

Oral Presentations

01

Further clues to the aetiology of type 1 diabetes: spatial clustering amongst 0–29 year olds in Yorkshire, UK

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Objective: The aetiology of type 1 diabetes in children and young people has a strong environmental component. The presence of geographical or spatial clustering would suggest localised excesses of relevant environmental exposures. We studied spatial clustering amongst 0–29 year olds using population-based data from a register in Yorkshire, UK.

Research Design and Methods: Two datasets of children and young people diagnosed with type 1 diabetes while living in Yorkshire were analysed: (i) cases aged 0–14 years diagnosed between 1978–2002 and (ii) cases aged 15–29 years diagnosed between 1991–2002. The Pothoff-Whittinghill method was used to test for spatial clustering.

Results: A total of 3019 cases of type 1 diabetes aged 0–14 years and 989 cases of type 1 diabetes aged 15–29 years were analysed. There was statistically significant spatial clustering for 0–14 year olds diagnosed during the period 1978–1985 only ($p = 0.009$), mainly involving younger children ($p = 0.01$ for 0–4 year olds and $p = 0.005$ for 5–9 year olds). There was also significant clustering for 15–29 year olds ($p = 0.003$ and $p < 0.001$ for cases diagnosed during the periods 1991–1995 and 1996–2002, respectively), especially involving 20–24 year olds ($p = 0.002$ and $p = 0.01$ for cases diagnosed during the periods 1991–1995 and 1996–2002, respectively).

Conclusion: The present study is the first to analyse spatial clustering of type 1 diabetes amongst older teenagers and young adults. The findings show that geographical clustering of cases is present and differs by age and time period. This pattern suggests that environmental factors associated with persistent localised exposure may influence the risk of developing type 1 diabetes in different age groups during different time periods.

02

Circulating insulin mRNA levels in whole blood as a predictive test for type 1 diabetes mellitus (T1DM)

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Abstract withdrawn.

03

The prevention of diabetes progression trial (PDPT): preservation of β -cell function using daclizumab in new onset type 1 diabetes

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Type 1 diabetes (T1DM) results from the autoimmune T-cell mediated immune destruction of pancreatic β -cells and loss of

insulin production. Stimulated C-peptide (SCP) reveals significant endogenous insulin production at the time of diagnosis. Prior studies have implicated IL-2 and its receptor (IL-2R) in the pathophysiology of β -cell destruction. Daclizumab (DZB), a humanized IgG-1 monoclonal antibody binds specifically to the α -subunit of the human IL-2R and functions as an IL-2R antagonist. The safety, efficacy and pharmacokinetic profile of DZB have been demonstrated in adults with uveitis and psoriasis, in adult transplant patients, and in 60 pediatric renal transplant recipients. DZB also prevents rejection of human pancreatic islet transplants. We report analyses of an open label phase I/II trial to test the safety and efficacy of DZB in children with newly diagnosed T1DM. β -cell function preservation was assessed by exogenous insulin requirement, HgA1c, and glucagon SCP. Subjects were monitored for infusion-related toxicities, frequency and type of infections, and chemistry and hematological profiles. 36 patients (18 treated) were randomized. IL-2R+ cells were eliminated by 4 weeks in treated subjects but not in controls. The change in insulin requirement, HgA1c and SCP were analyzed by repeated measures ANOVA, each subject as a random effect and Log transformation of C-peptide + 1. On average, treatment subjects had a significantly higher mean C-peptide AUC ($p = 0.015$), lower insulin requirement ($p = 0.0001$) with similar HgA1c during 39 weeks of treatment. The mean differences (\pm SE) were 2.84 (1.09) ng/ml/10 and -0.26 (0.06) units/kg/day for +C-peptide and insulin requirement, respectively. Two subjects developed autoimmune thyroid disease but had (+) antibodies at study entry. This pilot trial demonstrates that daclizumab therapy is safe and, when initiated within 11 weeks of T1DM diagnosis, preserves more insulin production. Further study must confirm whether DZB can improve T1DM management and reduce long-term complications.

