7/100,000.
**Conclusion:** In the year 2001–2005, the average and standardized incidence of T1DM in children's population in RF were similar to most European countries. The decrease of incidence was observed in a direction from northwest on a southeast of RF.

## P/FRI/54

## Type 1 diabetes (T1DM) in children and adolescents of immigrated families in a region of north Italy

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**Objectives:** The aim of this study was to investigate some variables in diabetic children of immigrated families compared with Italian diabetic children.
**Methods:** We recruited 73 diabetic children from immigrant families resident in Emilia-Romagna, one of 20 regions of Italy. The patients came from families where just one or both parents originated from countries outside Western Europe, North America or Australia (49% came from North Africa, 25% from East-Europe, 14% from Asia, the remainder from Sub-Saharan Africa, South America and the Middle East). Data were collected by questionnaire sent to all Pediatric Diabetes units of Emilia-Romagna (10 centers) in December 2006. The variables investigated were: gender, current age, place of birth, parents' country of origin, age at diagnosis, HbA1c (the last value registered). These variables were compared with those of 707 Italian diabetic children living in the same region. Characteristics of ethnic groups were described using proportions and means with range, and analyzed using $\chi 2$ test and *t*-test two tails. A *P*-value, $< 0.01$ was accepted as statistically significant. Analyses were performed using SPSS.
**Results:**

| | Italian (91%) | Immigrant (9%) | p |
|---|---|---|---|
| Gender: M (%) | 356 (50.6%) | 34 (46.6%) | n.s. |
| Current mean age (range) | 13.3 (1.5–23) | 13.4 (6.15–23) | n.s. |
| Mean age at diagnosis (range) | 7.4 (0.8–17) | 7.8 (1–15.5): | n.s. |
| | | A) Born outside Italy (52%) 9.6 | $P < 0.000$ |
| | | B)Born in Italy (48%) 5.7 | $P < 0.003$ |
| | | | A vs. B $P < 0.000$ |
| Mean HbA1C % (range) | 8.2 (4.7–14.3) | 8.8 (4.3–15.9) | $P < 0.009$ |

**Conclusions:** Our results confirm that immigrants' children have significantly poorer metabolic control than Italian patients. Furthermore, a younger age at diagnosis of T1DM in immigrant children born in Italy compared with those born in country of origin, and with Italian patients, suggests the existence of some environmental determinants acquired with a more westernized lifestyle.

## P/FRI/55

## Parental country of birth is a major determinant of childhood type 1 diabetes in Sweden

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**Objectives:** To test the hypothesis that, the risk of childhood diabetes type 1 increase with emigration from a low incidence region to a high incidence region.
**Methods:** Register study of a national cohort of 7,83,547 children born from 1987 to 1993, who remained in Sweden in 2002, including 3225 children with childhood type 1 diabetes identified in hospital discharge data. Logistic regression analysis was used to test the hypothesis.
**Results:** Offspring of two parents born in very low (Asia excluding middle east and Latin America) and low (southern and eastern Europe and the middle East) incidence regions had the lowest adjusted odds ratios (OR:s) of childhood type 1 diabetes; 0.21 (0.11–0.41) and 0.37 (0.29–0.48) respectively compared to the Swedish majority population. When one parent was born in a low incidence country and one parent was Swedish born the adjusted OR:s increased but remained lower than in the majority population of Sweden.

**Conclusions:** Parental country of birth is an important determinant of childhood type 1 diabetes in Sweden. Heritable factors seem most likely to explain this pattern.

## P/FRI/56

## The prevalence of diabetes and impaired fasting glucose in Beijing school children

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**Objective:** To learn the prevalence of diabetes mellitus and impaired fasting glucose in schoolchildren, describe the age, gender and district distribution characteristics of Beijing schoolchildren.

**Methods:** A cross-sectional screening program was carried out in 19,593 schoolchildren in 7 areas of Beijing from March to October in 2004, the screening test was fasting capillary blood glucose (FCBG). According to the WHO diagnostic criteria, diabetes mellitus (DM) was assumed if FCBG $\geq$ 6.1 mmol/l, impaired fasting glucose (IFG) was assumed if 5.6 mmol/l $\leq$ FCBG $<$ 6.1 mmol/l.

**Results:** The total aggregate age-adjusted prevalence of DM and IFG was 5.7‰ and 13.5‰ respectively. The prevalence of DM and IFG in male was significantly higher than that of in female (7.7‰ vs. 3.6‰ and 26.8‰ vs. 11.3‰). Among seven districts, east district had the highest prevalence of DM and IFG, 8.9‰ and 27.4‰ (companied with high prevalence of obesity, 28.68%), Ping-Gu district had the lowest one, 2.0‰ and 7.5‰ respectively. The DM prevalence among districts ranged from 2.0‰ to 8.9‰, the IFG prevalence among districts ranged from 7.5‰ to 27.4‰. The prevalence of DM increased with age, the highest prevalence of IFG was in the 10–14 age group. Among boys, the highest prevalence of DM and IFG was in the 15–18 and 10–14 age group respectively. The highest prevalence of both DM and IFG among girls was in the age group 10–14.

**Conclusions:** The high prevalence of DM and IFG in Beijing existed, and it had significant distribution discrimination of age, gender and district. Developed district and male had a higher prevalence and companied with higher obesity prevalence. Age might be the risk factor of DM for boys; the puberty development was the risk factor for girls.

## P/FRI/57

## Mortality in patients with childhood-onset type 1 diabetes in Norway: a population-based study

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**Objectives:** Norway has one of the highest incidences of childhood-onset type 1 diabetes (T1D) in the world with 28/100,000 person-years during 1999–2003. The aims were to examine the mortality rates and excess mortality in childhood-onset T1D, in a population based cohort, in relation to gender and age at onset of diabetes.

**Methods:** All individuals in Norway with the onset of T1D from 1989 to 2003 and age at onset $<$ 15 years, reported to the Norwegian Childhood Diabetes Registry (3137 subjects, 1688 males and 1449 females) were included. Deaths were recorded from diabetes onset until 31st December 2005, representing 27,695 person-years of risk. Mean age at diagnosis was 8.6 years (SD 3.7). By end of follow-up mean age was 17.5 years (range 1.8–31.7) and mean diabetes duration 8.8 years (0.03–17.0). The subjects' status as alive, deceased or emigrated was determined by matching the unique personal identification number assigned to each resident of Norway to the National Death Registry. Survival curves were calculated by using the Kaplan–Meier method.

**Results:** During follow-up, 23 individuals emigrated and 24 individuals (0.8%) died: 15/1688 males (0.9%) and 9/1449 females (0.6%). The overall mortality rate was 0.9 per 1000 person-years. Mean age at death was 17.9 years (range 1.8–28.4). The overall standardized mortality ratio (SMR) was 2.9 (95% CI 1.8–4.2) and was similar between males and females, 3.0 and 2.7 respectively. The estimated cumulative survival according to diabetes duration was 99.3% at 10 years. The mortality rate was 1.4 times higher in males than in females (1.0/1000 vs. 0.7/1000; RR 0.71, 95% 0.31–1.61). Subjects with age at diabetes onset 10–14 years had increased mortality rate compare to onset $<$ 10 years of age (RR 1.98, 95% 0.88–4.45).

**Conclusions:** Mortality was markedly higher among subjects with diabetes compared to the non-diabetic population, similar for males and females. The overall mortality in T1D continues to be increased.

## P/FRI/58

## Frequency of DKA in children diagnosed with type 1 diabetes in Montenegro between 1997 and 2006

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**Objective:** To study the frequency of diabetic ketoacidosis (DKA) over a 10-year period among children with newly diagnosed and established diabetes in Montenegro.

**Methods:** The data from a period of 1997 to 2006 were obtained from hospital records. Over last 20 years all diabetic children have been followed in the same institution. The study criteria were pH $<$ 7.3 and for bicarbonate $<$ 15 mmol/L.

**Results:** A total of 184 new cases of type 1 diabetes were diagnosed among the children ($<$ 14 years) during 1997–2006. The incidence for that period was 11.8/100,000. At onset of diabetes, any degree of DKA (pH $<$ 7.3) was present in 25% (19 males and 27 females) of subjects, while severe DKA (pH $<$ 7.1) was present in 5.7%. The 5–9 year old children suffered more frequently ($P < 0.001$) from DKA at the time of diagnosis. In last five years (2001–2006), the percentage of patients presenting with DKA was 18%. During the subsequent course of diabetes, the frequency of acute hospital admission due DKA was 3.5 events/100 patient/year. DKA events in established patients affected more often girls than boys ($P < 0.001$), especially adolescent girls. Most of the cases of DKA happen in the first five years after the moment of establishing the diagnosis (73%). HbA1c was 11.3 $\pm$ 1.8% in newly diagnosed patients, and 12.4 $\pm$ 1.57 % in established diabetic children. All children recovered completely and no deaths were recorded.

**Conclusion:** The proportion of DKA in children with newly diagnosed diabetes mellitus is decreased which reflects the awareness of diabetes among pediatricians/communities. DKA during the course of diabetes was less frequent compared to reports in the literature from other parts of the word. Most cases of DKA occurred in adolescent girls.

## Immunology and Genetics of Diabetes

P/FRI/59

### Disturbance of immune regulatory mechanisms in high risk relatives of type 1 diabetic patients

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**Objectives:** The basal *in vitro* production of regulatory cytokines (IL-10 and TGF-beta1) by peripheral blood mononuclear cells vs. the production after stimulation with diabetes-associated β-cell autoantigens was analyzed. Further, the kinetics of regulatory T lymphocytes (Tregs; identified by CD127- and FoxP3+) after specific stimulation were evaluated.

**Methods:** Cytokines were detected by protein microarray, ELISA and ELISPOT. Cell activation was measured by surface expression of IFN-gamma on activated CD4+ T cells by using flow cytometry. Stimulation was performed with the synthetic peptides (GAD-65, IA-2 and pro-insulin derived peptides). The study cohort for analysis of cytokines: 60 recent onset T1D patients, 70 of their first- degree relatives (10/70 = pre-diabetes group i.e. at least one autoantibody positive) and 60 age-, sex- and HLA-risk matched healthy controls. The cohort for Tregs kinetics study: 11 high-risk relatives of T1D patients (according to HLA-linked T1D genetic risk, autoantibody negative) and 14 controls.

