Monogenic and Type 2 Diabetes, Obesity

O/THU/1/01

Maternal obesity is the strongest predictor of overweight in offspring of women with gestational diabetes mellitus

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Objectives: Offspring of women with gestational diabetes mellitus (GDM) are at increased risk for obesity and diabetes mellitus in later life. Fetal imprinting by intrauterine diabetic environment and early postnatal determinants affects the development of these chronic diseases in addition to socio-economic and genetic determinants. The purpose of this study was to identify the strongest predictor of childhood obesity in offspring of women with GDM and to evaluate the development of insulin resistance depending on Body Mass Index (BMI).

Methods: Offspring of women with GDM (n = 331) were recruited since September 1989 for our German GDM prospective study. Venous blood sampling and collection of questionnaire data of mother and child were performed at birth as well as at ages 9 months, 2, 5, 8, 11 and 14 years. Following determinants were analysed: maternal obesity before pregnancy, insulin treatment during pregnancy, LGA status, exclusive breastfeeding 3 months, smoking behaviour during pregnancy. Furthermore, we analysed the influence of overweight on the development of insulin resistance.

Results: Determinants of overweight in early childhood (age 2 years) were LGA status (OR = 5.23; P = 0.000), insulin treatment during pregnancy (OR = 2.39; P = 0.018) and maternal obesity (OR = 3.53; P = 0.017). Overweight in early adolescence (age 8 and 11 years) was decisively influenced by maternal obesity (OR = 12.0; P = 0.012 and OR = 7.58; P = 0.021), whilst LGA status had decreasing to no significant influence at age 8 and 11 years (OR = 3.25; P = 0.049 and OR = 3.47; P = 0.063) and insulin treatment during pregnancy was no longer significant. Multivariate analysis confirmed maternal obesity and LGA status as independent determinants of risk at age 8 years (P = 0.027 and P = 0.037). Exclusive breastfeeding 3 months and smoking behaviour during pregnancy did not significantly affect risk for obesity in offspring of women with GDM. Insulin sensitivity was significantly reduced in overweight children in comparison to normal weight children (HOMA-IR, median: 1.82; IQR: 1.31–2.60 vs. median: 0.94; IQR: 0.62–1.35; P = 0.000).

Conclusions: The following determinants influenced the development of overweight in early childhood: LGA status, insulin treatment during pregnancy and maternal obesity. In early adolescence maternal obesity is the strongest predictor of overweight in children of women with GDM. Overweight in childhood and early adolescence correlated highly significant with insulin resistance.

O/THU/1/02

Contribution of resting energy expenditure to weight gain in young children – a longitudinal study

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Objectives: Resting energy expenditure (REE) is the largest component of total daily energy expenditure and potentially important in the regulation of body weight. However, its role remains controversial and little is known of its contribution to weight gain or changes in body composition (fat mass and %fat) in young children. Our aim was to evaluate the contribution of REE at 7 years to weight gain and changes in body composition over 36 months.

Methods: REE was measured by indirect calorimetry and body composition by DEXA in 179 children (97 boys) from the EarlyBird Diabetes Study, annually from 7 years to10 years. The effect of REE at 7 years on subsequent change in weight, excess weight (SDs), and body composition was analysed using linear mixed effects models with body composition and age at baseline entered as covariates.

Results: In girls there were small but statistically significant negative associations between REE at 7 years and subsequent change in fat mass ($\sim$ −0.1 kg/year/100 kcal, P = 0.01), %fat ($\sim$ −0.4%/year/100 kcal, P = 0.0002), and excess weight ($\sim$ −0.02 SDs/year/100 kcal, P = 0.01). In boys there were no significant effects of REE at 7 years on change in fat mass, %fat or weight SDs (all P > 0.34) but a small positive association was found between REE at 7 years and change in weight ($\sim$ 0.2 kg/year/100 kcal, P < 0.001).

Conclusions: The association between REE and change in weight and body composition was small yet statistically significant, together suggesting with some certainty that REE has little impact on the wide variation in weight gain at this age. REE may be of more importance in longer term changes in weight and/or body composition.

O/THU/1/03

The influence of insulin resistance on weight loss in obese pre-pubertal children

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Objectives: Childhood obesity has reached epidemic proportions and is associated with several metabolic and cardiovascular complications. Obesity-related insulin resistance (IR) has been demonstrated to be one the main causes for the development of these complications already in youth.

Methods: The aim of our study was to evaluate whether the degree of IR influences weight loss during a weight management program. We recruited 65 pre-pubertal Caucasian children (age mean ± SD: 8.7 ± 1.9years), affected by severe obesity (BMI > 97th percentile). At baseline (T0), all children underwent anthropometric measurements, assessment of blood pressure, plasma lipids and fasting insulin and glucose. Homeostasis model assessment of IR (HOMA-IR) was calculated and patients were divided into two groups: group A HOMA-IR > 97th percentile (n = 38) and group B HOMA-IR < 97th percentile (n = 27)[1]. Children were encouraged to follow a hypocaloric diet for the subsequent 6 months (T6) and assessed again at the end of this period.

Results: Differences between and within the groups were analysed by unpaired and paired t-tests respectively. Associations between variables were assessed by regression analysis. At baseline there were no differences in terms of age, gender, SDs-BMI, WHR and lipid levels between the two groups; whereas diastolic blood pressure was significantly higher in group A (P = 0.01). The change in SDs-BMI between T6 and T0 was significantly different between group A and group B (−0.04 ± 0.11 vs. −0.11 ± 0.12; P = 0.004). In particular, whereas in group A there was not significant change in SDs-BMI between T6 and T0 (2.28 ± 0.44 vs. 2.32 ± 0.38; P = 0.09), a significant improvement in SDs-BMI was found in group B (2.12 ± 0.3 vs. 2.24 ± 0.28; P = 0.001). In a multiple regression, HOMA-IR at baseline was an independent

predictor of changes in SDs-BMI ($\beta = 0.50$; $P < 0.001$; $R^2 = 0.40$), after adjusting for age, gender, and BMI at baseline.

Conclusions: In conclusion, this study shows that IR significantly influences weight loss during a weight management program. In particular, a higher degree of IR is associated with a resistance in weight loss, thus suggesting that obese insulin-resistant children might need a stricter program to obtain effective results.

Reference:

1. Capanna R, Masuccio F, Giannini C, Chiarelli F, Mohn A. Validation of percentiles for insulin sensitivity indexes in healthy paediatric subjects: HOMA-IR AND WBISI. Pediatr Diabetes 2007; ISPAD 2007, Berlino

O/THU/1/04

Metabolic impact of a ketogenic diet as compared to a hypocaloric diet in obese children and adolescents

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Objectives: To evaluate and compare the efficacy and metabolic impact of a high-protein, low-carbohydrate ketogenic diet (K) and a hypocaloric diet (HC) in obese children and adolescents.

Methods: Forty-one obese (OC) and 39 lean (LC) children and adolescents were studied. Anthropometric measurements, blood pressure, fasting glucose, insulin, lipidemic profile and high molecular weight (HMW) adiponectin, measured by ELISA, were obtained in all subjects. In the OC an oral glucose and insulin tolerance test was performed which revealed normal glucose tolerance in all except for three children. Whole Body Insulin Sensitivity (ISI) and HOMA-IR were also determined. The OC randomly began a K or HC diet. Changes were assessed after a weight loss of 10% from their initial body weight (iBW). Student's *t* test was used for statistical analysis.

Results: Twenty percent of the OC children followed the K diet and 15% the HC diet. On the K diet 62.5% lost 10% of their iBW (mean weight loss = −9.6 ± 4.7 kg, mean fat mass loss = −7.0 ± 4.75 kg) and all reduced their waist circumference (WC) (mean = −10.7 ± 5.4 cm). On the HC diet 66.6% of the children lost 10% of their iBW (mean weight loss = −4.7 ± 2.76 Kg, mean fat mass loss = −3.9 ± 4.0 Kg) and 83.3% reduced their WC (mean = −8.96 ± 1.54 cm). HOMA-IR decreased in 62.5% of the K diet children (mean = −1.81 ± 1.6) and in 66.6% of the HC diet children (mean reduction = −1.6 ± 2.18). HMW adiponectin was found significantly decreased in the OC that had central obesity and an abnormal lipidemic profile before their weight loss, when compared with the rest of the OC and HC ($P = 0.04$). Seventy-five percent of the K and 33% of the HC children increased their HMW adiponectin after their 10% iBW loss while the ISI was significantly increased ($P = 0.006$) only in the OC on the K diet.