04

Weaning to a highly hydrolyzed formula in infancy decreases the cumulative incidence of beta-cell autoimmunity in young children with increased genetic risk for type 1 diabetes

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Early nutrition may modify the risk of later type 1 diabetes (T1D). We aimed at determining whether weaning to a highly hydrolyzed formula decreases the cumulative incidence of signs of beta-cell autoimmunity, i.e. diabetes-associated autoantibodies, in children

at increased risk for T1D. We randomized 230 newborn infants who had a first-degree relative with T1D and carried risk-associated *HLA-DQB1* genotypes to a double-blinded pilot trial, in which the infants were weaned after exclusive breastfeeding to either a casein hydrolysate or conventional, cow's milk-based formula until the age of 6–8 months. Islet cell antibodies (ICA) were analyzed with conventional immunofluorescence, while autoantibodies to insulin (IAA), GAD65 and IA-2 (IA-2A) were measured with specific radiobinding assays during a mean observation period of 6.5 years. The hazard ratios (HR) of seroconversion to autoantibody positivity during follow-up were estimated with life-table survival regression. Fourteen children in the hydrolysate group (14.1%) tested positive for a minimum of one autoantibody reactivity at least once during the observation period, whereas the corresponding proportion among the control subjects was 28 (25.7%). Seven subjects in the hydrolysate group (7.1%) and 17 in the control group (15.6%) had two or more autoantibodies at least once. The cumulative incidences of at least one autoantibody [HR 0.51 (95% CI 0.26–0.95); $p = 0.033$], ICA [HR 0.41 (CI 0.18–0.86); $p = 0.017$], and IA-2A [HR 0.34 (CI 0.11–0.86); $p = 0.022$] were reduced in the hydrolysate group. After adjustment for duration of study formula feeding, the HR for at least one antibody was 0.47 (CI 0.24–0.89; $p = 0.020$), ICA 0.39 (CI 0.17–0.84; $p = 0.014$) and IA-2A 0.30 (CI 0.10–0.77; $p = 0.012$). After adjustment the HR for at least two autoantibodies was 0.43 (CI 0.16–1.03; $p = 0.057$). These data provide further support that it may be possible to manipulate spontaneous beta-cell autoimmunity by dietary intervention in infancy in children with increased susceptibility to T1D.

05

CNS function in young people with type 1 diabetes 12–15 years after disease onset

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Subtle cognitive deficits have been documented previously in childhood onset type 1 diabetes but the biological correlates of these deficits are not well understood.

Aim: This study combined neuroimaging and neuropsychological assessment to examine CNS function in young people with T1DM studied prospectively from diagnosis 12–15 years previously.

Methods: *Subjects* Young people with T1DM ($n = 106$, mean age 20.5 years SD 4.2) and healthy community controls (C) ($n = 69$, mean age 20.7 years SD 4.1). There were no group differences on baseline Full Scale IQ (FSIQ) assessed on study entry 12–15 years previously, socioeconomic status, gender distribution or age. *Neuropsychological assessment* Wechsler Abbreviated Scale of General Intelligence. *Neuroimaging* Structural and T2 relaxation measurements were performed at 3T (T1DM $n = 75$, C $n = 50$). Proton MRS was recorded from 2 cm isotropic voxels placed bilaterally in frontal and temporal lobes and basal ganglia.

Results: T1DM had lower Verbal IQ than C ($p = 0.05$). T1DM with onset <6 years (EOD) ($n = 40$) had lower Performance IQ than T1DM onset 6+ (LOD) ($p < 0.01$) and C ($p < 0.01$). EOD

showed more negative change (baseline to current) in FSIQ than LOD ($p < 0.01$) and C ($p < 0.05$). Gray matter was decreased in thalamus and medial frontal gyrus in T1DM and correlated with years since diagnosis. Increased white matter fraction was observed in the inferior temporal gyrus. T2 relaxation times were increased in the superior temporal gyrus and decreased in the lentiform nucleus in T1DM, compared to C. T1DM had higher levels of myoinositol (MI) and lower levels of total *N*-acetylaspartyl (NAA) in frontal lobes and basal ganglia. MI levels were higher in temporal lobes in T1DM (all $p < 0.01$).