**Results:** Relatives had lower basal IL-10 secretion compared to controls ($P = 0.006$). Pre-diabetes relatives had lower basal as well as stimulated production of TGF-beta1 compared to the controls (basal; $P = 0.003$ and stim.; $P < 0.001$) as well as compared to recent-onset T1D patients (stim.; $P = 0.002$). An inverse correlation of basal IL-10 and TGF-beta1 was observed in pre-diabetes relatives. Approximately at manifestation of T1D an increased production of Th3 cytokines was observed. High-risk relatives of T1D patients have significantly lower pre- and post-stimulatory numbers of Tregs than healthy controls ($P < 0.05$). The autoantigen activation of Tregs was significantly higher in high-risk relatives of T1D patients than in controls ($P < 0.02$).

**Conclusion:** Shortly prior clinical manifestation of T1D the immune regulatory mechanisms are probably intensively activated but does not protect from destructive insulitis. Supported by IGA MZCR NR 9355-3.

P/FRI/60

### Circulating nucleic acids as inducers of T cell hyperactivity in juvenile diabetes

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Type 1 diabetes is associated with T-cell hyperactivity. Excess of circulating nucleotides activate TLRs, redirecting the immune response from a Th2 to a Th1 phenotype, and Th1 cytokine production and can be mitogenic *in vitro*. In our previous study a significant decrease of extra-cellular nuclease activity in IDDM patients was documented, which lead to increased circulating nucleic acids and different-sized oligo-nucleotides. The aim of the present study was to detect the concentration of circulating RNA in juvenile IDDM patients, to characterize their spectro-photometric properties compared to control and standard samples and to examine their T-cell proliferative potential. Examined groups were: juvenile diabetic children (25) and control children (15). Circulating RNA was measured by using commercial RNA isolation reagent set (TRI Reagent BD-T3809). Thymocyte proliferating nuclear cell antigen (PCNA) expression was measured by flow cytometric analysis. Rat thymocites were placed in CM/10% FCS, cultured in 96-well flat-bottom plates, containing a 100 μl of cell suspension (1×106 cells) in each well, allocated into groups treated with: optimal (5 μg/ml) concentration of ConA as standard, RNA (5 μg/ml), polyC (5 μg/ml), PolyIC (5 μg/ml), CpG (5 μg/ml), RNA purified from plasma of juvenile diabetics and RNA purified from plasma control samples. Circulating RNA (mg/L) in juvenile diabetics was 175.3 ± 17.8 vs. control 29.6 ± 5.5 ($P < 0.001$). It expressed maximal absorbance peak on spectrophotometric scanning similar to polyC. The percent of PCNA expression after incubation with diabetic samples was 30.38 ± 7.97 vs. control 11.47 ± 6.99 ($P < 0.001$), significantly lower compared to ConA (76.5%), but significantly higher compared to any synthetic polynucleotide (RNA-11.8%; PolyA-10.1%; polyA:U-3.6%; PolyC-19.5%; CpG-5.4%). In conclusion, it was documented at first time that circulating nucleic acids may be responsible for T-cell hyperactivity in juvenile diabetes.

P/FRI/61

### Coxsackie B virus acts as a triggering environmental factor in the pathogenesis of type 1 diabetes mellitus

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Aetiopathogenesis of type 1 diabetes mellitus (T1DM) includes genetic, immunologic and environmental factors. Among the latter, conflicting results on the role of Enteroviruses, like Coxsackie B4 have been reported. Our aim was to establish whether Coxsackie B4 is involved in T1DM pathogenesis. We used pooled IgG immunoglobulins derived from 58 patients (35 male and 23 female) aged 0.8–18.7 years with newly-diagnosed T1DM to screen a random peptide library to identify autoantigen peptides involved in the development of the autoimmune process against β-cells. As controls 50 blood donors were enrolled. We identified an immunodominant peptide showing similarities with human autoantigens such as phogrin (ICAAR) and 6-phosphofructokinase (6PFK), expressed by β-cells; indeed such 12 amino acid peptide was recognized by 43/58(74%) of patientś sera but by none of the controls'sera. The peptide sequence shows similarity also with viral protein1-VP1, a protein expressed on Coxsackie virus capsid. IgG antibodies against the peptide were affinity purified from patientś sera and recognized autoantigens and the viral protein VP1. We suggest that in genetically pre-disposed individuals, Coxsackie B virus infection may induce an antiviral response able to trigger destruction of β-cells through a molecular mimicry mechanism between VP1 and human autoantigens, leading to the onset of type 1 diabetes mellitus.

P/FRI/62

## No association between routinely recorded infections in early life and subsequent risk of childhood onset type 1 diabetes: a matched case-control study using the UK General Practice Research Database

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**Objectives:** To determine whether children with infections in early life (recorded routinely in General Practice) have a reduced risk of type 1 diabetes, as would be expected under the hygiene hypothesis.
**Methods:** Children with type 1 diabetes and up to 20 matched (on year of birth, sex and region) controls were selected from a cohort of children born in the UK at General Practice Research Database practices. For each child, the frequency of GP consultations for infections and prescriptions for antibiotics in the first year of life were determined. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using conditional logistic regression.
**Results:** The main analysis included 367 cases and 4,579 matched controls. There was no evidence of any reduction in the subsequent risk of type 1 diabetes in children with at least one infection in the first year of life (OR = 1.03, 95% CI 0.79, 1.34) or in children prescribed antibiotics in the first year of life (OR = 1.03, 95% CI 0.82, 1.29). Further analyses also revealed little evidence of a difference in subsequent risk of type 1 diabetes after different types of infection in the first year of life (including gastrointestinal, conjunctivitis, otitis media and upper and lower respiratory tract).
**Conclusions:** This study provides no evidence of an association between infections in early life and subsequent risk of childhood onset type 1 diabetes and therefore does not support the hygiene hypothesis. To our knowledge, only two previous studies have investigated type 1 diabetes and routinely recorded infections in the first year of life and both had comparatively small numbers (58 and 108 cases). Other studies of type 1 diabetes and infections in early life have ascertained infection from parental recall which is open to disease dependent recall bias and is an unreliable source of infection data.

P/FRI/63

## Serum cytokines and chemokines in an IgA deficient child between birth and development of celiac disease and type 1 diabetes

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Because the genetic backgrounds of celiac disease (CD) and type 1 diabetes (T1D) partly overlap it is possible that similarities exist in the pathogenesis of CD and T1D. We explored immunological processes occurring during development of CD hoping that these might help understanding the immunopathogenesis of T1D. Cytokines and chemokines have been implicated in the pathogenesis of CD and T1D but changes in serum cytokine (CK) and chemokine (ChK) values between early infancy and development of CD and T1D have not been studied in children with HLA-conferred genetic risk for the two diseases. In type 1 Diabetes Prediction and Prevention Study (DIPP) a child with HLA-conferred genetic T1D and CD risk and IgA-deficiency was followed-up at 3–6 months intervals from birth. He seroconverted to GADA and anti-gliadin antibody positivity at the age of 16 months and to ICA positivity at the age of 20 months and developed transglutaminase antibodies (TGA) and CD at 29 months and T1D at the age of 79 months (6.5 years). 21 CKs and ChKs were measured in serum samples collected during the follow-up visits using Luminex instrument and xMAP technology. Serum CK and ChK values increased clearly before T1D- and CD-associated auto-antibodies emerged. IL-1a and IL-4 increased by age 9 months and G-CSF by age 12 months, and both peaked first at the age of 24 months. At the 24th month, most CKs and ChKs showed a remarkable increase and the values stayed high until the age of 75 months when the last sample before T1D development was drawn. In conclusion, this IgA deficient child with HLA-conferred genetic risk for CD and T1D showed marked increases in serum concentrations of most studied CKs and ChKs before or at the time of seroconversion to TGA, GADA and ICA positivity. Values remained excessively elevated at least until development of overt T1D at the age of 79 months.

| pg/ml | 3 months | 9 months | 12 months | 24 months | 34 months | 62 months | 75 months |
|---|---|---|---|---|---|---|---|
| IL-1a | 8.8 | 336.5 | 940 | 5745 | 1395 | 2749 | 8354 |
| IL-4 | < 3.2 | 221.9 | 661.9 | > 10000 | 9124 | > 10000 | > 10000 |
| G-CSF | 28.2 | 43.7 | 288.5 | > 10000 | 7604 | > 10000 | 6421 |

P/FRI/64

## Diabetes and immunity: unusual presentation of IPEX?

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IPEX syndrome (immunodysregulation, polyendocrinopathy, and enteropathy, X-linked syndrome) is a rare disorder, usually fatal in early childhood. The molecular defect is the result of mutation in the FoxP3 gene. When scurfin, the FoxP3 gene product, is absent or inactive, T cells proliferate, resulting in early-onset autoimmune disease. We report the story of a patient with an unusual presentation of IPEX, only diagnosed at the age of 19. JD, a Caucasian 19-year old boy, became insulin-dependent diabetic at the age of 22 months. HLA-DQ genotype was not at increased risk for type 1 diabetes and there were no increased levels of ICA and IAA. At 8.5 years, a severe exfoliating hemorrhagic gastritis was diagnosed. The search for etiopathogeny and extended screening for auto-antibodies, including parietal cell auto-antibodies, or allergic markers, were negative. Development of an intestinal metaplasia in the antrum and an esophageal-like mucosa in the upper part of the stomach led to a total gastrectomy at 14.8 years. He had also failure to thrive, delayed puberty but no diabetic complications. Moreover, irregularly he displayed severe hypogammaglobulinemia that is treated monthly with IV gamma-globulin administrations. In view of the recent description of the IPEX syndrome, the association of symptoms led to the suggestion of a possible defect of FoxP3 expressing regulatory T cells in this young boy. Analysis by flow cytometry of the circulating CD4+ T cells revealed a nearly total absence of CD4+ CD25high Foxp3+ T cells, a result that was highly suggestive of IPEX. Molecular analysis of the FoxP3 gene (L Perroni, Human Genetic Laboratory, Genoa) confirmed the diagnosis by identifying a mutation in the C-terminal portion of the gene. In conclusion, this unusual presentation of IPEX with delayed diagnosis, absence of early fatal issue, and with hypogammaglobulinemia, underlines the need for further studies to understand the pathophysiology of this disease.