Conclusion: The K and HC diets revealed positive results towards body weight, fat mass and WC reduction, with a decrease in fasting insulin and HOMA-IR. It was observed though that the obese children on the ketogenic diet lost more body weight and fat mass than those on the hypocaloric diet and a greater percent increased their HMW adiponectin after their 10% iBW loss. Also, only the children on the ketogenic diet had a significant improvement of their ISI. These results infer that the ketogenic diet may be able to better improve the metabolic profile of obese children than the hypocaloric diet.

O/THU/1/05

The influence of physical activity on ghrelin, adiponectin and IGFBP-3 levels in children and adolescents with type 1 diabetes

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Objectives: There is a strong relationship between ghrelin, glucose and IGF-1/IGFBP-3 metabolism in healthy children and adolescents. The aim of our study was to evaluate the influence of ghrelin (total and acylated) and adiponectin in glucose and IGF-1/IGFBP-3 metabolism in children and adolescents with type 1 diabetes mellitus (T1DM), before and after a period with increased physical activity and improved quality of metabolic control.

Methods: Twenty-eight children and adolescents (14 boys; mean age 12.14 years) with T1DM (mean duration of diabetes 4.8 years) attending a two-week-diabetes-camp that features increased regular activities were studied. Serum levels of ghrelin (total and acylated), adiponectin, cortisol, GH, IGF-1, IGFBP-3, insulin and leptin were measured on day 1 and on day 14. Improvement of metabolic control was documented with HbA1c-levels on day 1 and day 14, glucose levels and insulin doses were determined daily.

Results: Mean insulin dosage decreased from 0.87 U/kg (day 1) to 0.78 U/kg (day 14), mean HbA1c levels decreased from 8.6 (day 1) to 8.3 (day 2), but the changes failed to be significant. We found significant changes in total ghrelin ($P = 0.04$) with a decrease of levels from day 1 (768.9 ± 178.1) to day 14 (716.3 ± 168.6). HbA1c levels were significantly and inversely related to acylated ghrelin ($r = -0.35$, $P = 0.03$) and they were significantly related to the difference of adiponectin before and after the two weeks ($P = 0.04$).

Changes in IGFBP3 were inverse significantly related to changes in total ghrelin ($r = -0.43$, $P = 0.012$).

Conclusions: The changes of ghrelin suggest that improvement of metabolic control might be associated with lower ghrelin levels. Thus ghrelin may play an important role in metabolic control of T1DM. The changes in our study may describe an influence in insulin sensitivity although the observed period was very short and further studies will be needed to confirm this information. IGFBP-3 levels seem to have opposite effects on circulating ghrelin concentrations in children and adolescents with T1DM, suggesting that IGFBP-3 may have a positive feed-back effect on ghrelin.

O/THU/1/06

Risk of type 2 diabetes affects all socio-economic groups in an urbanised population: a prospective childhood study

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Objectives: In today's rapidly changing society, we question whether socio-economic deprivation is still a risk factor for excess weight gain and thus risk of type 2 diabetes (T2D) in contemporary children. The evidence is largely historical and merits re-examination. We also question whether *change* in adiposity or metabolic risk over time is associated with low socio-economic status (SES).

Methods: Two hundred and fifty-one healthy pre-pubertal children (146 boys) from the prospective EarlyBird cohort, recruited from

53 primary schools, covering a wide range of SES. Deprivation: postcode-based Index of Multiple Deprivation (IMD). BMI SDs (UK 1990 norms), waist circumference, sum of five skinfolds, composite metabolic risk z-score (MetRisk) from fasting triglycerides, cholesterol/HDL, and HOMA-IR and BP, all measured at 5 years and again at 8 years.

Results: Mean IMD score was 21.7 (range 6.5–73.0), similar to the UK mean of 26.3. In boys, mean BMI SDs was 0.21 ± 1.08 at 5 years and 0.30 ± 1.10 at 8 years. BMI tended to be lower, rather than higher, with increasing deprivation, both at 5 years ($r = -0.18$, $P = 0.04$) and 8 years ($r = -0.17$, $P = 0.05$). Waist circumference was also inversely related to IMD score at 5 years ($r = -0.21$, $P = 0.01$) and at 8 years ($r = -0.20$, $P = 0.02$). Boys' skinfolds were not significantly related to IMD at either age (both $P > 0.12$). Importantly, changes in adiposity from 5–8 years were unrelated to IMD score (all $r < 0.14$, $P > 0.10$). There were no significant associations between IMD and MetRisk at 5 years ($r = -0.05$, $P = 0.59$) or 8 years ($r = -0.15$, $P = 0.08$), or change in MetRisk ($r = -0.14$, $P = 0.10$).In girls, mean BMI SDs was 0.51 ± 0.98 at 5 years and 0.55 ± 1.10 at 8 years. No measure of adiposity was related to IMD score (all $r < 0.10$, all $P > 0.31$), nor were changes in adiposity from 5–8 years related to IMD (all $r < 0.15$, $P > 0.11$). MetRisk and change in MetRisk were both unrelated to IMD (all $r < 0.1$, $P > 0.27$).

Conclusions: Our data do not support the popular assumption that obesity, metabolic disturbance and risk of diabetes is still more prevalent among poorer children. Indeed, we found evidence to the contrary in boys, making lack of power an unlikely cause. Findings were consistent when using three alternative measures of SES: free school meal entitlement, parental income and occupation, suggesting robust data. With all urban neighbourhoods affected by an increasingly obesogenic environment, all youngsters may now be vulnerable, with population-wide implications for the prevention of type 2 diabetes in contemporary youth.

O/THU/1/07

Disposition modeling of blood glucose control in children: novel insights from a longitudinal study

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Diabetes is preceded by a prodrome during which the feed-back loop that controls blood glucose seeks to compensate for failing function by adjusting its call on beta cell reserve (%B) relative to insulin sensitivity (%S). We tracked the changing disposition of glucose control over time in children.

Methods: We monitored 218 healthy children (126 boys) from the EarlyBird cohort annually from 5 to 10 years, measuring change in BMI SDs, fasting glucose, HOMA-%S, HOMA-%B and their product, the disposition index (DI). The relationship between %B and %S was plotted year-by-year; children were divided into tertiles of BMI SDs at 5 years (H = heaviest, L = lightest) to examine the impact of BMI on disposition.

Results: Glucose rose (4.3–4.8 mmol/l, $P < 0.001$) throughout the 5-year-period, consistent with the fall in DI (186.3–115.6, $P < 0.001$) and progressive weakening of loop control. BMI did not change significantly from 5 to 7 years (+ 0.02SD, $P = 0.4$) but rose substantially from 7 to 10 years (+ 0.17SD, $P < 0.001$). The disposition map for the cohort (figure) shows that, from 5 to 7 years, the fall in DI was attributable to loss of %B, with some compensatory rise in %S. From 7 years, however, %S ceased to rise further, the trajectory reversed, and the continuing fall in DI became attributable to falling %S (rising insulin resistance) with a compensatory rise in %B. When analyzed by BMI tertile, %B was higher and %S lower in H than L at each age ($P < 0.01$ at 5, 7, 8, 9, 10 years; not significant at 6 years). The switch in trajectory occurred earlier (6–7 years), and at lower sensitivity (221%), in H than L children (7–8 years, 331%).

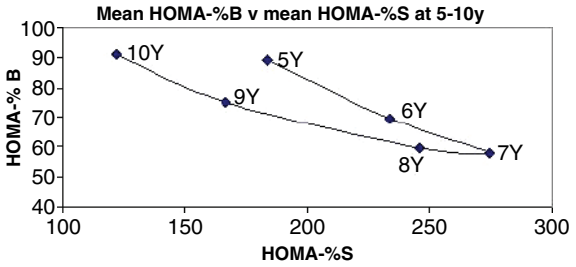

Figure 1. *Disposition map.*

Conclusions: The switch in disposition is a novel observation, demonstrating how the loop reverts to beta cell reserve once insulin sensitivity nears its limit. The inflexion may be a crucial prelude to beta cell insufficiency, and BMI appears to be a key determinant of the stage at which it occurs. Disposition mapping may help us better understand the changes that lead to childhood diabetes.

O/THU/1/08

Relationship between the K121Q polymorphism of ectonucleotidepyrophosphatase/phosphodiesterase 1 and obesity in children and adolescents

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Background: Obesity is considered to be a multifactorial trait resulting from the combined influence of genetic and environmental determinants. Nucleotide pyrophosphatase/phosphodiesterase (ENPP1) is an inhibitor of insulin-induced activation of the insulin receptor. Clinical studies have demonstrated theK121Q variant in the 4 exon of the ENPP1 gene might be associated with the obesity and insulin resistance in western children.