Conclusions: This study is the first to document CNS changes (cognitive deficit, altered metabolite profiles and structural brain changes) 12–15 years after diagnosis in a sample of T1DM with normal neuropsychological profiles at disease onset. Higher levels of MI may be a marker of fluid imbalance resulting from disruption of glucose homeostasis and are also associated with increased gliosis. Lower NAA is a marker of reduced neuronal population or function.

06

Newer tests of autonomic nerve function: entropy of heart rate variation and the light reflex

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Meta-analysis of 15 studies has confirmed association of cardiovascular autonomic neuropathy with increased mortality in diabetes (*Diabetes Care 2003: 1895–1901*). The tests used to determine neuropathy were the 'Ewing battery' (EB). Subsequently, measurement of the resting pupil diameter and the phasic light reflex (pupillometry) has been shown to be more sensitive, especially in adolescents. Heart rate variability (HRV) can now be analysed using time domain, frequency domain (power spectral analysis) and nonlinear techniques (based on chaos theory). In this study we compared parameters from the Ewing battery, analysis of HRV recorded over 20 minutes and pupillometry in a cohort of young adults with childhood onset diabetes ($n = 35$) and age-matched controls ($n = 36$). The diabetic group had mean age of 22.8 ± 4.2 years, duration 16.3 ± 5.4 years and median HbA1c $8.1\% \pm 1.2\%$. Comparison of mean values is given in the Table with significant differences (*).

ROC curve analysis of parameters which showed significant differences indicated that the best discrimination between diabetes and controls was achieved with reflex amplitude (AUC 0.75) and ApEn (AUC 0.71). These results confirm that pupillometry and HRV analysis are more sensitive than Ewing battery of cardiovascular tests in detecting change in diabetes. The cardiovascular autonomic system and the pupil are both affected early in the course of diabetes.

	Diabetes	Control	p*
Deep breathing heart rate variation (EB)	27.2	26.5	0.5
Lying standing heart rate ratio (30:15) (EB)	1.48	1.36	0.6
Lying standing systolic BP fall (mmHg) (EB)	-1.8	-3.0	0.5
Max pupil diameter (mm)*	5.6	6.0	0.002
Reflex amplitude (mm)*	1.6	1.9	0.0002
Max constriction velocity (mm/s)*	5	5.5	0.04
Sqrt pNN50 (time domain)*	3.2	4.4	0.02
Ln triangular index (time domain)*	2.4	2.9	0.033
Ln SD1 (time domain)*	3.1	3.4	0.03
Sqrt SD1/SD2 (time domain)*	0.56	0.61	0.027
Approximate entropy* ApEn	1.15	1.28	0.002

07

Smoking prevalence and its relation to metabolic control, blood pressure and serum lipids in 25 605 paediatric patients with T1DM from 212 centres in Germany and Austria

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Introduction: Smoking is generally accepted as a major risk factor for vascular disorders in adulthood, however, smoking receives little focus in paediatric and adolescent diabetology during routine care, even in specialised units.

Aims: To relate self-reported smoking frequency to metabolic control and other cardiovascular risk factors in adolescents with T1DM.

Methodology: In the multicentre DPV database from Germany and Austria, anonymised records on 25 605 patients <20 years of age (52% males, mean age at onset: 8.2 years, mean diabetes duration: 5.1 years) with documented smoking status were available for analysis. The most recent year of observation was evaluated, HbA1c-values were mathematically standardised to the DCCT normal mean (MOM-method).