P/FRI/65

## The non-inherited maternal HLA haplotype affects the risk for type 1 diabetes

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**Objectives:** The aim was to test the hypothesis that the non-inherited maternal HLA haplotype affects the risk of developing type 1 diabetes.
**Methods:** A total of 563 children with type 1 diabetes, and 286 non-diabetic control children from Sweden were genotyped for DRB1, DQA1 and DQB1 alleles. The frequency of positively (DR4-DQA1*0301-B1*0302 and DR3-DQA1*0501-B1*0201), negatively (DR15-DQ A1*0102-B1*0602) and neutrally (all other) associated HLA haplotypes were compared between non-inherited maternal haplotypes (NIMA) and non-inherited paternal haplotypes (NIPA). All comparisons were carried out between HLA matched patients and controls.
**Results:** Both DR4/X ($P < 0.00003$) and DR3/X ($P < 0.0009$) positive healthy individuals more often had type 1 diabetes positively associated NIMA compared to DR4/X and DR3/X patients, respectively. No such difference was observed for NIPA. High risk NIMA was increased compared to NIPA among healthy DR3/X and DR4/X children ($P < 0.05$). There was no difference in frequency of positively associated haplotypes between patient NIMA and NIPA.
**Conclusion:** The NIMA but not the NIPA is affecting the risk for type 1 diabetes, suggesting that not only the inherited but also the non-inherited HLA haplotype of the mother may influence the risk for the disease.

P/FRI/66

## The evaluation of transmission disequilibrium of parental susceptibility genes to patients with childhood-onset type 1 diabetes mellitus (T1DM)

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**Background:** Both genetic and environmental factors are needed for the development of T1DM. Two major susceptibility loci have been identified for T1DM, IDDM1 in the MHC class II HLA region and IDDM2 in the insulin genes (INS) region. In Japanese, HLA haplotypes that influence the risk of adult-onset T1DM have been identified, and it was reported that class I alleles (variable number of tandem repeats (VNTR); approx.25 to 38 repeats) in the insulin genes were significantly increased in T1DM.
**Objectives:** To identify susceptibility genes for childhood-onset T1DM and to investigate the transmission disequilibrium of the disease susceptibility genes from parents to type 1 diabetic children and their unaffected siblings.
**Methods:** In 38 Japanese childhood-onset type 1 diabetic patients (m/f 17/21, mean age at onset 6.56 ± 3.80 y/o), their parents, their 27 unaffected siblings and 97 healthy controls, the penetration rates and the transmission disequilibrium of the disease susceptibility genes were analyzed by case-control study. HLA-DRB1, -DQA1, -DQB1 alleles were determined by the PCR-sequencing-based typing method. INS VNTR was determined by ABI GeneScan. A parent-of-origin effects on the transmission of these genes were analyzed by the transmission disequilibrium test.
**Results:** The penetration rates of HLA DQB1*0901-DQA1*0301-DQB1*0303 haplotype and class I alleles in the insulin genes in type 1 diabetic patients were higher than that of control subjects (Pc = 0.0354, 0.0509 respectively). Furthermore paternally transmitted susceptibility genes in patients and their unaffected siblings showed higher transmission disequilibrium than that of maternally transmitted the same genes. In contrast, maternally transmitted resistance genes to T1DM were increased in their unaffected siblings.
**Conclusion:** Our results suggest that paternally transmitted HLA haplotypes and class I alleles in INS VNTR are the disease susceptibility genes in childhood-onset T1DM.

P/FRI/67

## Association of interleucine 12 P40 (Il-12 P40) polymorphisms with asthma and diabetes mellitus type 1 (T1DM)

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**Objectives:** The balance of Th1 and Th2 cytokines during antigen presentation and initiation of the T cell response has been shown to be critically important in determining the downstream effects of the antigen presentation process. IL-12 p40 drives the differentiation of T-lymphocytes into the Th1 subset, characterized by production of cytokines leading to autoimmunity and may therefore be important in T1D susceptibility. Genetic polymorphisms in the IL-12 p40 gene could affect function and lead to polarization of the cytokine response toward the Th2 phenotype, which has been shown to dominate the response profile in patients with atopic asthma. The aim of our study was to assess the IL-12 p40 polymorphisms in a group of 100 children with atopic asthma, in 100 patients with T1DM as well as in a number of 71 controls.
**Methods:** The detection of the IL-12 p40 polymorphisms was carried out by using PCR-RFLP method.
**Results:** Patients with asthma carried the 1188 AA polymorphism in a significantly higher frequency (61% vs. 45%, OR: 1.9, $P = 0.024$) and the 1188 AC in a significantly lower frequency compared to patients with T1DM (34% vs. 48%, OR: 0.6, $P = 0.045$). The 1188 AA polymorphism was found more frequently in patients with asthma compared to controls, however, the difference was marginally significant (OR: 1.8, $P = 0.059$). The frequency of the 1188 AC polymorphism did not differ in patients with T1DM compared to controls.
**Conclusions:** The results of our study indicate that the IL-12 p40 polymorphisms might be implicated in the pathogenesis of asthma and T1DM and may contribute to an inverse association of the two diseases in individual level.

P/FRI/68

## Association of alleles at polymorphic sites in the Osteopontin encoding gene in young type 1 diabetic patients

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In the complex interplay of genes related to both the immune response and the autoimmune process in pathogenesis of type 1

diabetes (T1D), several candidates can be envisaged as susceptibility genes. In this context, we have studied polymorphisms in the Osteopontin (OPN) encoding gene by comparison of genotype, allele and haplotype frequencies between T1D cases and unaffected controls and immunological characteristics in T1D cases.We evaluated 238 T1D patients (130 male and 108 female), aged 0.8–20.4 years, and 137 unaffected adult control individuals (68 males and 69 females, mean age 42 years). All patients and controls were genotyped for three OPN intragenic variants: –156 (G/GG) and –66 (T/G) in the promoter region and a biallelic ins/del variant (TG/TGTG) at +245 in the first intron of the gene. The results of the case/control association study indicate that the G allele at the –66 SNP had significantly higher frequency in controls than T1D cases ($P = 0.04$). Accordingly, the B haplotype combination, that includes the –66 G allele, showed significantly higher frequency in controls than cases ($P = 0.026$).Considering patients with 1 b-cell autoantibody vs. those having two or more auto-antibodies, the T allele at the –66 SNP showed a relative increase of genotypic frequency in T1D cases with high number of auto-antibodies. This was also the case in patients with two or more b-cell auto-antibodies who were carriers of 4 HLA-DQ risk heterodimers. These data suggest that OPN plays a role in the autoimmune process independently on the HLA haplotype.

## Miscellaneous II

### P/FRI/69

### Mean blood glucose and biological variation have greater influence on HbA1c levels than glucose instability

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**Objective:** To assess, the relative influence of mean blood glucose (MBG), glucose instability (GI) and biological variation of glycohemoglobin (BVG) on HbA1c.
**Methods:** The study included 378 young type 1 diabetic patients with diabetes duration > 1 year. There were 1409 visits with simultaneous HbA1c determinations and self-monitoring of BG meter downloads. GI was quantified by measuring the standard deviation (SD) of the recorded BG values. A statistical model was developed to predict HbA1c from MBG. Hemoglobin glycation index (HGI) was calculated (HGI = observed HbA1c - predicted HbA1c) for each visit to assess BVG based on the directional deviation of observed HbA1c from that predicted by MBG in the model. Afterwards, the population was divided by thirds into high-, moderate-, and low-HGI groups, i.e. high-, moderate-, and low-glycators, reflecting BVG.
**Results:** A total of 246,000 pre-prandial BG measurements were analyzed, with a mean of 177 per visit. Grand MBG ± SD was 171 ± 40 mg/dl. Predicted HbA1c was calculated from the equation: $3.8399 + 0.0242 \times$ MBG ($r = 0.66$; $P < 0.0001$). A MBG change of 40 mg/dl corresponded to 1% change in HbA1c, within the range 6–12%. Multiple regression analysis showed no significant relationship between SD and HbA1c, after adjustment for MBG. MBG was 10 times more important than SD to predict HbA1c. MBG was not statistically different between the three subgroups of glycators, but HbA1c was significantly different. Multiple linear regression was used to predict HbA1c from MBG, SD and BVG (measured by HGI), adjusted for age, duration, gender and ethnic origin. BVG and MBG had large influences on HbA1c, the impact of BVG being 84% of the impact of MBG. On the other hand, GI had only 17% of the impact of MBG.
**Conclusion:** The effect of BVG on HbA1c is independent and much greater that the influence attributable to GI. Hemoglobin glycation phenotype, responsible for BVG, may be important for the clinical assessment of diabetic patients.

### P/FRI/70

### High glycated hemoglobin levels influence injection pain in diabetic children and adolescents

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**Objective:** The aim of the study was to investigate pain when injecting insulin with two lengths of needles usually used.
**Methods:** A total of fifty children and adolescents, aged 7.5–18 years, with diabetes duration of 1–12 years, were included. Two needles were evaluated: B-D MicroFine + 31G/12.7 mm and B-D MicroFine + 29G/8 mm. Arm injection was given in a 45°angle with a lifted two-finger skin fold, scoring pain on a 10 cm visual analogue scale (VAS).
**Results:** With the short needle, pain was felt in 40% of patients, but in 68% of patients when using long needles. The median VAS score were respectively 0.9 and 2.1 cm ($P = 0.0014$). In these 2 subgroups of patients, multiple and stepwise regression analyses showed a significant relationship with glycated hemoglobin (HbA1c) ($P = 0.05$ and $F = 9.2$; $P = 0.02$ and $F = 10.1$). In 20 children experiencing pain with the short needle, there was an inverse relationship with skin fold ($P = 0.05$; $F = 23.4$), whereas in the 37 patients having pain with the long needle, pain was inversely related to age ($P = 0.01$; $F = 4.8$).
**Conclusion:** A big difference in injection pain exists between the 2 needles, and needles of 8 mm should be preferred. More surprising, in patients experiencing pain with needles of 8 or 12.7 mm, higher the HbA1c higher the pain, maybe because higher levels of HbA1c are associated with more worries, more anxiety and poorer health perception as demonstrated in other studies (1,2).
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### P/FRI/71

### Human insulin allergy of immediate type and insulin-induced vasculitis in a patient with diabetes mellitus type 1

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**Rationale:** With human recombinant (r) DNA insulin, allergy, resistance to insulin, and other forms of immune-mediated reactions to human insulin are rare. Insulin-induced vasculitis, after an uneventful period following de-sensitization for IgE-mediated reaction to human rDNA insulin, was developed a patient.
**Methods:** After 3-year duration of treatment with human rDNA insulin, a 7-year old girl, had IgE-mediated reactions, such as urticaria, cough, and eventually anaphylaxis to insulin. Successful de-sensitization was carried out and for 8 months she had no problem with insulin. At some point, she started having complains of headache and abdominal pain, while upon every insulin injection

and at the injection site an erythematous, non-urticarial, indurated, 2–4 mm × 3–4 mm, rash was present for 48 or more hours. In one occasion, the same lesion developed on her right arm, at a site of previous injection, for 5 days, giving the clinical impression of 'granuloma'. A thorough work-up was initiated.