Objective: To study the relationship between K121Q variant and insulin resistance in obese children and adolescents among Chinese Han populations.

Method: Four hundred and sixty-four obese/overweight and 223 normal children and adolescents were recruited. The k121Q variant of the ENPP1was genotyped by Taqman-MGB technology; their Body mass index (BMI), fasting insulin level, total cholesterol, triglyceride, and plasma glucose were determined. HOMA-beta and HOMA-IR were calculated.

Result: i) The frequencies of K alleles the 0.894, Q allele is the 0.106 in the obese group, 0.907 and 0.093 in the overweight group, 0.879 and 0.121 in the normal group, respectively. There were no significant statistic differences in obesity/overweight group and normal group with different genotypes ($OR = 0.48$, $P = 0.452$).

ii) Logistic regression analysis showed that the K121Q variant of the ENPP1 gene were not associated with the fasting Insulin, glucose and lipid.

iii) No association was found between the k121q variants of ENPP1 and HOMA-beta (0.28) or HOMA-IR ($P = 0.94$); No significant association existed between the different sex with HOMA-beta or HOMA-IR.

Conclusions: We find no evidence that the ENPP1 K121Q genotype is associated with obesity and insulin resistance in Chinese children and adolescents.

O/THU/1/09

Clinical and genetic heterogeneity among children with pancreatic developmental disorders

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Objectives: Pancreatic agenesis is a rare condition and only a limited number of cases have been described so far. Although some patients show isolated pancreatic involvement, it may also present in association with several different extrapancreatic features. Biallelic mutations in either *IPF1* (two cases) or *PTF1A* (three patients from two unrelated families) have been described; however, the cause of the disease remains unknown in most patients. The aims of this study were to evaluate the relative contribution of pancreatic developmental disorders (agenesis or hypoplasia) to permanent neonatal diabetes (PNDM), to assess the clinical phenotype of those patients, and to test the known genetic causes of pancreatic agenesis.

Methods: We identified those patients with pancreatic agenesis or hypoplasia among a large cohort of patients with PNDM (diagnosis <6 months). Relevant clinical information was obtained from the patients clinical records. The coding regions and the intron-exon boundaries of *IPF* and *PTF1A* were sequenced.

Results: A pancreatic developmental disorder was found in 23 patients (14 males) out of a cohort of 308 patients with PNDM (7.5%). Thirteen patients showed isolated pancreatic agenesis, whilst associated extrapancreatic features were reported in 10 cases (43.5%). Among them, six children (60%) had a congenital heart defect (mainly conotruncal anomalies) and four patients (40%) had biliary tract defects, including gallbladder agenesis or hypoplasia. Other developmental disorders, such as duodenal atresia, diaphragmatic hernia or holoprosencephaly, were present in isolated cases. Consanguinity was reported in all but one of the patients with isolated pancreatic agenesis. In contrast, only one patient with a complex phenotype (pancreatic and gallbladder hypoplasia, duodenal atresia and anterior anus) was born to consanguineous parents. A homozygous P191T mutation in *PTF1A* was found in a patient with isolated pancreatic agenesis. No mutations in *IPF1* were identified.

Conclusions: Pancreatic developmental disorders are responsible for 7.5% of cases of PNDM. 55% of cases have isolated pancreatic agenesis and this seems to be a recessive condition. The remaining 45% show associated extrapancreatic features and the majority of cases are spontaneous. The underlying genetic defect is unknown in the majority of patients.

O/THU/1/10

Congenital hyperinsulinemic hypoglycemia: glucose metabolism after subtotal or limited pancreatectomy

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Objective: To describe the postoperative evolution of congenital hyperinsulinemic hypoglycemia. Diffuse hyperinsulinism requires subtotal pancreatectomy when resisting to medical treatments; focal adenomatous hyperplasia can be treated by limited pancreatectomy.

Methods: One hundred and ten patients have been operated between 1984 and 2006, 87 diagnosed in the neonatal period, 23 after 1 month; 58 (52 neonates, six infants) had a diffuse form, 52 (35 neonates, 17 infants) had a focal form. Follow-up: periodic measurements of pre- and postprandial plasma glucose levels over 24 hours, OGTT and IVGTT. Cumulated incidence of hypo- or hyperglycemia/insulin treatment was estimated by Kaplan–Maier analysis.

Results: Children with diffuse CI: 59% still had hypoglycemias after extensive surgery, but symptoms were mild or absent, mainly pre-prandial; they responded to medical treatments and disappeared within 5 years. A specific situation, combining pre-prandial hypoglycemia and postprandial hyperglycemia was observed in 1/3 of the patients. Hyperglycemia was found in 53% of the patients immediately after surgery; its incidence increased regularly to 100% at 13 years of age. Insulin was needed immediately after surgery and definitely in only eight patients. The progression to insulin dependence was variable for the other patients: insulin was started in six patients (three postoperative, three at 0.5–3.3 years), but it was stopped after 8–21 months; 13 patients had definitive insulin treatment at 0.5–14.8 years (8.4 ± 4.2 years). The cumulated incidence of insulin-treated patients was 42% at 8 years, 91% at 14 years. For the focal forms, hypoglycemia was rare ($n = 6$) and transient; hyperglycemia was rare ($n = 4$), mild (>11 mmol/l at 30–60 min of the OGTT) and transient. Plasma insulin responses to IVGTT correlated with plasma insulin levels and inversely to plasma glucose levels, at 30 min of the OGTT.

Conclusion: Follow-up should consist in pre-prandial plasma glucose measurements and OGTT during the first 5 years in diffuse forms, the first year in focal forms; OGTT should be performed after 1 year in focal forms and after 5 years in diffuse forms. The incidence of early insulin-dependent diabetes is extremely high in operated diffuse forms; it should not be totally excluded in the very long-term in focal forms.

Diabetes Care, Education and Psychosocial Issues

O/FRI/1/01

African youth ambassadors are helping to improve the lives of people with diabetes

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Objectives: In order to increase world awareness of the need for a United Nations Resolution on Diabetes (UNR), the International Diabetes Federation (IDF) selected 25 Youth Ambassadors (YAs) from around the globe. Five young adults with diabetes were chosen from Africa, based on their leadership abilities and their demonstrated commitment to changing the lives of people with diabetes. The countries they represented included Ghana, Kenya, Rwanda, South Africa, and Zimbabwe.

Methods: The African YAs met at an IDF conference in Cape Town in 2006 to formulate action plans for their respective countries. Together with their national diabetes associations, they worked to gain local signatures of support for the UNR. To raise worldwide awareness, they wrote blogs sharing their personal stories of living with diabetes in countries with limited access to life-saving diabetes medications, supplies and education. They met personally with government officials to persuade them to support the resolution's passage.

Results: The UN Resolution on Diabetes was passed in December 2006, and the first World Diabetes Day was held on November 14, 2007. The African YAs continue to lead advocacy efforts for persons with diabetes in their countries. Through a diabetes education video, public speaking and media engagement, the Ghanan YA has spread the message that children get diabetes. The Kenyan YA successfully applied to the World Diabetes Foundation for a grant to fund camps to train youth with diabetes as peer educators. The Rwandan YA has worked to strengthen diabetes education in her community. The South African YA established a non-profit organization entitled 'For Youth with Diabetes', to give a voice to youth living with diabetes and provide financial support. In Zimbabwe, the Youth Ambassador worked with the local diabetes association to launch a series of workshops in the schools to provide education on the prevention and care of diabetes.
Conclusions: The Youth Ambassadors were a catalyst to show the world why a UN Resolution on Diabetes was urgently needed. They encouraged others to ignore stereotypes and to understand that people with diabetes can achieve their life goals and can affect change in their communities. Committed young people, through their individual and collective efforts, can make a significant difference on the African Continent, by their work to advocate, educate and facilitate the lives of those living with diabetes.

O/FRI/1/02

Transition towards adult care: smooth or slippery?

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Objectives: Evaluation of current attitudes and practices of ISPAD (International Society of Pediatric and Adolescent Diabetes) members toward transition from pediatric to adult diabetes care.
Methodology: A short questionnaire was sent by e-mail to all ISPAD members (n = 578) to investigate current beliefs and approaches among these members regarding transition of adolescents with diabetes to adult care. A follow-up e-mail with the questionnaire was sent to the membership 4 months later.
Results: In total, 92 questionnaires were completed and returned, representing 16% of the membership and 36 different countries. Although 76% of the responders report that youth are followed in their pediatric clinics at least until the age of 18 years, 36 % of pediatric clinics are seeing adults beyond the age of 25 years. Conversely in 30% of the centers, children < 16 years are followed by adult diabetologists or internists. While the majority of responders propose to begin preparing youth for transition to adult care at least 1 year prior to the actual transfer, a structured transition approach exists in only about half of the centres, generally targeting youth between 16 and 25 years of age. The effectiveness of transition is monitored in 34% of the centers; two centers (with structured transiton programs) have evaluated their drop-out rates (6% and 10–20% respectively).
Conclusion: As adolescence comes to an end and youth leave home to go to college or enter the workforce, they experience many competing priorities and are at high risk for dropping out of health care. Consequently they miss important opportunities for complication screening, the early detection and treatment of problems as they arise. More than ever teens require access to uninterrupted, comprehensive and accessible care. According to this survey among ISPAD members in 36 countries, the actual situation for transitioning teens is far from optimal and requires major improvement.