Results: Self-reported smoking was negligible in patients younger than 11 years (0.3%), increasing to 5.9% in 11–15 year-old patients and 30.2% in the age-group 15–20 years. Male patients reported smoking more frequently than females (15–20 years: 31.4% vs. 28.8%, $p < 0.0001$). Multivariate analysis (SAS proc mixed) with adjustment for age, diabetes duration, insulin therapy and centre differences, revealed that smokers had higher HbA1c-levels compared to nonsmokers (9.1% vs. 8.0%, $p < 0.0001$) and had a higher BMI-SDS (+0.56 compared to +0.51, $p < 0.0001$). Diastolic blood pressure was higher (67.7 vs. 67.0 mmHg, $p < 0.001$) and the lipid profile was unfavourable in smoking patients: Triglycerides, total cholesterol and LDL cholesterol were higher and HDL-cholesterol was lower (all $p < 0.0001$).

Conclusions: A considerable proportion of adolescents with T1DM diabetes report cigarette smoking. Assuming a relevant degree of underreporting, the true rate is likely to be even higher. Smokers display significantly worse metabolic control and a higher cardiovascular risk profile. Education about smoking, smoking prevention and psychological help for smoking cessation should be an integral part of comprehensive paediatric care for adolescent patients with T1DM.

08

Sensitivity of retinopathy screening: comparison of 7 field with 2 field photography

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Screening for diabetic retinopathy increasingly involves nonmydriatic photography of the central retina, allowing more patients to

be screened for treatable retinopathy including those in remote areas. The question remains whether this reduces sensitivity, because mydriasis enables screening of seven fields. We aimed to compare screening using 2 vs. 7 field, stereoscopic photography in our adolescent population with T1DM.

Patients with T1DM, aged <22 years ($n = 161$), with mild or moderate background retinopathy from seven fields (defined as ≥ 31 using the modified Airlie House grading system) were included and all occasions of retinopathy reviewed (677 individual eyes). Retinal slides were taken using a Topcon Retinal Camera following mydriasis. Reproducibility of our seven field grading has a weighted Kappa score of 0.88 (very good). For the present analysis, assessments with retinopathy were regarded using two fields and results compared with seven fields (Table). Retinopathy grade using two fields was unchanged for 435 (64%) of eyes reviewed. In 148 eyes (22%), screening of the two fields did not detect microvascular changes. In the remaining 94 eyes, retinopathy was graded as less severe when only the central fields were assessed. The sensitivity of 2 vs. 7 field photography was 78%. Weighted kappa for agreement between 2 and 7 fields for retinopathy was 0.56 (fair).

7 fields	2 fields					Total
	10	21	31	41	45	
21	116	213				329
31	32	87	205			324
41		2	1	16		19
45				4	1	5
Total	148	302	206	20	1	677

In summary, screening with two fields misses 14% of adolescents with retinopathy and underestimates severity by 22% of mild to moderate background retinopathy. This indicates that limited retinal screening involving only central fields reduces sensitivity. Adolescents are potentially more motivated to adhere to treatment goals when retinopathy is detected.

09

Activating mutations in the ABCC8 gene coding for SUR1, the high affinity sulfonylurea receptor, cause neonatal diabetes

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Neonatal diabetes, defined by mild to severe hyperglycemia within the first months of life, can be either permanent (PND) or transient (TND) when showing early remission with possible relapse during adolescence. A significant number of PND cases, and rare cases of

TND, are attributable to mutations in *KCNJ11* encoding the $K_{IR6.2}$ subunit of the K_{ATP} channel expressed at the surface of the pancreatic β -cell. The ATP-gated potassium (K_{ATP}) channel, composed of SUR1 and $K_{IR6.2}$ proteins, is a key regulator of insulin release. It is inhibited by the binding of adenine nucleotides to $K_{IR6.2}$ which closes the channel, and activated by nucleotide binding and/or hydrolysis on SUR1, which opens the channel. The balance of these opposing actions determines the open channel probability, which controls the excitability of pancreatic β -cells. We hypothesized that over-stimulating mutations in *ABCC8* could reduce insulin secretion and cause ND. We found nine heterozygous mutations in the *ABCC8* gene in 13 out of 45 patients diagnosed with PND or TND of unknown origin from 88 patients of the French network for the study of neonatal diabetes. In unrelated cases with vertical transmission, five mutations co-segregated with diabetes. Functional analysis of two de novo mutations, from both PND and TND subjects presenting with severe hyperglycemia and ketoacidosis, demonstrated a novel molecular mechanism by which the increased activity of the channels, under physiologic conditions, is due to an increase in the Mg-dependent stimulatory action of SUR1 on the pore whereas the net-inhibitory action of ATP on ND-SUR1 mutant channel is unchanged (compared with wild-type SUR1). Furthermore, ND-SUR1 channels retain sensitivity to inhibitory sulfonylureas providing a better metabolic control than insulin in probands with four separate *ABCC8*/SUR1 mutations. Thus, dominant SUR1 mutations account for a significant fraction (~15%) of ND cases, effectively treatable with oral hypoglycemic agents.