**Results:** Prick skin tests: initially positive and negative, post-desensitization, to insulin preps (of all sources); negative to Latex, food, and aeroallergens. Within normal limits: all routine blood work, Immunoglobulins and subclasses, except for total IgE (elevated during IgE-mediated reactions, dropped to normal levels post-desensitization), RAST to aeroallergens, foods, latex, insulins), tryptase, complement component levels, autoimmunity related antibodies and against the most common viral infections, *Helicobacter pylori*; but, positive IAA and anti-GAD antibodies. C-peptide: non-detectable. Interestingly, circulating immuno-complexes, were elevated above the normal limits before de-sensitization, very low over the uneventful period, and resurged after the appearance of the non-urticarial rash. Negative: CNS and abdomen imaging studies. Skin lesion histology revealed insulin-induced vasculitis. After a 3-month methylprednisolone treatment, the rash disappeared.

## P/FRI/72

## The role of ghrelin in the regulation of metabolism in children with IDDM- the influence of the kind of therapy

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Ghrelin not only stimulates release of growth hormone but also administration stimulates food intake and carbohydrate and fat utilization. The aim of the study was the evaluation of total ghrelin in children with IDDM and estimates the influence of the kind of therapy.

**Subjects and methods:** A total of 67 patients and 15 age-matched, healthy children were included into the study. All children were pre-pubertal (T < 2). Patients were divided into groups according to the kind of therapy: 22 were treated with conventional insulin therapy (CIT), 21 received multiple insulin injections (MIT) and 24 were treated with continuous subcutaneous insulin infusion, All groups were similar as to: age, sex, weight, height, BMI and metabolic control (HbA1c). Children were suffering from IDDM from more then 2 years and there were no change in the kind of therapy during last year. Blood samples were obtained fasten, morning in normoglycemia after the night without episodes of hypo or hyperglycemia. All analysis was made by ELISA commercial kits.

**Results:** Total ghrelin levels were lower in diabetic children (the lowest in pumps group, the highest in CIT group).

**Conclusions:** Total ghrelin levels were lower in IDDM children and depend in a statistically significant way on the kind of therapy but not on the quantity of insulin (it's a new clinical observation).

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## P/FRI/73

## Blood glucose profile in Beijing children and adolescents

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**Objectives:** To learn the BG profile of Beijing children and adolescents.

**Methods:** The survey population was selected as a stratified cluster sample from 8 urban and 10 rural areas in Beijing. Fasting capillary blood glucose (FCBG) were performed in 19,593 children and adolescents aged 6 to 18 years in 4 urban and 3 rural areas using hemosaccharometer model II (Roche Diagnostic (Shanghai) Ltd).

**Results:** There were 19,112(97.5%) individuals with complete records were studied, the mean age was 12.6 years (ranged from 6–18.9 years). 9514 (49.8%) were boys, 9598 (50.2%) were girls, 9792 (51.2%) from urban areas and 9320 (48.8%) from rural areas. The FCBG of boys was higher than that of girls (4.7 ± 0.5 vs. 4.5 ± 0.5), $u = 28.0$, $P < 0.01$), the trend of FCBG was similar between boys and girls, both of them had two peaks, during the age from 6 to 11 years, FCBG of both boys and girls increased by age growing, both of them arrived the first peak at the age of 11 years, at 13 years old, there was a obviously drop in FCBG level. From 14 years old on, it could be seen a rise of FCBG in both boys and girls, and the second peak of FCBG was arrived at 15 and 16 years old in girls and boys respectively, the lower points of both boys and girls were at the age of 6, 13 and 18 years. The FCBG of urban children was higher than that of rural children (4.7 ± 0.5 vs. 4.6 ± 0.5, $u = 13.8$, $P < 0.01$). The level of FCBG in overweight and obese children was higher than that of control children. Linear correlation analysis indicated that there was no correlation between FCBG and age ($r = -0.01$, $P > 0.05$), weak positive correlation between FCBG and height, weight, BMI, WC ($r = 0.07$, 0.09, 0.08 and 0.10 respectively, $P < 0.01$).

**Conclusions:** The blood glucose was correlated with age, gender, obesity and district.

## P/FRI/74

## Studies on the age-relation of insulin requirement within the first 10 days after manifestation of type 1 diabetes mellitus

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**Objective:** Does the analysis of prospectively collected data from the DPV data bank provide any predictors for initial insulin therapy in type 1 diabetes?

**Method:** We evaluated data from the DPV data bank (as of October 2006) over the first 10 days after manifestation of type 1 diabetes in 8106 children and adolescents from 185 children's hospitals in Germany and Austria. By multiple correlations we investigated whether there was significant correlation between the parameters age, sex, pH-value, initial HbA1c, day of treatment on one hand, and the daily insulin requirement per kg body weight (BW), prandial insulin requirement/kg BW, insulin /bread unit ratios and basal insulin requirement/ kg BW on the other hand. By Wilcoxon's rank sum test we examined whether there were significant differences between the age groups ≤ 10 years, and > 10 years, ≤ 5 years, and > 5 – < 10 years, ≤ 10 < 15 years and > 15 – < 20 years.

**Results:** There are significant correlations indeed (significance level $P = 0.0001$) between age, sex, initial HbA1c, pH-value and the day of treatment on one hand and insulin doses on the other hand. Evaluation of the age-dependency of insulin doses/kg BW revealed significant differences in the age group above 10, and in the age group younger than 10 as to daily and prandial insulin

requirements, but not with regard to basal insulin requiremen. When subdividing the groups ≤ 5 years and > 5 – < 10 years, we saw no significant differences between these age groups. The age groups ≤ 10 < 15 years and > 15 – < 20 years did not show any significant differences either. A suggestion to compute the prandial and basal insulin requirement with reference to age groups is made on the basis of a multi-regression analysis.

**Conclusion:** Our studies permit the conclusion that the impact of age on insulin dosage is mainly puberty-related. Our method of computing the insulin dosage provides a good basis for starting insulin therapy in non-keto-zidotic patients.

## P/FRI/75

### Ovulatory function in adolescents with type 1 diabetes mellitus

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**Introduction:** Adolescents with type 1 diabetes mellitus T1DM may exhibit a delay in pubertal development. The attainment of regular ovulatory function, which occurs after menarche, has not been evaluated in girls with T1DM.

**Aim:** To determine the proportion of ovulatory menstural cycles in adolescents with T1DM during the years following menarche (M).

**Method:** Adolescents with T1DM ($n$ = 14) and healthy girls ($n$ = 30) who had developed menarche during the previous 28 months were recruited. Both groups were matched for gynecological age (time post-menarche) and body mass index. Menstrual cycles were evaluated with a prospective calendar and assessment of ovulation by salivary progesterone (days 13, 18, 23 y 28 of each cycle) during 6.1 ± 2.6 cycles in each girl. A progesterone level detecting ovulation (≥ 0.05 ng/ml) was established from the values obtained from simultaneous saliva and blood samples in 10 adult women with regular menstrual cycles. Statistical analysis was performed using $t$-test and McNemar test. Data are shown as mean ± standard deviation.

**Results:** A total of 77 and 185 menstrual cycles were evaluated in T1DM and control (C) groups, respectively. Girls with T1DM exhibited a lower rate of ovulatory cycles than C beyond 2 years post-menarche (Table). However, within the first 2 years of menarche the frequency of ovulatory cycles was similar in both groups.

| | T1DM | C |
|---|---|---|
| Gynaecologycal age (year) | 1.5 ± 1.0 | 1.6 ± 1.3 |
| BMI-SDS | 0.5 ± 0.6 | 0.9 ± 0.7 |
| HbA1c (%) | 8.2 ± 0.8 | |
| Mentrual cycles studied ($n$ by subject) | 5.5 ± 2.1 | 6.4 ± 2.7 |
| Ovulatory cycles (%) | | |
| Cycles < 2 year post-menarche | 21.3 | 29.1 |
| Cycles > 2 year post-menarche | 33.3 | 61.0** |

**$P$ < 0.01

**Conclusions:** The presence of ovulatory cycles after 2 years post-menarche may be delayed in girls with T1DM.

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## P/FRI/76

### Short-term glucose concentration predictions based on a hybrid model for children with type 1 diabetes using continuous glucose monitoring sensor

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**Objectives:** Recently many computer-based simulations of glucose-insulin metabolic system have been proposed aiming at the prevention of dangerous metabolic states, such as hypo/hyperglycemic events and the overall improvement of diabetes mellitus. A hybrid model of glucose - insulin metabolism able to make short-term glucose concentration predictions based on data from children with Type 1 diabetes is presented.

**Methods:** The hybrid model is based on the combined use of mathematical models, and an artificial Neural Networks (NNs). The used NN is a Recurrent NN (RNN), which can be adjusted in real time, in order to provide personalization to a specific patient data. The proposed model uses data from patient's recent history containing information about glucose levels taken from Continuous Glucose Monitoring Sensor (CGMS), insulin intake, and food intake, along with corresponding time. The model's output is the short-term prediction of glucose concentrations. The hybrid model has been developed and evaluated using data from eight children with Type 1 diabetes. CGMSs are used for glucose measurement and insulin delivery is performed either by Multiple Daily Injections (MDI) (four children), or subcutaneously through insulin pumps (four children).

**Results:** In order to assess the performance of the proposed hybrid model, the Root Mean Square Error (RMSE) and the correlation coefficient (cc) between predicted and measured glucose concentrations have been calculated. The RMSE was in the order of 24, while the cc in the order of 0.95 for all processed data.

**Conclusion:** The results of the model show the potential of the proposed approach to efficiently approximate glucose metabolism, and to accurately predict short-term blood glucose levels. Furthermore the integration of the model to an automatic advisor is foreseen, aiming at providing personalized recommendations about the appropriate time and dose of insulin injections and/or insulin pump settings.

# New Insulin and Pharmacologic Agents

## P/FRI/77

### Experience with long-acting analogues insulin on the pediatric diabetes treatment

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**Aim:** To study characteristics of the treatment with slow analogues insulin regarding to needs of insulin (U/kg/d), percentage of new long-acting insulin (basal) and rapid-acting (bolus) and repercussion on the metabolic control.