O/FRI/1/03

Is pre-bed blood glucose level (BGL) predictive of 3 am or waking BGL in adolescents with TIDM on glargine?

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Background: It has been common past practice to advise a pre-bed BGL of 7–10 mmol/l as 'safe' although pre-bed BGL has been shown to be poorly predictive of overnight hypoglycaemia in young patients receiving isophane insulin (Porter et al. J Pediatr 1997). Anecdotal experience with glargine suggests that advising this range often results in morning hyperglycaemia and patients can safely go to bed with lower BGLs. Educators are commonly asked if a safe pre-bed BGL range can be given and data is lacking on this question.
Aim: To examine overnight BGL readings in adolescents receiving glargine and examine whether pre-bed BGL predicts 3 am or waking BGL.
Methods: BGLs were analysed from 812 nights in 29 subjects (age 13–18 years) who were participating in a study examining Flexible Eating Insulin Dose Adjustment. All subjects received multiple daily injections (MDI) with pre-prandial short-acting analog or regular insulin and once daily glargine. Pre-bed, 3 am and waking BGL were measured by standard home BGL monitoring and diarized. Data from each night were treated as independent for the purpose of this analysis. Median and IQR are shown.
Results: Extra food was taken as a precaution pre-bed on 56 nights (7%) or because of hypoglycaemia on 86 nights (11%). This subgroup had pre-bed BGL of 4.4 [3.7–6.0] mmol/l and woke with 8.0 [5.3–11.9] mmol/l. For those with no reported extra food or hypoglycaemia (n = 513 nights), pre-bed BGL was 9.7 [7.2–12.8], 3 am 9.8 [7.0–12.3] and waking 8.4 [6.2–11.9] mmol/l. The change of -1.3 [-4.6–2.5] mmol/l from pre-bed to waking was significant (P < 0.0001). No threshold pre-bed BGL value (< 6, 6–7, 7–8 or > 8 mmol/l) predicted waking BGL > 4 or > 5 mmol/l. There was a very weak relationship between pre-bed BGL and 3 am BGL (r = 0.29, P = 0.0002) and between pre-bed BGL and waking BGL (r = 0.15, P = 0.001) which is of little practical significance.
Conclusion: Overall the reported incidence of nocturnal hypoglycemia was low in these subjects. Pre-bed BGL was not predictive of 3 am or waking BGL but median BGL fell gently through the night. These data suggest that a modified pre-bed BGL target of 5–7mmol/l is not unsafe, although it is likely that other factors may prove to be more predictive of night-time BGL (e.g. food intake, exercise) and require further evaluation.

O/FRI/1/04

Self monitoring of blood glucose in CSII-treated adolescents with type 1 diabetes

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Many diabetic clinics in Sweden recommend four self monitoring of blood glucose (SMBG) per day for CSII treated adolescents, however it is common that CSII treated adolescents with type 1 diabetes perform fewer SMBG than recommended.
Objectives: To compare age, diabetes duration, HbA1c value, frequency of daily bolus doses and health related quality of life (HRQOL) measured with the 'Disabkids' questionnaire, between CSII treated adolescents who perform < 4 four SMBG per day and CSII treated adolescents who perform four or more.

Methods: Data were obtained from 91 CSII treated adolescents (aged 12–18), who were regularly attending four different paediatric diabetes clinics in Sweden, all recommending four SMBG per day. Unpaired *t*-test was used to compare the group who took < 4 SMBG/day with the group who took ≥ 4 SMBG/day. Nominal logistic regression analysis was used to compare the two groups.

Results: The mean frequency of SMBG/day was 3.2. Forty-four percent (40/91) of the adolescents performed four or more SMBG/day. The adolescents who performed the recommended frequency of SMBG were younger, had shorter diabetes duration, had lower HbA1c, took more daily bolus doses and perceived less impact of the medical treatment. There were no differences in general HRQOL between the two groups. Nominal logistic regression analysis showed that of these factors, only HbA1c was independently associated to ≥ 4 SMBG/day ($P < 0.001$).

	< 4 SMBG/day $n = 51$	≥ 4 SMBG/day $n = 40$	*P*-value
Age years	15.3 + 1.9	14.2 + 2.2	0.008
Duration of diabetes years	8.8 + 3.5	6.7 + 3.8	0.007
HbA1c*%	7.8 + 1.1	6.7 + 0.8	< 0.0001
Daily boluses Freqency	4.1 + 1.8	5.5 + 1.6	< 0.001
HRQOL (general) Scores (0-100, higher scores higher satisfaction	76.8 + 11.6	78.2 + 9.1	0.527
HRQOL (medication) Scores (0-100, higher scores higher satisfaction)	72.4 + 18.0	81.2 + 11.9	0.01

*Measured with Mono S: normal reference: 3.4–5.0%, compared with the DCCT's HbA1c units the Mono-S method gives approximately 1% unit lower results.

Conclusion: Fifty-six percent of the adolescents performed fewer SMBG than recommended. The frequency of SMBG was associated with the metabolic control. The diabetes teams need new strategies to motivate adolescents to perform more SMBG.

O/FRI/1/05

No association between capability for abstract reasoning and glycemic control in children and adolescents with type 1 diabetes (T1D) treated with pump or injection therapy

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Objectives: Raven's Progressive Matrices are multiple choice tests of abstract reasoning. In each test item, a candidate is asked to identify the missing segment required to complete a larger pattern. Large normative cohorts are available. We investigated a possible association of capabilities for abstract reasoning with glycemic control in insulin pump (CSII) or multiple injection therapy (MDI).

Methods: After informed consent was taken patients aged between 6 and 18 years with type 1 diabetes and a blood glucose in the normal range at the time of testing completed 60 items on a computer screen (Raveńs Standard progressive Matrices Version 31.0, Schuhfried GmbH, Austria). This test is non-verbal for use from 5 years on, with items becoming increasingly difficult, requiring greater cognitive capacity to encode and analyze information. All items are presented in black ink on a white background. HbA1c (DCA 2000), pre-test laboratory blood glucose and clinical data were recorded and evaluated by SPSS.

Results: A total of 105 consecutive eligible patients with T1D (49.5% male) visiting our outpatient department were included and completed the study (mean age 12.9 ± 3.1 years; diabetes duration 5.1 ± 3.5 years). Forty-seven patients were on CSII (age: 12.8 ± 2.9 years), the remaining 58 on MDI (age: 13.0 ± 3.3 years). HbA1c ranged from 4.9 to 11.1% with a mean of 7.5 ± 1.1%. The patients took 19.0 ± 6.0 min for the test and had on average 39.8 ± 9.9 correct answers. This result corresponds well to the normative data (41.3 ± 29.1% of the norm corresponding to a non-verbal IQ of 95.4 ± 15.2). As expected correct answers increased with age ($r = 0.26$, $P = 0.007$) with no influence of gender or diabetes duration. Patients with a HbA1c within the target range (≤ 7.4%, $n = 59$) and those above showed identical results even after correction for age: 39.6 ± 9.9 vs. 40.0 ± 10.2 ($P = 0.77$). Also patients treated with CSII or MDI were not different: 40.2 ± 9.5 vs. 39.7 ± 10.4 ($P = 0.82$).

Conclusions: Testing of abstract reasoning in children and adolescents with diabetes show a normal distribution of test results. Glycemic outcomes are unrelated to test results of practical intelligence also in potentially more challenging forms of therapy such as insulin pump treatment. Provided that patients receive proper individualized diabetes education, lower capabilities of practical intelligence in children and adolescents with diabetes should not preclude the use of modern therapies such as insulin pump therapy.

O/FRI/1/06

'Physiological bolus' – possibility of insulin pump therapy

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Introduction: Insulin pump (IP) therapy gives possibility for the most physiological insulin supplementation in TYPE 1 diabetes mellitus (T1DM) patients. But lag time for insulin transport to cell is present even in patient on IP, and makes covering of meal with insulin different from physiological secretion of insulin in two phases.