010

Kir6.2 birth weight and postnatal growth as bioassay for insulin secretion

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Introduction: Birth weight is a bioassay for fetal insulin secretion as altered insulin secretion in utero alters insulin mediated growth. Activating mutations in Kir6.2 are the major cause of neonatal diabetes and reduce insulin secretion by altering the closure of the beta cell K_{ATP} channel in the presence of ATP.

Aim: Our objective was to examine fetal and post-natal growth in patients with activating Kir6.2 mutations and identify if this was modified by severity of mutation or maternal diabetes.

Methodology: We used Standard Deviation Scores (SDS) for birth and postnatal growth in an international series of patients ($n = 49$) with Kir6.2 mutations and related this to their clinical phenotype.

Results: Birth weight was greatly reduced [-1.73 (-3.68–1.41) median (range)] SDS but there was postnatal catch up as present weight was normal [-0.37 (-4.37–2.34)] SDS. Catch up growth for height and weight was not seen until insulin treatment was started. Birth weight was not influenced by severity of postnatal phenotype but was increased by maternal diabetes (-0.12 vs. -1.81 SDS $p = 0.037$). Patients with the severe neurological DEND syndrome did not catch up (present weight -2.2 vs. -0.24 SDS $p = 0.003$).

Conclusion: Kir6.2 mutations greatly reduce insulin secretion and hence fetal growth but this is independent of mutation severity. Increased fetal growth in response to maternal diabetes suggests either the Kir6.2 mutated fetal beta cell is still glucose responsive or alternatively there is a noninsulin-mediated increase in fetal growth. Postnatal catch up requires insulin treatment but is complete except in those with epilepsy.

011

The PTPN22-associated risk for type 1 diabetes in the Czech population

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Introduction: The PTPN22 is a negative regulator of the T-cell response. Its +1858C > T (R620W) polymorphism has been associated with a risk for autoimmune diseases, including type 1 diabetes (T1D). A recent study showed a complete absence of the minor allele in a large Asian dataset, but indicated a possible involvement of another polymorphism located within the promoter of the PTPN22 gene.

Aims: We sought to analyze the association of three PTPN22 polymorphisms in the Czech population.

Methodology: The single nucleotide polymorphisms (SNP) at positions -1123 (rs2488457), +1858 (rs2476601, the R620W substitution), and +2740 (rs1217412) were genotyped using TaqMan assays in 372 subjects with childhood-onset T1D, and 297 control subjects. Haplotypes were reconstructed from unphased genotype data via the expectation-maximization algorithm. Association was tested in bivariate models, as well as in models adjusted for other polymorphisms associated with T1D.

Results: The SNPs were in strong linkage disequilibrium, $D'(-1123, +1858) = 0.89$, $D'(-1123, +2740) = 0.92$, $D'(+1858, +2740) = 0.95$. Four haplotypes exceeded the frequency of 1% in either cases or controls. Relative to the haplotype carrying the three wild-type alleles ('w-w-w', 68% haplotypes in cases, 78% in controls), only the haplotype consisting of three minor alleles ('m-m-m', 21% haplotypes in cases, 9.4% in controls) was associated with T1D (OR 2.5, 95% CI 1.8–3.5). The haplotype having the wild-type allele at the +1858 position and two minor alleles ('-1123m +1858w +2740m') was neutral as to the T1D risk (9.1% haplotypes in cases, 10.4% in controls, OR = 1.0). The risk conferred by positivity for the +1858 T allele (620W) was OR = 3.5, 95% CI 2.2–5.5 when adjusted for other T1D-associated gene polymorphisms (HLA-DQ, insulin gene, NEUROD).