**Methods:** Ninety patients transferred from short-acting + NPH to basal insulin (Glargina or Detemir) + bolus, and those treated since the onset. 63.1% men, pre-pubertal 18%, pubertal 82%. We made a subgroup in which the change of treatment coincided with transfer from pre-pubertal to pubertal. Mean age ± SDS: 13.56 ± 2.93 years (range 1–19) and diabetes duration 6.28 ± 3.90 years (range 1–15).

**Results:** Proportion average of basal insulin : Before change (NPH): 67.57%. Change to Glargina 53.3%. Change to Detemir:

62.71%. Characteristics of the detemir treatment since the onset (first year of evolution) (n = 9): Doses: 0.78 U/Kg/d ± 0.3. % detemir: 63.97% ± 8.75. HbA1c was lower in patients with four bolus (7.52%, ± 0.8) than in those with three bolus (8.53% ± 0.97).

**Conclusions:** Patients transferred from NPH to Glargina need to decrease basal dosage in a 10–15%, and the proportion is 50–55% of total dose. If they are transferred to Detemir they need to increase in a 8–10% and proportion is 60–65% of total dose. Metabolic control improves with the Basal/Bolus treatment (except on the group changing to pubertal stage),significatively in pre-pubertal changed to Detemir and pubertals changed to Glargina. Decrease in HbA1c is related to number of bolus per day.

| Insulin (U/Kg/d) | n | NPH (Pre-change) | Glargina (n:49) | Difference (%doses NPH) | NPH (Pre-change) | Detemir (n:32) | Difference (%doses NPH) |
|---|---|---|---|---|---|---|---|
| Total | 81 | 1.08 ± 0.42 | 0.94 ± 0.18 | -0.14 (12.9%) | 1.02 ± 0.34 | 1.12 ± 0.29 | 0.10 (9.8%) |
| Pre-pubertal | 18 | 0.69 ± 0,38 | 0.85 ± 0.09 | 0.16 (23%) | 0.87 ± 0.18 | 0.96 ± 0.22 | 0.09 (10.3%) |
| Pubertal | 63 | 1.11 ± 0.41 | 0.94 ± 0.18 | -0.17 (15.3%) | 1.15 ± 0.39 | 1.25 ± 0.28 | 0.10 (8,6%) |
| Pre-pubertal to pubertal | 14 | 1.08 ± 0.69 | 0.98 ± 0.20 | -0.10 (9.2%) | 0.82 ± 0.18 | 1.06 ± 0.21 | 0.24 (29.2%) |
| HbA1c | n | NPH (Pre-change) | Glargina (n:49) | Difference (%doses NPH) | NPH (Pre-change) | Detemir (n:32) | Difference (%doses NPH) |
| Total | 81 | 8.06 ± 0.88 | 7.83 ± 0.86 | -0.23 (ns) | 8.20 ± 0.98 | 8.09 ± 1.01 | -0.11 (ns) |
| Pre-pubertal | 18 | 7.30 ± 1.12 | 7.03 ± 0.98 | -0.27 (ns) | 7.99 ± 0.59 | 7.72 ± 0.55 | -0.27 (p = 0.01) |
| Pubertal | 63 | 8.11 ± 0.86 | 7.89 ± 0.84 | -0.22 (p = 0.05) | 8.31 ± 1.21 | 8.39 ± 1.20 | 0.08 (ns) |
| Pre-pubertal to pubertal | 14 | 7.90 ± 0.72 | 7.93 ± 0.46 | 0.03 (ns) | 7.46 ± 0.3 | 8.03 ± 0.7 | 0.57 (ns) |

## P/FRI/78

## About an effect of combined therapy of long-acting insulin (insulin glargine) and rapid-acting insulin analog

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**Introduction:** Use of long-acting insulin (Insulin glargine) was started in Japan science November 2003. The type I diabetes mellitus patient expected it for stabilization of blood glucose level, reducing the number of times of nocturnal hypoglycaemia and reducing the number of times of an injection. But about usage for a child, dosage, administration time, there is not yet an established thing. We started use of Insulin glargine for 19 children patients of this center ambulant follow this time. We considered the dosage, an effect.

**Patients and method:** We intended for 17 patients (5 boys, 12 girls) with type I diabetes mellitus. They changed NPH insulin to Insulin Glargine and regular human insulin to Rapid-acting insulin analog. Patient injected Rapid-acting insulin analog before every meal and injected the Insulin Glargine before sleeping. We set the initial dosage to 30% of Total Daily Dose. The patient changed dosage into an index in fasting blood glucose early in the morning. We reviewed comparison about a change of HbA1c, dosage of Insulin Glargine, body weight and Total Daily Dose.

**Results:** HbA1c accepted improvement of an average of 2.8 ± 3.64% after use in 3 months. Total Daily Dose per body weight (TDD/kg) is an average of 1.09 ± 0.37 U/kg. Dosage of G per body weight (G/kg) is an average of 0.37 ± 0.12 U/kg. A ratio of G to occupy in Total Daily Dose (G/TDD) was an average of 35 ± 8.54%. G/TDD tended to increase with increase of BMI. The change of body weight in about beginning to use did not accept it. About use dosage of Insulin Glargine, age, sexuality, the onset history did not have the large correlation. When HbA1c after beginning to use and BMI were high, G/TDD (%) became high.

**Discussion:** Hypoglycemia decreased by combination with Rapid-acting insulin analog, and the eating habits became free. Now after several years, we wants to evaluate current glycemic control and a living habit

## P/FRI/79

## Clinical setting assessment of multiple daily injections (MDI) with insulin glargine in 48 adolescents with type 1 diabetes (T1D)

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**Aim:** Multiple Daily Injections (MDI) regimens is used with increased frequency but is not accepted by all adolescents. The approval in France of the long-acting insulin analog glargine was used to further promote MDI in adolescents. The aim of this study was to evaluate a one year experience in the first 48 adolescents with T1D treated with glargine in an all analog MDI regimen (MDIG).

**Methods:** Forty-eight adolescents with T1D treated with 2 (44%) or ≥ 3 daily injections (56%), with NPH as basal insulin, accepted MDIG for improving metabolic control (47%) or increasing their daily life flexibility (53%). They were 22 boys and 26 girls, aged 12–19 years (median: 16), with median duration of diabetes of 6.7 years, and median HbA1c of 9.1% (6.2–14.7) at initiation of MDIG (baseline). A retrospective case-based analysis comparing the first year of treatment to the prior year was performed regarding HbA1c levels, insulin doses, body mass index, and severe hypoglycemia.

**Results:** Median decrease in HbA1c was -0.8% at 3 months, and -0.7% at 6 months compared to baseline, with respective median HbA1c values of 7.9% and 8.2%. After three to six months of therapy, 71% of the adolescents met the criteria of success defined in the study, i.e. a decreased HbA1c ≥ 0.5% (median = -1.1%) or an HbA1c value ≤ 8% (median = 7.6%). Although, HbA1c levels at one year were identical to baseline in the whole population (8.9 vs. 9.1%), variations compared to baseline differed in the success group vs. the others (-0.3 vs. +0.4%, p = 0.02). In the questionnaires filled in at one year, 94% of the adolescents expressed their satisfaction and chose to go on with MDIG.

**Conclusions:** Multiple Daily Injections regimen (MDIG) is well accepted and allows clinical improvement in glycemic control in three out of four adolescents in poor control. However, this improvement is not sustained after 6 months. Reinforcement of adolescent's motivation and therapeutic adherence must be regularly planned after 6 months of MDIG in order to maintain better glycemic control in this challenging population.

## P/FRI/80

## Insulin glargine improves morning glycemia and HbA1c in adolescents with type 1 diabetes

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Long-acting insulin analogues in combination with short-acting analogues can be a therapy of choice in adolescents with diabetes compared with other insulins. Insulin Glargine is known by the length of its action.

**Objective:** To compare the four insulin injections therapy regimen including NPH with the same regimen with insulin glargine as a long acting analogue.

**Methods:** Forty adolescents, 11–17 years of age (mean 13.5 ± 3.2) who were on four injection therapy including NPH

insulin for at least 6 months were included in the study. All were pubertal. Short education about the use of insulin glargine was conducted. The single change was the introduction of insulin glargine. Morning glycemia was regularly recorded. HbA1c was measured at 3 month intervals for a period of one year. The average of four measurements was taken for comparison with the previous values. Questionnaire about the satisfaction with the new protocol was filled in by adolescents. Episodes of hypoglycemia were recorded and compared with the previous protocol.

**Results:** Twenty-three adolescents were males and 17 were females. Dose of insulin was 0.9 + 0.2 IU/kg before and 0.7 ± 0.1 IU/kg after switching to glargine. Morning glycemia decreased from 9.2 ± 1.1 to 6.7 ± 0.8 mmol/dl. HbA1c decreased from 9.5 ± 1.3 to 7.8 ± 1.6 ($p < 0.05$). Number of hypoglycemia also decreased from average 4.3 ± 0.5 per month per child to 2.1 ± 0.3 per month. No severe hypoglycemia was noted with insulin glargine. Questionnaire about the patient satisfaction confirmed better feeling of adolescents with therapy with insulin glargin.

**Conclusion:** We conclude that insulin glargine is a good solution for adolescents with type one diabetes since it provides more stable control of HbA1c, less hypoglycemia and is well accepted by the adolescent children.

## P/FRI/81

## Switching from glargine to detemir can improve glycaemic control and reduce hypoglycaemia in basal-bolus insulin-treated paediatric patients with type 1 diabetes. 3-month data from a European cohort of PREDICTIVE™

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**Objective:** To examine clinical endpoints following a switch from insulin glargine to insulin detemir in basal-bolus insulin-treated children and adolescents with type 1 diabetes enrolled in the PREDICTIVE™ study (Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation).

**Methods:** PREDICTIVE™ is a prospective, open-label, non-interventional study in an everyday clinical setting that includes patients (type 1 or 2 diabetes) empirically treated with insulin detemir. Among the European cohort (> 20 500 patients from 11 nations), 138 individuals aged ≤ 18 years were included following a switch in basal insulin from glargine to detemir. For these patients (61% female, mean age 14.1 years, mean BMI 21.8 kg/m$^2$), clinical endpoints were assessed immediately preceding this switch and after a mean follow-up of 14.8 wk.