Aim: To test our concept of more physiological bolus in pediatric patients on IP therapy. Bolus consists of normal and dual bolus given during same meal.

Methodology: Correction bolus, if it is necessary, was given regularly before meal, and meal starts 10–15 min after it. Estimated bolus dose of insulin for meal was given divided in three parts: first at the beginning of meal, than 10 min later other two thirds like dual bolus (ratio and length of square depends of carbohydrate contents of meal). Blood glucose (BG) was taken before meal, after meal (average duration of meal 20 min), 1 hour and 2 hours after meal. Patients were randomized in 'physiological bolus' and plane bolus group which were compared.

Results: This study lasted 6 months and average number of analyzed meals in both groups was 88 per patient. BG results taken 10 min after start of meal were less different than target in 'physiological bolus' group ($P < 0.05$). Frequency of hypoglycemia during and after meal was also less in this group (3.2 per patient monthly vs. 5.5, $P < 0.05$). BG results after meal were under 10 mmol/l in in 93% patients with 'physiological bolus' group. Average glycosylated hemoglobin (HbA1c) was significantly lower better in 'physiological bolus' group 7.3% vs. 8.1 % ($P < 0.001$).

Conclusion: Concept of 'physiological bolus' resulted in better metabolic control of T1DM in our IP treated patients and in less variability of glucose. We recommend this pattern of bolus for all IP treated patients.

O/FRI/1/07

Growth hormone increases intrahepatic rates of glycogen synthesis in growth-hormone deficient adults

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We have previously shown that growth hormone replacement is associated with a 40% increase in intrahepatic rates of glycogen synthesis during refeeding in children with idiopathic growth hormone deficiency.

Objectives: To see whether growth hormone replacement in adults with growth hormone deficiency would be associated with a similar increase in the rates of intrahepatic glycogen synthesis and to determine whether such an increase in the rates of intrahepatic glycogen synthesis was due to increased direct uptake of glucose by the liver (direct pathway) and/or increased rates of gluconeogenesis (indirect pathway).

Methods: Five adults with growth hormone deficiency were randomly studied twice, off and on growth hormone replacement (OFF and ON, respectively). Patients were fasted overnight and then infused with glucose (15.7 ± 0.4 μmol/kg/min). Intrahepatic rates of glycogen synthesis were estimated by infusing [1-^{14}C]galactose to steady state, administering acetaminophen, and measuring the specific activity (SA) of [^{14}C]acetaminophen glucuronide in the urine in order to calculate steady state intrahepatic uridine diphosphate glucose (UDP-glucose) flux. The percentage of UDP-glucose coming from direct uptake of glucose was estimated by infusing [3-^{3}H]glucose, and measuring the SA of [^{3}H]acetaminophen glucuronide in the urine.

Results: Growth hormone replacement was associated with a 34% increase in estimated rates of intrahepatic glycogen synthesis (4.42 ± 0.76 vs. 5.90 ± 0.81 μmol/kg/min for OFF and ON, respectively; $P < 0.05$) The percentage of glucose coming from direct uptake of glucose was not affected by growth hormone treatment (44.6 ± 5.9% vs. 47.4 ± 5.8% for OFF and ON, respectively). In summary, growth hormone treatment in growth hormone deficiency adults increased estimated rates of intrahepatic glycogen synthesis by increasing the amount of glucose entering UDP-glucose via the direct and indirect pathways equally.

Conclusion: Decreased hepatic glycogen stores seen in children with growth hormone deficiency may be not only due to decreased rates of gluconeogenesis, but also to decreased rates of conversion of glucose to UDP-glucose.

O/FRI/1/08

Association between blood glucose, HbA1c and glucagon levels as glycemic indicators in children with type 1 diabetes of longer than 2 years' duration

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It has been reported that glucose stimulates glucagon secretion at both high and low concentrations, in a dose-dependent manner. This glucose-sensing glucagon secretion presumably acts via the KATP channel complex, Kir6.2/SUR1, occurring in pancreatic aipha-cells. Pörksen et al. reported a strong association between the glucagon levels and postprandial blood glucose levels, but not HbA1c levels, in adolescents with type 1 diabetes at 6 and 12 months after the diagnosis.

Objectives: We investigated the association between the blood glucose, HbA1c and glucagon levels to elucidate the significance of these parameters as indicators of glycemic control in children with type 1 diabetes of longer than 2 years' duration.

Methods: The study was conducted on 60 Japanese children, 25 males and 35 females, aged 13.3 ± 4.6 years, having type 1 diabetes of longer than 2 years' duration. Most of the patients had absent pancreatic beta-cell function, with a serum C-peptide level of < 0.2 ng/ml. None of the patients had chronic diabetic complications, including diabetic neuropathy and lack of awareness of hypoglycemia. We concurrently examined the blood glucose, HbA1c and glucagon levels on an outpatient basis in the patients.

Results: The mean blood glucose, HbA1c and glucagon levels were 174 ± 97 mg/dl, 7.7 ± 1.3% and 84.0 ± 32.6 pg/ml, respectively. The glucagon levels were highly correlated with the blood glucose levels ($r = 0.553$, $P < 0.0001$) and mildly, but significantly, correlated with the HbA1c levels ($r = 0.301$, $P = 0.0192$). Patients with high blood glucose levels (> 300 mg/dl: 302–399 mg/dl) had significantly higher blood levels of glucagon than those with lower blood glucose levels of 50–100, 100–200 and 200–300 mg/dl, i.e. 139.4 ± 47.2 vs. 78.4 ± 17.3, 82.4 ± 21.0 and 98.3 ± 29.2 mg/dl, respectively; $P = 0.0003$, 0.002 and 0.017, respectively). There were no significant differences in the blood glucagon level between patients with low blood glucose levels (< 50mg/dl: 42–49 mg/dl) (93.8 pg/ml) and those with blood glucose levels of 50–100, 100–200 or 200–300 mg/dl. On the other hand, patients with high HbA1c levels (> 9%) had significantly higher blood levels of glucagon as compared with those with lower HbA1c levels (< 7%), i.e. 113.3 ± 53.4 vs. 80.8 ± 18.4 pg/ml, $P = 0.0291$). The blood glucagon levels were not associated with the age or sex of the patients.

Conclusions: Our results suggest that patients with poor glycemic control are likely to exhibit high blood levels of glucagon, as high blood glucose levels of 302–399 mg/dl can effectively evoke glucagon secretion. High glucagon levels might aggravate glycemic control progressively, leading to elevation of the HbA1c levels. On the other hand, low blood glucose levels of 42–49 mg/dl, which does not represent severe hypoglycemia, were not sufficient to stimulate counter-regulatory glucagon release.

O/FRI/1/09

Cerebral blood flow during experimentally induced moderate hypoglycaemia in diabetic children

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Glucose is carried to the brain by the circulating blood flow and it is the main fuel utilized by the brain tissue. It has been demonstrated that the human brain is relatively resistant to the detrimental effects of moderate hypoglycemia. The observed lack of severe detrimental effects of hypoglycemia on the human brain is believed to be the result of protective mechanisms against the consequences of decreased glucose availability. Increasing cerebral blood flow in order to supply the required amount of substrate when blood sugar is low is thought to be one of these protective mechanisms. We have studied the effect of moderate hypoglycemia (serum glucose level 3.4 ± 0.1 mmol/l: mean ± SEM) on cerebral blood flow of 36 insulin dependent diabetic children (12–18 years), 13 insulin dependent diabetic adults (19 years and older), and 12 control adult (19 years and older). Intravenous xenon-133 clearance method was used to measure the regional cerebral blood flow. Euglycaemia and moderate hypoglycaemia was induced by insulin-glucose clamp technique. Cerebral blood flow at euglycaemic baseline showed marked inter-subject variability (58.0 ± 11.49; mean ± SD). Cerebral blood flow at euglycaemia is significantly

higher in young diabetic children when compared to older group of diabetic subjects; 65.45 ± 10.09 at 12–15 years, 56.01 ± 9.17 at 19+ years ($P = 0.000$). Cerebral blood flow showed a small but significant increase during hypoglycaemia when compared to the cerebral blood flow at baseline euglycaemia in all age groups (from 58.01 ± 11.49 to 61.04 ± 11.06 at 12–18 years, $P = 0.000$ and from 54.01 ± 9.17 to 56.91 ± 7.99 at 19+ years, $P = 0.000$). There was a marked inter-subject variability in CBF changes during hypoglycaemia. When we investigated the changes in cerebral blood flow with age, there was a trend that showed the youngest children with the highest baseline CBF to have the least change in cerebral blood flow (4.7% ± 6.71% at 12–15 years, 6.8% ± 7.04% at 16–18 years, 8.8% ± 8.05% at 19+ years).

Conclusion: This study demonstrates that age is a determinant of cerebral blood flow. The youngest children had the highest baseline CBF. However, inter-subject variability suggests that there are factors other than age that influence CBF at euglycaemia. Our data confirms the finding that experimentally induced moderate hypoglycaemia causes a variable degree of change in CBF.

O/FRI/1/10

Stimulated C-peptide levels below 200 pmol/l 1 month after diagnosis can predict C-peptide levels after 6 and 12 months. Results from the Hvidøre Study Group

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Background and aim: Measurement of mixed-meal-stimulated C-peptide has been described to be the most appropriate primary efficacy endpoint for trials aimed at demonstrating the effect of therapies to preserve β-cell function in Type 1 Diabetes. In 1987 the DCCT group described in an adult patient group, that stimulated C-peptide level above 200 pmol/l was associated with significantly lower mean fasting glucose and lower HbA1c levels and characterised these patients as C-peptide responders. The aim of this study was to investigate whether there were still differences in a paediatric patient group with stimulated C-peptide values below 200 pmol/l 1 month after diagnosis with respect to C-peptide levels, HbA1c, insulin dose (u/kg/24 h), stimulated blood glucose after 6 and 12 months with type 1 diabetes.

Material and methods: Fifty-three children and adolescents under 16 years were enrolled in the study. Mixed-meal-stimulated C-peptide was measured 1, 6, and 12 months after diagnosis. The patients were divided into three groups according to their C-peptide value at 1 month: 1. 0–49 pmol/l, 2. 50–99 pmol/l, 3. 100–199 pmol/l. HbA1c was determined centrally at 0, 1, 3, 6, 12 months. Prediction of C-peptide (logarithmic scale), HbA1c, insulin dose and stimulated blood glucose at 6 and 12 months was done by multiple regression analysis including covariates for age, gender and the 3 C-peptide subgroups (1 month).

Results: Thirteen patients had stimulated C-peptide between 0–49 pmol/l, 16 between 50–99 pmol/l and 24 between 100–199 pmol/l. The analyses showed that patients with a stimulated C-peptide level between 0 and 49 pmol/l 1 month after diagnosis had 52% lower C-peptide (estimate -0.74, $P = 0.05$) after 6 months and 66% lower C-peptide (estimate -1.07, $P = 0.009$) after 12 months compared to the other subgroups. There were no associations of stimulated C-peptide below 200 pmol/l with HbA1c, insulin dose and stimulated blood glucose.

Conclusion: Even within the patient group with stimulated C-peptide levels < 200 pmol/l 1 month after diagnosis the actual value can predict C-peptide levels at 6 and 12 months. There was no association to the other clinical endpoints in this rather restricted C-peptide range which may indicate that the relationship of each endpoint to stimulated C-peptide may be different.

Acute and Chronic Complications, Genetics and Immunology

O/FRI/2/01

Influence of blood glucose level on QT interval in children and adolescents with type I diabetes at long glucose and ECG monitoring

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Background: Clinical hypoglycemic episodes in Type I diabetes patients can lead to lengthened QT intervals which is associated with the risk of sudden cardiac death. Regular insulin injections can also influence the QT interval. The influence of hyperglycemia on the length of the QT interval in this category of patients is not sufficiently studied. The main aim of this investigation is to ascertain blood glucose levels leading to lengthened QT intervals.

Methods: Simultaneous ECG and blood glucose monitoring was carried out in 43 Type I diabetes patients at the age of 7–17 (12.8 ± 2.7). A group of 37 healthy children and adolescents aged 7–16 (11.0 ± 3.4) was used as control. ECG monitoring was made in three leads within 1–3 days, software including a module of automatic QT interval measurement and QT correction on the heart rate was made by Bazett formula.

Results: A reliable QTc lengthening was observed during 24 hours with blood glucose levels below 3 mmol/l and above 19 mmol/l as compared with other blood glucose values (437 ms and 447 ms against 430 ms, $P < 0.01$). With these blood glucose values the frequency of QTc lengthening reliably increased above 440 ms (46% and 62% against 335, $P < 0.01$). In healthy children and adolescents the mean duration and frequency of QTc interval lengthening was reliable to a lower degree than in Type I patients irrespective of blood glucose levels in Type I diabetes patients ($P < 0.01$) a moderate correlation between 24-hour-insulin dose injected and QT duration was also ascertained (correlation coefficient = 0.35, $P = 0.02$).

Conclusions: Both hypoglycemia and hyperglycemia are the cause of a lengthened QT interval which can be a pathogenic link in development of sudden cardiac death syndrome in Type I diabetes children and adolescents.

O/FRI/2/02

Accelerated ageing in type 1 diabetes demonstrated with Voxel-based analyses of volume and T2 images

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Introduction: Over the course of life, the brain of a person with diabetes features many symptoms that has been described as

'accelerated brain ageing' (Biessels GN et al. Eur J Pharmacol 2002, 441), but this largely remains an unproven hypothesis. This study investigates the rate of age-related structural change in a cohort of young adults with type 1 diabetes (T1DM) using MRI morphometry techniques.

Methods: Seventy-nine subjects with T1DM (age: 20.3 ± 4.3, 48 males) and 50 healthy controls (C; age: 20.7 ± 3.9, 25 males) were scanned on a 3T GE scanner. Both T1-weighted structural scans and T2 maps were acquired using a high-resolution FSPGR sequence (voxel size: $1.2 \times 1.2 \times 1.2$ mm) and an 8-echo CPMG relaxometry sequence (voxel size: $0.9 \times 1.81 \times 5$ mm) respectively. Analysis was carried out using voxel-based morphometric approaches (voxel-based morphometry, VBM, for volume and voxel-based relaxometry, VBR, for T2), with a smoothing kernel of 6 mm and inclusion of standard covariates in SPM2. Regression analyses were used to investigate the influence of age on volume and T2. In addition, regions-of-interest (ROI) were drawn in selected areas on the normalized images and extracted data analysed with a standard statistical package.

Results: T1DM relative to C had decreased grey matter in areas including the thalami, while T2 was decreased in areas including the lentiform nuclei (both $P < 5 \times 10^{-4}$ uncorrected). The voxel-based age regression indicated widespread areas of age-related volume and T2 reduction in T1DM that was accelerated in comparison to the normal rates of change seen in the C ($P < 5 \times 10^{-5}$ uncorrected). This was confirmed by ROI analysis using regions drawn in several of the structures identified as abnormal when compared to C. Age-related reduction of T2 in the lentiform nuclei is expected due to increasing iron deposition (Schenker C et al. Neuroradiology 1993, 35), but was greatly accelerated in the T1DM.

Discussion: The study provides the first evidence from quantitative structural imaging of age acceleration in a young population of T1DM patients relative to C. Increased rates of volume and T2 decrease are observed in widespread regions across the brain, including the basal ganglia and the thalamus, demonstrating the detrimental influence of T1DM on the CNS.

O/FRI/2/03

Neuropsychological profiles of young people with type 1 diabetes 12–15 years after disease onset

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We have previously documented central nervous system effects (lower IQ and structural and metabolite brain changes) in a controlled study of a T1DM cohort followed prospectively from diagnosis 12–15 years previously (ISPAD, 2006).

Aim: This abstract describes specific neuropsychological profiles in this cohort and their relationship to illness-related variables, such as age of disease onset, history of severe hypoglycaemia (SH) and chronic poor metabolic control.

Method: *Subjects.* Youth with T1DM ($n = 106$, mean age 20.5 years) and healthy community controls (C) ($n = 75$, mean age 20.7 years) seen at the Royal Children's Hospital, Australia. There were no group differences on baseline Full-Scale IQ measured at T1DM onset. SH was indicated by a history of ≥ 1 seizure/coma in the context of hypoglycaemia. Subjects with ≥ one third of lifetime HbA1c measurements greater than 9% were classified as having chronic poor metabolic control. *Neuropsychological assessment.* Scores on standardised tests were combined to form cognitive domains measuring language, perceptual reasoning, new learning, working memory, processing speed, mental efficiency and divided and sustained attention.

Results: T1DM showed reduced working memory capacity compared to C ($P < 0.05$). Within T1DM, youth with early onset disease (EOD; ≥ 5 years) performed more poorly than those with later onset disease (LOD) on tasks of sustained and divided attention, perceptual reasoning, new learning (all $P < .01$), working memory and mental efficiency (both $P < .05$). SH was associated with slower non-verbal processing speed and poorer verbal abilities (both $P < .05$). Chronic poor metabolic control was not significantly related to neuropsychological functioning. Of note, significantly fewer T1DM than C completed year 12, the final pre-tertiary school year in Australia ($P < .05$).