**Results:** Mean $HbA_{1c}$ decreased from 9.3 to 8.7% ($p < 0.005$), with the patient proportion at < 7.0% rising from 5.6 to 18.7%. FBG decreased from 9.4 to 8.5 mol/l ($p = 0.010$). Overall hypoglycaemia rate (assessed during 4-wk intervals immediately before switching and final follow-up) decreased from 51 to 29 events/patient/year ($p < 0.005$). Respective reductions in nocturnal and major hypoglycaemic events were from 7.9 to 4.4 ($p = 0.019$) and from 2.1 to 0.8 events/patient/year ($p = 0.043$). Total insulin dose increased from 54.1 to 57.6 U (basal +2.5, bolus +1.0 U).

**Conclusion:** Pediatric patients with basal-bolus insulin-treated type 1 diabetes that are not adequately controlled with/tolerant of insulin glargine as a basal insulin may benefit from a switch to insulin detemir with subsequent dose adjustment.

## P/FRI/82

## The rate of improvement in metabolic control in children with diabetes mellitus type 1 on insulin glargine depends on age

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**Objectives:** To evaluate the changes in the glycemic profile and metabolic control after introducing glargine in children with DMT1 in a one-year follow up.

**Methods:** Seventy children (36 boys and 34 girls) at the average age of 12.03 ± 2.50 with the mean diabetes duration of 3.35 ± 2.19 years were observed. Glargine was substituted for NPH in children treated with multiple daily injections.

**Results:** The analysis showed the differences in the dynamics of changes in mean glycemia based on home blood glucose monitoring and HbA1c between pre-pubertal children (Group 1) and teenagers (Group 2). A significant reduction in mean glycemia from baseline to 12 months was observed at all chosen points in Group 2: fasting glycemia (125 ± 27mg/dl vs. 117 ± 17mg/dl, $p < 0.05$), bedtime glycemia (128 ± 24mg/dl vs. 117 ± 20mg/dl, $p = 0.001$) and 3 a.m. glycemia (143 ± 47mg/dl vs. 90 ± 25 mg/dl, $p < 0.001$). A significant decrease in mean glycemia in Group 1 was observed from the beginning of treatment only at bedtime (0–12 months: 129 ± 27mg/dl vs. 112 ± 25mg/dl, $p = 0.001$) and at 3 a.m with the delay (6–12 months: 122 ± 36 mg/dl vs. 90 ± 22 mg/dl, $p < 0.05$). A significant improvement in HbA1c between baseline and 12 months was observed in both groups but with different dynamics of changes: 6.91 ± 0.77% vs. 6.59 ± 0.65% ($p < 0.05$) and 7.44 ± 1.26% vs. 7.18 ± 1.58% ($p = 0.001$) respectively in the groups. A trend towards decreasing the number of hypoglycemic episodes and no changes in BMI and insulin requirement were noted.

**Conclusions:** Treatment with glargine provides diabetic children with a better stabilization of the daily glycemic profile even in the cases of baseline good metabolic control. The rate of reaching the target in a long-term observation depends on age - a slower reduction of glycemia being typical of smaller children. The project was partially supported by the Polish State Committee for Scientific Research (KBN), grant no 3T11F 010 29

## P/FRI/83

## Long-term improvement of fasting glycemia after switching basal insulin from NPH to detemir in children with type 1 diabetes: A one-year multicentre study

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**Objectives:** To evaluate diabetes control after switching from NPH insulin to detemir in children with type 1 diabetes (T1D).

**Methods:** We performed a non-randomized, observational, multicentre study examining the first children switched from NPH to detemir in four centers of pediatric diabetes. A total of 72 children (39 boys and 33 girls) were included in the analysis. The mean age at intervention was 10.6 ± 4.7 year (range 1.5–19), the mean age at T1D onset was 6.2 ± 4.3 year (range 0.9–16.0). All the children were monitored for a period of 6 months; 68 out of 72 completed the one-year study protocol. All the subjects were

treated with an intensified insulin regimen with the basal insulin applied once or twice a day. No other intervention was done except from switching the basal insulin. Diabetes control was assessed in 3 month intervals. The endpoints assessed were HbA1c (IFCC), fasting glycemia, insulin dose, and the frequency of severe hypoglycemic events.

**Results:** The mean HbA1c decreased from 7.1% at baseline to 6.6% after 3 months of detemir therapy ($p = 0.0003$). However, in the next months we observed a trend toward an increase in HbA1c, and no statistically significant difference in HbA1c was observed at the 6, 9 and 12 months visits vs. the baseline. Fasting glycemia decreased significantly during the treatment with detemir. The mean the decrease between the baseline and month 3 was 2.1 mmol/l ($p < 10–9$), and this effect was detectable during the whole observational period (month 12 vs. baseline 2.6 mmol/l, $p < 10–8$). The basal as well as the total insulin doses did increase from initial doses of 0.25 U/kg and 0.81 U/kg resp., to 0.3 U/kg and 0.91 U/kg, resp. at 12 months ($p < 10–4$).

**Conclusion:** Switching basal insulin from NPH insulin to detemir resulted in a transient improvement of HbA1c, and a long-term decreasing of fasting glycemia in children with T1D.Support: Grants MSMT CR (No. 21620819) and MH CR (No. 64203/6902).

## P/FRI/84

## Higher insulin need after transfer to insulin detemir at bedtime particularly in younger children with type 1 diabetes

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**Introduction:** A 12 week crossover-study showed a dosing factor of 1.7 for the transfer to insulin Detemir (DET) at bedtime from NPH Insulin or Semilente MC (SEM) in children with dawn-phenomenon. This resulted in unchanged HbA1c but less night-time hypoglycaemic events. Aim of this study was to investigate clinical course over a period of 6 months (m) and to analyse clinical factors that are associated with a higher dose of DET in children with type 1 diabetes after having changed bedtime insulin.

**Methods:** Forty-four patients (pat)(27 boys, 17 girls, age: 14.5(7-18)years, BMI: 22.9kg/m$^2$ (15.9-33.3), BMI-SDS: 1.06(-1.10 to 3.15), HbA1c: 7.4 (5.9-14.0)% at baseline) were followed up over a period of 3m,28pat over 6m,after having changed the bedtime insulin from SEM ($N = 36$) or NPH($N = 8$)to DET. HbA1c, hypoglycaemic events, BMI, BMI-SDS, and insulin need were studied before, 3 and 6m after the transfer to DET.

**Results:** After 3m insulin need changed significantly from 0.87 (0.43–1.19) U/kg to 0.98 (0.49–1.41) U/kg($p < 0.001$), total basal insulin increased from 0.29 (0.08–0.48) U/kg to 0.37 (0.11–0.69) U/kg ($p < 0.001$), bedtime insulin dose was 1.52(0.88–2.97) times higher than before. Pat with a higher demand of DET (factor ≥ 1.50) were significant younger when changing therapy (13.8 year (7.0–17.6) and at diabetes onset (5.8 year, 1.2-12.8) than those with a lower factor (age: 16.4(9.5–18.0) year ($p = 0.017$) at diabetes onset: 9.9 years, 2.8–14.7 ($p = 0.004$)). After 6m we found a further increase in total basal insulin to 0.39 (0.11–0.73)U/kg ($p = 0.032$). Dose of DET was 1.55 (0.92–2.59) ($p = 0.04$) higher compared to the dose at change. No significant change in HbA1c ($p = 0.65$) and BMI ($p = 0.76$) was seen. Gender, duration of diabetes, BMI and need of insulin at beginning did not influence the dose of DET. Number of hypoglycaemic events did not increase (1 in 6 m).

**Conclusion:** Children with type 1 diabetes and dawn phenomenon need a higher dose directly after change to DET. Titration phase can last up to 6m. A longer period is seen particularly in younger children.

## P/FRI/85

## Lower within-subject variability in pharmacokinetic profiles of insulin detemir in comparison to insulin glargine in children and adolescents with type 1 diabetes

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**Objectives:** This randomised, double-blind, cross-over trial compared the within-subject variability of pharmacokinetic profiles of insulin detemir and insulin glargine in children and adolescents with type 1 diabetes.

**Methods:** Thirteen children (8–12 year of age, BMI: 19.4 ± 2.0 kg/m$^2$, HbA1c: 8.0% ± 1.0%) and 19 adolescents (13–17 years of age, BMI: 22.8 ± 2.7 kg/m$^2$, HbA1c: 7.9% ± 1.0%) with type 1 diabetes were randomised to two s.c. doses (0.4 units/kg) of each insulin. Insulin detemir and insulin glargine were injected 24 h apart at each of two dosing visits. Insulin concentrations were measured at frequent intervals for 16 h post dosing.

**Results:** Insulin detemir showed statistically significantly less within-subject variability compared to insulin glargine (3.1 and 2.9 fold lower %CV for AUC (0–16 h) and Cmax, respectively). Similar findings were observed when insulin profiles for children and adolescents were analysed separately, see table below. No safety concerns were raised during the trial.

| | | Children and adolescents | Children | Adolescents |
|---|---|---|---|---|
| AUC(0–16 h) | Insulin detemir | 10% | 10% | 9% |
| | Insulin glargine | 31% | 25% | 36% |
| Cmax | Insulin detemir | 12% | 13% | 9% |
| | Insulin glargine | 35% | 38% | 34% |

**Conclusion:** In conclusion, within-subject variability in pharmacokinetic properties was significantly lower for insulin detemir than for insulin glargine in children and adolescents with type 1 diabetes. This indicates a less variable absorption with insulin detemir, which is expected to be associated with a more predictable therapeutic effect in this population.

## P/FRI/86

## Advantages of treatment children manifesting T1D with insulin analogues

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**Objectives:** Insulin analogues are less use in children with new onset T1D.The purpose of research is to estimate T1D compensation and insulin dose needed in children were treated with different insulin therapy from onset and during the first year of T1D.

**Methods:** We studied 93 T1D children. The one group included 30 children (9.5 ± 2.8 year) were treated with "traditional" therapy

(short human insulin and middle effect human NPH insulin). Two group included 32 children (10.6 ± 1.4) were treated with ''mixed'' therapy divided into two variants (Variant 1 - short human insulin combined with basal analogue of insulin glargin (15 patients); variant 2 is short analogue as part or lispro combined with NPH insulin (17). Three group included 31 children (9.3 ± 1.1) were treated with only insulin analogues (''analogue'' scheme).

**Results:** HbA1c, basal, and bolus doses per kg at onset, 6 and 12 months after were analyzed in each group. Results are in the Table.