Cognitive domain	Illness variable	*P*-value
Verbal abilities	SH	.051
Perceptual reasoning	EOD	.001
New learning	EOD	.008
Working memory	T1DM EOD	.021 .046
Non-verbal processing speed	SH	.043
Mental efficiency	EOD	.012
Divided attention	EOD	.001
Sustained attention	EOD	.001

Conclusions: This study is the first to document neuropsychological profiles 12–15 years after diagnosis in a sample of T1DM whose IQ did not differ from C at disease onset. While the cognitive abilities of this group remain within the average range, even small decrements may have a significant effect on ability to acquire new skills and learn effectively in the classroom as evidenced by the lower number of TIDM to complete the final year of schooling.

O/FRI/2/04

Decreased esRAGE levels are associated with increased kidney volume and renal resistive indexes in normoalbuminuric pre-pubertal children and adolescents with type 1 diabetes

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Objectives: The AGE-RAGE pathway has been continuously considered as an important key mediator of early glomerular changes in patients with diabetes. Several growth factors and vasoactive molecules involved in early nephropathy have been shown to be directly produced as a consequence of RAGE activation. Furthermore, the C-truncated form of the endogenous secretory RAGE (esRAGE) has been shown to reveal the system function. Therefore, we tested whether impaired esRAGE concentrations are associated with early signs of diabetic nephropathy (DN), defined as changes in kidney volume and renal resistive indexes (RIs).

Methods: A group of 56 pre-pubertal and pubertal normoalbuminuric patients with type 1 diabetes (T1D) with at least 4 years diabetes duration were recruited and compared with 54 age, sex and pubertal stage matched controls. In all subjects, anthropometric measurements (height, BMI) were evaluated and

esRAGE was measured in fasting blood samples. Kidney ultrasonography was performed and renal volume was calculated using the ellipsoid formula and adjusted for body surface. In addition, Doppler ultrasonographicregistration of intrarenal RI was performed.

Results: No significant differences were found between pre-pubertal and pubertal patients with T1D and their matched controls in terms of height ($P = 0.48$ and $P = 0.139$, respectively) and BMI ($P = 0.06$ and $P = 0.12$, respectively). esRAGE was significantly lower in pre-pubertal ($P = 0.013$) and postpubertal ($P = 0.02$) patients with T1D compared with controls. In both pre-pubertal and pubertal subjects, mean-kidney volume ($P = 0.03$ and $P = 0.01$, respectively) and mean Doppler RI values ($P = 0.013$ and $P = 0.002$, respectively) were significantly increased in T1D patients when compared with controls. In a multiple regression analysis, an inverse relationship between esRAGE and adjusted kidney mean volume ($P = 0.042$, beta = -0.367) was documented in diabetic patients.

Conclusions: This study demonstrated decreased levels of esRAGE which appeared to be strongly related to increased kidney volume and RI in normoalbuminuric pre-pubertal children and adolescents with T1D, suggesting a potential role of esRAGE in the development of kidney disease. However, further longitudinal studies are required in order to define a causal-effect relationship between esRAGE and the risk of DN later in life.

O/FRI/2/05

Incidence of severe hypoglycaemia in children and adolescents with type 1 diabetes: a population-based study

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Objectives: Hypoglycaemia remains a central problem in the management of Type I DM, and limits the achievement of good glycaemic control, especially in children and adolescents.The diabetes Control and Complication Trial demonstrated that strict glycaemic control carries an increased risk of severe hypoglycaemia. On the other hand a high incidence of severe hypoglycaemia has been reported in patients with poor glycaemic control. The incidence of severe hypoglycaemia also varies, in different studies, from 3.1 to 85.7 episodes per 100 patients/year. Aim of our study was to determine the frequency of severe hypoglycaemia, and to identify associated risk factors in a population of children and adolescents with Type I diabetes.

Methods: We performed a 7 years prospective study enrolling 195 patients aged 13.9 ± 6.6 years, carried out by referring to the type I diabetes population-based register of the Abruzzo region of Italy. The incidence of severe hypoglycaemia, defined as seizures, unconsciousness, or both, was recorded. Glycated haemoglobin (HbA1c), insulin requirement, insulin therapy, duration of disease, age at onset, was also recorded. Wilcoxon test was applied to the interval variables. Value of $p < 0.05$ was considered statistically significant.

Results: There was 125 severe hypoglycaemic events during the study period; the prevalence was 39.5%, and the overall incidence was 8.25 per 100 patient-years. Significant predictors of hypoglycaemia were: diabetes duration < 5 years ($p < 0.01$), oldest age (a significant higher risk was recorded in patients older than 12 years: $p < 0.01$). Also a long-acting/short-acting insulin ratio lower than 0.5 seems to be associated to a higher number of severe hypoglycaemic episodes ($p < 0.01$). No relationship was found between hypoglycaemic episodes and HbA1c levels, insulin requirement, and number of insulin injections. The most common causes of severe hypoglycaemia were: incorrect insulin dose (33.8%), intense physical activity (31.2%), and dietary errors (29%).

Conclusions: In our patients we recorded a relatively lower incidence of severe hypoglycaemia, without any pronounced risk associated to lower HbA1c, or multiple injection insulin therapy.Risk factors for severe hypoglycaemia seems to be related to management of diabetes (short disease duration, peripubertal age). We believe that the main method to prevent severe hypoglycaemia is to educate patients and families to manage type I DM.

O/FRI/2/06

Angiotensin converting enzyme gene polymorphism, serum ACE and risk of nephropathy in Egyptian type 1 diabetic patients

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Objectives: To determine the relationship between polymorphisms in the angiotensin converting enzyme (ACE) gene, serum ACE activity and the risk of diabetic nephropathy.

Methods: A longitudinal study was carried out in a population of Egyptian type 1 diabetic children and adolescents (aged 12–18 years).Cases (40 type 1 diabetic patients with diabetic nephropathy) and controls (30 type 1 diabetic patients with normoalbuminuria) were genotyped with PCR protocols for detecting two DNA polymorphisms in the ACE gene: one in intron 7 detected with the restriction enzyme Pst I and the other in intron 16 identified as an insertion/deletion (I/D). Baseline urinary albumin/creatinine and serum ACE were measured at baseline and 6 months after treatment with ACE inhibitor for patients with nephropathy.

Results: The distributions of the genotypes for the I/D polymorphism in the ACE gene differed significantly between cases and controls ($P < 0.01$). The difference was due to an excess of DD homozygotes in cases than controls, implying a risk of nephropathy 1.29 times higher than other genotypes. As regards the gene distribution for pst I polymorphism, cases had significantly more +/+, +/- genotype while controls had excess -/- genotype which indicate that -/- genotype had a renoprotective role. Baseline serum ACE was significantly higher in cases compared to controls ($P < 0.001$). Urinary albumin/creatinine ratio and serum ACE were significantly reduced in patients with diabetic nephropathy after 6 months of treatment by ACE inhibitor and the response was more evident in diabetics with II or -/- genotype.

Conclusion: The results of the present study imply that the risk of diabetic nephropathy is influenced by genetic variability at the ACE locus, the responsible variant is mostly the I/D polymorphism intron16. Moreover, the deletion polymorphism in ACE gene could predict the therapeutic efficacy of ACE inhibition on proteinuria.

O/FRI/2/07

Diabetes-free survival among young children at high risk for type 1 diabetes (T1D) recruited from the general population

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Objectives: To evaluate risk factors associated with distinct diabetes-free survival rates among children with persistent positivity for multiple diabetes-related autoantibodies (DAA).

Methods: Children with HLA-conferred disease susceptibility, recruited from the general population, were observed since birth for beta-cell autoimmunity and T1D. The insulin secretion and sensitivity of the 218 children that developed persistent positivity for multiple DAAs (ICA, IAA, GADA and/or IA–2A) were assessed by an intravenous glucose tolerance test.

Results: The median age at diagnosis among the 70 progressors (32.1%) was 4.3 years, and the median follow-up time for the non-progressors 7.1 years. In the Cox regression analysis, T1D was predicted by the age at persistent multipositivity, IAA-level, weight-for-height, and relative insulin resistance (HOMA-IR/FPIR). After binary classification of the predictors by their medians (2.4 years, 11.8 RU, 99%, and 0.021 mmol/l, respectively), and the 10th percentile of FPIR in a healthy reference population (32.9 mU/l), the cumulative disease risks were: young age (68.8%; $P < 0.001$), low FPIR (65.2%; $P < 0.001$), high IAA (54.8%; $P < 0.001$), and increased relative insulin resistance (53.9%; $P = 0.002$). Among children aged < 2.4 years at persistent multipositivity, those with low FPIR ($n = 38$) had the highest progression rate (81.9%; $P < 0.001$), and their median age at diagnosis was 3.3 years. In all, low FPIR was related to a short diabetes-free survival time (median 1.8 years vs. 3.0 years in those with FPIR ≥ 32.9 mU/l, $P < 0.002$).

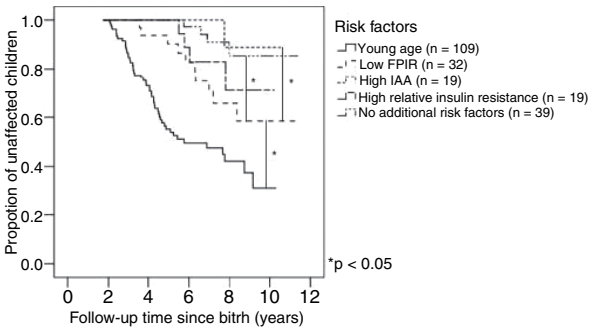

Figure 1.

Conclusions: Progression rates to T1D differ significantly even among children at high disease risk, judged by their autoantibody status. The highest disease risks associate with young age at persistent positivity for multiple DAAs and low FPIR. In this study population, relative insulin resistance and weight-for-height failed to explain the distinct progression rates.

O/FRI/2/08

Genetic risk markers related to diabetes-associated autoantibodies in pediatric patients with newly diagnosed type 1 diabetes

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Objectives: In the past years, several genetic risk markers of type 1 diabetes (T1D) such as HLA DR-*DQ* haplotypes and the *PTPN22* 1858T polymorphism have been identified. The aim of this study was to determine the prevalence of these markers in pediatric patients with T1D diagnosed at a single center in Germany and to assess their relation to diabetes-associated autoantibodies at the time of onset of the disease.

Methods: Blood samples of 243 patients were used for genotyping for the high-risk HLA haplotypes *DR3-DQ2 (DQA1*05-DQB1*02)* and *DR4-DQ8 (DRB1*0401/2/4/5-DQB1*0302)* ($n = 242$) and of *PTPN22* C1858T polymorphism. The patients (51.4% male) were diagnosed with T1D at a median age of 8.6 years (range 0.1–17.8 years). The T1D-related autoantibodies against GAD, insulin, and IA-2 (GADA, IAA, IA–2A) were analyzed at diagnosis.

Results: One hundred and sixty-six patients (68.6%) carried the *DR3-DQ2*, 114 (47.1%) the *DR4-DQ8* haplotype, while 41 (16.9%) patients were negative for both. The *PTPN22* CC genotype was detected in 177 (72.8%), CT in 58 (23.9%) and TT in eight (3.3%) patients, respectively, corresponding to an 1858T allele frequency of 15.2%. The prevalence of T1D-related autoimmunity at diabetes onset was 77.0% for IA–2A, 71.6% for GADA and 43.6% for IAA. There was no significant difference between patients with and without the 1858T allele in terms of the frequency of T1D-related autoantibodies (GADA $P = .173$, IA–2A $P = .679$, IAA $P = .096$) or number of autoantibodies ($P = .173$). However, IA–2A were positively related to HLA *DR4-DQ8* ($P = .004$) and inversely associated with HLA *DR3/DQ2* ($P = .002$). IA–2A were positive in 68.4% of *DR3/DQ2* patients and in 82.5% of subjects with *DR4-DQ8*. GADA patients were significantly older at diagnosis than those without GADA ($P = .005$). Age differences were also observed for the *PTPN22* polymorphism ($P = .010$), but not for HLA haplotypes, IAA or IA–2A. There were no differences in gender distribution. In multivariate logistic regression analysis including gender and age as confounding variables, *DR4-DQ8* (OR 2.56, 95%CI 1.35–4.86) and *DR3-DQ2* (OR 0.36, 95%CI 0.19–0.68) were the only independent factors of IA–2A positivity.

Conclusions: The results of our study confirm the high prevalence of genetic risk markers of T1D in Germany. The presence of IA–2A at diagnosis is strongly associated with the HLA risk haplotypes, but not with *PTPN22* polymorphism. No association was seen between genetic risk markers and IAA or GADA positivity.

O/FRI/2/09

Combination therapies for the reversal of Type 1 Diabetes: the NOD mouse model

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Objectives: The NOD mouse is the prototypic animal model for the study of autoimmune Type 1 Diabetes (T1D). Most studies have explored the natural history and prevention of T1D with few

investigating the reversal of recent onset disease. The objectives of this study were to explore the utility of combination therapies (directed at reversing autoimmunity and restoring beta cell mass/function) to reverse T1D. We hypothesized that short term immunosuppression with polyclonal rabbit anti mouse thymocyte globulin (ATG) combined with the incretin hormone analogue extendin-4 (Byetta) or the dipetidyl peptidase-4 inhibitor (Januvia) or the immune modulating/stem cell mobilizing cytokine granulocyte colony stimulating factor (G-CSF/Neupogen) would reverse T1D.

Methods: When mice were diagnosed with T1D (240 mg/dl or higher on two consecutive measurements 24 hours apart), they were randomized to the various treatment arms of this study. All animals were initially treated with a subcutaneous slow release insulin pellet. Within the various study groups the following treatment protocols were followed as applicable, ATG (500 μg $\times$ 2 72 hours apart), Neupogen (6 μg daily for 8 week)s, Byetta (10 μM daily for 6 weeks) and Januvia (1 mg daily for 6 weeks) were administered in various combinations with control (saline) to 8–10 mice per group.

Results: No control animals treated with saline alone had reversal of diabetes. Neupogen and ATG monotherapies led to reversal of diabetes in 33% and 50% of the mice respectively. Byetta and Januvia alone did not reverse the disease. ATG plus Januvia led to a 50% reversal, ATG plus Byetta 70% and ATG plus Neupogen 86% reversal. Histologically, less insulitis and greater insulin preservation was observed in the successfully treated animals.

Conclusions: In summary, the combination of ATG and Neupogen resulted in a significant reversal ($P < 0.05$ vs. other groups; ANOVA) of recent onset diabetes in this mouse model, more than has ever been demonstrated. Future studies are warranted investigating the mechanisms of these agents. Efforts are underway to combine these two agents in human trials to reverse the disease in new-onset patients.

O/FRI/2/10

Genetic predictors of islet autoimmunity in early childhood. The Diabetes Autoimmunity Study in the Young (DAISY)

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Objectives: While multiple markers of genetic susceptibility for type 1 diabetes (T1D) are being reported from linkage and association studies, little is know concerning their independent predictive value on a population basis.

Methods: DAISY is following from birth to development of islet autoimmunity (IA) and T1D 2449 high-risk children who have a high-risk HLA-DR, DQ genotype or are first-degree relatives of someone with T1D. Blood is drawn for the detection of autoantibodies to insulin, GAD65, IA-2 and ZnT8 at nine and 15 months and annually thereafter. IA is defined as positivity for at least one of the four autoantibodies on two or more consecutive visits. By mean age of 7.0 $\pm$ 4.4 years, 163 children have developed IA and, of those, 53 have developed diabetes. Parametric models with Weilbull distribution and Cox proportional hazards models were used to examine genetic predictors of IA and diabetes, respectively.

Results: By age 12 years, the cumulative risk (95%CI) of IA was 36% (19–56%), 11% (3–35%), and 14% (8–25%) in, respectively, relatives with HLA-DR3/4, DQ8, all other relatives, and general population children with HLA-DR3/4, DQ8. The risk of T1D by age 12 in these groups was, respectively 24% (15–37%), 4% (3–7%), and 1% (0.4–3%).The HLA-DR, DQ genotype and, to a much lesser extend the PTPN22 and INS genotypes predicted development of IA and T1D.

Predictors	HR for IA (95% CI)	HR for T1D (95% CI)
HLA-DR3/4,DQ8	3.2 (2.3–4.6)	8.1 (4.5–14.6)
PTPN22 R620W	1.5 (1.1–2.1)	1.7 (1.0–3.0)
INS -23Hph1	1.1 (0.9–1.5)	1.6 (1.0–2.8)
CTLA-4 T17A	1.1 (0.9–1.4)	0.9 (0.6–1.3)

Conclusions: This prospective population analysis for the first time includes ZnT8, in addition to the classical islet autoantibodies, in defining IA. We confirm the dominant effect of genetic susceptibility conferred by the HLA-DR, DQ genotypes on the risk of IA and T1D in early childhood.