At onset basal insulin dosage in ''mixed'' and ''analogue'' scheme was less then in ''traditional''. Six months after basal dosage and HbA1c in ''analogue'' scheme was significantly less than in any other. 12 months after data show less dosage of insulin and HbA1c in ''analogue'' scheme.

| Scheme of insulin therapy | | ``Traditional'' | ``Mixed'' | ``Analogue'' |
|---|---|---|---|---|
| New-onset T1D | Bolus (IU/kg) | 0.42 ± 0.03 | 0.51 ± 0.07 | 0.45 ± 0.09 |
| | Basis (IU/kg) | 0.34 ± 0.3 | 0.17 ± 0.03 | 0.16 ± 0.03 |
| | HbA1C (%) | 11.6 ± 0.44 | 12.77 ± 0.6 | 11.86 ± 1.1 |
| 6 months after | Bolus (IU/kg) | 0.41 ± 0.13 | 0.45 ± 0.07 | 0.34 ± 0.15 |
| | Basis (IU/kg) | 0.38 ± 0.05 | 0.2 ± 0.03 | 0.1 ± 0.05 |
| | HbA1C (%) | 8.2 ± 0.96 | 8.1 ± 0.64 | 7.2 ± 0.2 |
| 12 months after | Bolus (IU/kg) | 0.48 ± 0.09 | 0.55 ± 0.08 | 0.38 ± 0.08 |
| | Basis (IU/kg) | 0.41 ± 0.06 | 0.31 ± 0.05 | 0.27 ± 0.09 |
| | HbA1C (%) | 9.6 ± 2.1 | 9.3 ± 1.8 | 7.8 ± 0.9 |

**Conclusion:** Treating children with insulin analogues is able to improve T1D clinical course with small insulin doses and maintain low HbA1c level. This theme needs continuation of researches.

## Intensified Insulin Treatment, Pumps, and Sensors III

### P/FRI/87

### Can the introduction of carbohydrate counting algorithms integrated into pump therapy decrease HbA1c in the children and adolescents with type 1 diabetes?

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Carbohydrate counting (CC) has not been used in Sweden during the past 20 years. Our aim was to study the introduction of this tool in the treatment of children with type 1 diabetes. 40 children, aged 13.8 ± 3.4 years (range 5.0–19.5) and diabetes duration 8.0 ± 3.8 (1.8–16.8), completed a one year multi-center study with 1 month run-in. HbA1c at start was 7.8 ± 0.9% (DCCT-equivalent). All had used pumps for > 6 months. They were randomized into: A control group, B manual CC and C CC with a Cozmo pump. B and C received education in CC with insulin: carbohydrate ratio. A received equal hours of traditional education. HbA1c and plasma glucose (PG) meter download was collected every 3 months. PG was measured before and 2 h after meals and the absolute difference was used for calculation of a mean value (delta glucose, DG) and SD. DISABKIDS life quality questionnaire was used at baseline, 6 and 12 months. We found no difference in HbA1c at 12 months between the groups. The fluctuation of PG measured as standard deviation (SD) was not different at 12 months. However, group C had a significant decrease in SD when compared to starting point ($p < 0.05$) and the SD of DG also decreased significantly ($p < 0.05$). The frequency of hypoglycemia, defined as PG < 3.5 mmol/l, was significantly reduced for the whole study group ($p < 0.05$) but there was no significant difference between the groups. There were no differences in body weight or in insulin doses/kg/24 h. between groups. Group A significantly increased their basal insulin dosage at 12 months while there were no differences in group B and C. In group C, all subjects wanted to continue CC after the study, and in group B 67%. DISABKIDS showed that group C significantly increased their independence scores. The insulin: carbohydrate ratio correlated significantly to weight, BMI, insulin dose/24 h and age ($p < 0.05$), but not to HbA1c, gender or diabetes duration. We conclude that CC can help decrease overall and meal-related PG fluctuations.

### P/FRI/88

### Benefits of a bolus calculator in the glycaemic control and meals flexibility of pediatric patients in CSII treatment

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The Bolus Wizard (BW) is a bolus calculator integrated in the insulin pump that estimates the insulin doses based on blood glucoses (BG) and carbohydrate (CHO) intake.

**Aims:** To evaluate the effectiveness of BW in the glycemic control of paediatric patients on CSII treatment.

**Methods:** Thirty-six patients (19M) mean age 17 ± 6.4 year, with T1D (duration 9 ± 4 year) in CSII treatment (duration 37 ± 23 months) were prospectively enrolled into a randomised two-period crossover study. 18 subjects had begun the phase A using the BW to determine pre-meal boluses, followed by phase B using their current insulin dosing method. The others subjects had begun the phase B followed by phase A. Each study period lasted 2 wk.

**Results:** BG levels before and 2 h after meals were lower in phase A respected to phase B. The number of correction bolus/week (for BG > 11.1 mmol/l) was significantly lower in phase A (3.3 ± 2.7 vs. 5.7 ± 3.8 $p = 0.00$).There was no differences ($p < 0.05$) between the two phase in: number of hypoglycaemic events, insulin requirement, % of daily insulin delivered as bolus and meals bolus quantity. The CHO intake (gr) at breakfast and lunch is higher ($p > 0.05$) in phase A respected to phase B while there was no difference at dinner.

| | Phase A | Phase B | P |
|---|---|---|---|
| Daily pre-prandial BG | 9.2 ± 1.8 | 10.4 ± 1.9 | 0.000 |
| BG pre-breakfast | 9.0 ± 2.6 | 11.1 ± 2.8 | 0.000 |
| BG pre-lunch | 8.9 ± 2.2 | 10.2 ± 2.5 | 0.002 |
| BG pre-dinner | 9.6 ± 2.3 | 10.1 ± 2.7 | 0.36 |
| Daily 2 h postprandial BG | 9.2 ± 1.4 | 10.5 ± 1.9 | 0.000 |
| BG 2 h-post-breakfast | 9.0 ± 1.9 | 10.5 ± 3.3 | 0.001 |
| BG 2 h-post-lunch | 9.1 ± 1.6 | 10.2 ± 2.7 | 0.005 |
| BG 2 h-post-dinner | 9.8 ± 1.7 | 10.6 ± 2.7 | 0.027 |

**Conclusion:** In the CSII treatment of pediatric patients the bolus insulin dose calculated using BW was more effective in improving pre/post-prandial glycemic control with fewer correction boluses, without differences in the prandial insulin requirements and without restriction in the CHO content of meals.

P/FRI/89

## Evaluation of post-prandial blood glucose levels using the continuous glucose monitoring system (CGMS, Medtronic) in type 1 diabetes mellitus children treated with lispro insulin in personal insulin pumps

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Post-prandial blood glucose levels are an independent risk factor for diabetic angiopathy, as important as fasting blood glucose levels.

**Aim:** To determine the usefulness of continuous glucose monitoring system (CGMS) in the evaluation of 24 h and post-prandial blood glucose levels in children with T1DM.

**Methods:** Twenty subjects with T1DM, 7 to 18 years of age (X 12.6 ± 3.6) treated with intensive insulin therapy using lispro insulin in personal insulin pumps were monitored three times (each 3 months) for blood glucose levels with CGMS and HbA1c.

**Results:** Mean blood glucose level > 135 mg/dl in 12 children in the 1st monitoring period, 16 children in the 2nd, and 14 children in the 3rd. All three mean HbA1c levels were similar, nevertheless in the 1st, 2nd and 3rd monitoring period HbA1c > 8.1% was recorded in 6 vs. 10 vs. 8 subjects. HbA1c < 6.5% in all three monitoring periods was recorded in two children. Fasting blood glucose levels < 105mg/dl in the first monitoring period was recorded in 27/59 assays whereas in successive periods in 19/60 vs. 18/56 assays. Elevation of post-prandial blood glucose levels was observed, particularly after lunch. In the first monitoring period post-prandial blood glucose levels > 161 g/dl was recorded in 17/59 assays, in the second one - 28/61 assays and after 6 months - in 34/59 assays.

**Conclusions:** 1.Rapid-acting insulin analogues administered in personal insulin pumps as normal boluses before mixed meals did not reduced effectively postprandial glycaemia. 2. CGMS offers a new option for tailoring treatment to achieve optimal glycaemia.

P/FRI/90

## Improvement of glycemic control in children with type 1 diabetes with continuous glucose monitoring systems (CGMS) and guardian RT

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**Objectives:** Aim of the study was to evaluate the efficacy of CGMS and Guardian RT in improving glycemic control in children with type 1 diabetes (T1D).

**Methods:** CGMS was placed for 1–6 days in 29 children and adolescents with T1D [13 males, mean age 11.18 years, mean duration of disease 6.13 years]. Weight, height, Body Mass Index (BMI), daily insulin requirements, hypoglycemic episodes and HbA1c were evaluated before and 3 months after CGMS. Guardian RT was placed in five children (15 months to 19 years old) for 7–134 days.

**Results:** Out of 25.078 CGMS measurements with mean blood glucose (SD) 150.89 (75.71) mg/dl, 9.081 were performed during the night [mean blood glucose (SD) 139.23 (71.81) mg/dl] and 15.997 during the day [mean blood glucose (SD) 157.5 (77.05)]. The percentage mean deviation from the capillary blood in 599 measurements was 1.4%. In Clarke's Error Grid analysis the majority of measurements were within A and B zone. Out of 3103 hypoglycemic episodes (< 70 mg/dl), 1378 observed during the night and 1725 during the day. Out of 10.691 episodes of hyperglycemia 3.277 (36.08%of the corresponding period) occurred during the night and 7.414 (46.34 %) during the day. HbA1c was significantly lower compared to the pre CGMS levels ($p < 0.007$) but not the daily insulin requirements. There was a slight increase in BMI $p = 0.012$. Guardian RT was evaluated with 47.884 measurements (18.205 during the night and 29.679 during the day). The percentage mean deviation from the capillary blood in 416 measurements was 13.9%. In Clarke's Error Grid analysis 92.95% of the measurements were within A and B zone and 4.69% within the D zone. There was a significant reduction in hyperglycemic and hypoglycemic episodes the first week vs. the last week of the observed period in all five patients.

**Conclusions:** CGMS and Guardian RT are very useful educational tools which help in reduction of hypo or hyperglycemic episodes and in improving the glycemic control.

P/FRI/91

## Efficacy of insulin detemir in children and adolescents with type 1 diabetes according to continuous glucose monitoring

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**Introduction:** Insulin detemir is known as a long-acting and peak less insulin analogue.

**Objectives:** The aim of this study was to review the efficacy of insulin detemir in children and adolescents with type 1 diabetes. We used CGMS to evaluate the frequency of hypo- and hyperglycaemic episodes after initiation of insulin detemir.

**Methods:** Seventeen diabetic patients (10 boys and 7 girls) aged from 5 to 16 years (12.3 ± 4.1 years) with duration of disease 0.5–12 years (5.3 ± 4.7 years) and HbA1c 5.6–12.8% (8.48 ± 3.6%) were entered into the study. CGMS (Medronic MiniMed, Sylmar, CA) was used during 3 days. All patients were treated with intensive insulin therapy (Detemir and NovoRapid).

**Results:** No serious adverse drug reactions were revealed. Asymptomatic hypoglycaemias were found out in 14 patients (82%). 12 episodes of nocturnal hypoglycaemia and 19 episodes of post-exercise hypoglycaemia were revealed. The duration of asymptomatic hypoglycaemia was equaled 3.8% per day. The hypoglycaemias were more frequently detected in patients with better control (HbA1c less than 7%). The time of hyperglycaemia composed 52% of the patient's CGMS time. 75% of hyperglycaemias were post-prandial ones. Three children had down phenomenon. Injections of detemir twice day have shown the best glycaemic control.

**Conclusions:** The CGMS results show that insulin detemir-based therapy provides good glycaemic control with a low risk of hypoglycemia in pediatric patients with type 1 diabetes.

P/FRI/92

## Continuous glucose monitoring in insulin pump treated children

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**Introduction:** Insulin pump therapy tries to improve glycemic control and decrease risk of hypoglycemia in type 1 diabetes.

**Objective:** To show using continuous glucose monitoring interstitial glucose levels, frequency, duration, and symptoms of

hypo and hyperglycemia in children and adolescents with insulin pump-treated type 1 diabetes, and whether this monitoring is well tolerated by these patients.

**Patient and methods:** Thirteen patients (four boys) with insulin pump treated type 1 diabetes were monitored, age 10.6 ± 3.5 year (range 3.2–13.6 year), diabetes duration 5.0 ± 3.2 year, pump therapy duration 12.0 ± 4.6 months, insulin dose 0.99 ± 0.19 U/kg/day, last hemoglobin A1c level 7.1 ± 0.8%. The minimed CGMS system was used during 72 h.

**Results:** A pre-school three year-old child did not tolerate the CGMS. Interstitial glucose concentration was 187 ± 40 mg/dl. Hypoglycemia (below 70 mg/dl) accounted for 3.6 ± 5.6 %, while hyperglycemia (above 180 mg/dl) occur 47.3 ± 17.4% of the time. Episodes of asymptomatic hypoglycemia were not detected.

**Conclusion:** Insulin pump-treated children and adolescents show an irregular interstitial glucose level and do not achive normoglycemia. In our patients adrenergic symptoms of hypoglycemia are preserved and CGMS is, mostly, well tolerated.

## P/FRI/93

## Continuous glucose monitoring in diabetes type 1 children

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**Background:** The achievement of satisfactory glycemic control in diabetes determines the necessity of frequent glucose monitoring. This can be provided by the modern method of continuous glucose monitoring (CGMS).

**Objectives:** To evaluate the significance of CGMS use for achievement of glycemic control compensation in Diabetes type 1 children.

**Methods:** Nineteen CGMS tests were performed. All children were treated by intensive basis-bolus therapy with insulin analogues. The first group comprises of 15 patients (Average age 12.07 ± 0.52 years.) with the diabetes duration of 4.2 ± 0.37 years and non-satisfactory glycemic control. The second group comprises of five children (average age 10 ± 1.74 years.) with the diabetes duration of 2.8 ± 1.83 years. Figures of glycemia data in the group were within the target ranges according to the meter tests up to eight times a day. The average daily dose in the group was not exceeding the index for the pubertal stage and the disease duration. Light symptomatic hypoglycemic episodes periodically occurred in the group but without meter confirmation. Continuous glucose monitoring was performed for 3–5 days by CGMS system Gold (Medtronic, USA).

**Results:** Seven patients from the first group (46.6%) demonstrated stable hyperglucemia that demanded insulin dose increase. Eight patients were detected (53.4%, $p > 0.05$) hypoglucemia episodes with post-gypoglycemia hyperglycemia that demanded insulin dose decrease. Hypoglycemia episodes in the second group were detected at night time, before meals that accompanied brief postprandial glycemic level elevation. The data demanded insulin dose decrease. Both groups achieved comparable glucemic control.

**Conclusion:** CGMS application lets to optimize insulin therapy and to achieve the maximum compensation of glucose metabolism in diabetes type 1 children.

## P/FRI/94

## Evaluation of a real-time glucose monitoring influence on glycemic profile in well controlled children with T1DM

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**Objective:** Evaluation of a real-time glucose monitoring influence on glycemic profile obtained using continuous glucose monitoring (CGM) Medtronic Guardian system in a group of well controlled children with T1DM.

**Materials and methods:** In group 1: 30 children (17 boys) aged 7.78 ± 2.82, HbA1c = 6.58 ± 0.55%, T1DM duration 3.19 ± 2.07 years, total daily insulin dose 0.67 ± 0.23 U/kg, a real-time CGM device with hyper and hypoglycemia alarms was applied. In group 2: 26 children (11 boys) aged 6.82 ± 2.53, HbA1c = 6.79 ± 0.78%, T1DM duration 2.64 ± 1.82 years, total daily insulin dose 0.69 ± 0.24 U/kg, a blinded CGM device was used. The groups were comparable in clinical characteristics. Analysis was performed in time intervals of full recording, night (22:00–7:00) and day (7:00–22:00). The following parameters were calculated: average glucose values, time intervals and areas under the glucose curve (AUC) above > 135 and below < 65 mg/dl ($p < 0.05$).

**Results:** Evaluated parameters did not vary in analyzed time periods. Time intervals and areas under the hypo and hyperglycemias curves were lower in group one, but the differences were not statistically significant.

| groups | mean glucose [mg/dl] | AUC >135 time > 135[%] | AUC >135 [mg/(dl•day)] | AUC < 65 time < 65[%] | AUC < 65 [mg/(dl•day)] |
|---|---|---|---|---|---|
| 1 | 118.04 ± 11.61 | 28.76 ± 10.27 | 10.43 ± 5.56 | 5.71 ± 4.71 | 0.35 ± 0.34 |
| 2 | 121.83 ± 19.49 | 30.90 ± 16.60 | 13.54 ± 10.14 | 6.05 ± 8.29 | 0.71 ± 1.30 |
| p | ns | ns | ns | ns | ns |

**Conclusions:** The CGM system confirmed a good glucose self-management. Occasional use of a real-time glycemia monitoring did not influence glycemic profile of well-controlled diabetics.

## P/FRI/95

## Australian sensor augmented pump (ASAP) study

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**Objectives:** Published data suggests that uninformed patient use of real-time continuous glucose monitoring (CGM) data can lead to improved glycemic control in type 1 diabetes mellitus (T1DM). The MiniMed Paradigm Real-time Insulin Pump and Continuous Monitoring System (MMT 722) incorporate this real time CGM data with insulin pump therapy. Our aim is to assess the impact of use of this system on glycaemic control in adolescents and young people with T1DM.

**Methods:** The ASAP study is a randomised control trial ongoing at five sites throughout Australia. Sixty two participants with T1DM aged 13–39 year have enrolled. All have used insulin pump therapy for > 3 months with HbA1C < 8.6%. Participants were recruited in age-matched, sex-matched pairs and randomised 1:1 to the 'intervention' or 'control' group. 'Intervention' group participants used the MMT 722 system while 'control' group participants continued using their original insulin pump throughout the 3 month study period. No specific instructive guidelines for use of the sensor augmented system were given to 'intervention' group participants. CGMS Gold monitoring and HbA1C were used to assess differences between and within groups before and after the study period. Primary outcome variable is difference in percent time spent in the euglycameic range (4–10 mol/l) during CGMS Gold monitoring before and after the study period. Secondary outcome variables are percent time spent hypoglycaemic ( < 4 mol/l) and hyperglycaemic ( > 10 mol/l) and change in HbA1C.
**Results:** ASAP study is ongoing; scheduled date of completion is July 2007. Data for the full study cohort will be available for discussion.
**Discussion:** The MMT 722 system comprises the only sensor-augmented insulin pump technology currently commercially available. It is unclear how patients on insulin pump therapy will use real-time glucose sensor technology in their diabetes management, and how this will impact upon their diabetes outcomes.

## P/FRI/96

## Real-time insulin pump (RTIP) and continuous glucose monitoring system (CGMS) in management of transient neonatal diabetes mellitus (TNDM)

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**Objectives:** Neonatal diabetes is a rare cause of diabetes in children. Continuous insulin infusion has been considered for its management but still needs repeated blood glucose (BG) measurement. We report a case of TNDM managed by Mini Med Paradigm RTIP and CGMS.
**Methods:** A ten week old baby, who had developed DKA at 8 wk of age, was referred to us for further management. He had been started on continuous feeds and a basal-bolus insulin regimen. After transfer to our unit we reintroduced breast feeds. Management was difficult on basal-bolus because:
• Neither insulin glargine nor detemir provided adequate control of BG
• Unpredictability of breast feeds resulted in high fluctuations in BG
• Multiple pricks (30/d) were needed for administering insulin and monitoring BG
• Difficulties in diluting the insulin as part to administer small doses
• Diluted insulin using normal saline had limited stability and was prone to errorsA decision was made to treat the infant with RTIP and CGMS.
**Results:** After introduction of the device, BG was more stable and HbA1C improved to 5.6% after one month of continuous use. No hypoglycaemic episodes were encountered. The number of pricks decreased to 5/d. 3 months later a diagnosis of ABCC8 mutation was made and he was successfully transferred to glibenclamide. Problems with RTIP and CGMS were:• Presence of small dead space and need to ensure that there is NO air within the system as one day's insulin is contained within the tubing• Very steep learning curve for parents and staff• Maternal reliance on sensor with expectation that BG's will be consistently normal• If BG's were high, insulin had to be given by SC bolus and NOT via pump.
**Conclusion:** In our experience RTIP and CGMS is effective in controlling the BG in neonatal diabetes pending a definitive diagnosis. We recommend the usage of this device in managing infants with neonatal diabetes. Larger studies are required to confirm the benefits of RTIP and CGMS.