Conclusions: In contrast to the Asian data, the +1858C > T (R620W) polymorphism seems to be causative in the Czechs, as shown by the neutrality of the '-1123m +1858w +2740m' haplotype. The PTPN22 association is relatively strong, comparable to that of the insulin gene.

012

Evidence for common genetic background between type 1 and gestational diabetes

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Children born to mothers with type 1 diabetes (T1D) have an increased risk of developing the disease. It is unresolved to what extent gestational diabetes (GDM) is associated with an increased risk for the child to develop diabetes. The aim of this study was to determine whether there is an association between gestational diabetes and HLA DQB1 genes. HLA genotypes were determined in dried blood spots of cord blood taken from 32 663 children born to nondiabetic mothers and 1179 children born to diabetic mothers. In addition, 1046 diabetic mothers were HLA typed. Out of this number, 208 reported having type 1 diabetes and 838 had gestational diabetes. GDM mothers positive for islet autoantibodies were excluded from the HLA distribution analysis. T1D was strongly associated with the high risk HLA DQB1 genotypes and the association was passed on to the offspring ($p < 0.0001$ for DQB1*0201/0302, 0302/X and 0302/0604). There was no positive association between HLA and GDM. The HLA DQB1*0602 allele

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was confirmed to be negatively associated with T1D ($p = 0.04$ for DQB1*0602-3-4/X), but was also negatively associated with GDM ($p = 0.01$ for DQB1*0602/02, $p = 0.04$ for DQB1*0602/0301 and $p = 0.0008$ for DQB1*0602/X), as was also the case for the offspring ($p = 0.0008$ for DQB1*0602/02 and $p = 0.02$ for DQB1*0602/X). A positive association was found between maternal age and GDM ($p < 0.0001$). T1D and GDM mothers gave birth prematurely ($< 37^{\text{th}}$ week) in a higher frequency than the control population ($p < 0.0001$). DQB1*0602 allele that is considered protective for type 1 diabetes seems to have a strong negative association with gestational diabetes, suggesting that there is a common genetic background between autoimmune and gestational diabetes. Therefore, children born to GDM mothers may have a slightly higher risk of developing autoimmune diabetes in the future.

013

Serum metabolite patterns between birth and development of autoantibodies and overt type 1 diabetes: Application of large-scale metabolomics to the Type 1 Diabetes Prediction and Prevention study (DIPP)

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Background: Over 8000 children carrying HLA-conferred genetic risk for T1D have been followed since birth at 3–12-month intervals for development of T1D-related autoantibodies and overt T1D in Type 1 Diabetes Prediction and Prevention Study launched in 1994. As changes in groups of metabolites may be descriptive of systemic responses to genetic or environmental exposures, they may function as a powerful tool for characterisation of complex phenotypes and as biomarkers. We thus hypothesised that extended serum metabolite patterns might differ between children remaining autoantibody negative (controls) and children who later develop autoantibodies and progress to T1D (cases), and that the changes might reflect etiopathogenetic events that by far precede development of autoimmunity.

Aims: Elucidate early events leading to autoimmunity and overt T1D by analysing our 11.5-year collection of longitudinal serum sample series from the case and control children.

Methodology: The metabolite profiles of the sample series collected from 46 cases (progressed to T1D) were compared with the series collected from 59 controls (remained autoantibody negative) matched for time of birth, gender, genetic T1D risk, and city of birth (total 1234 samples). Liquid Chromatography coupled to high resolution mass spectrometry (MS) and gas chromatography coupled to mass spectrometry were used.

Results: Metabolite profiles and identified key metabolites separate the cases from the controls much before autoantibodies emerge. The changes reflect alterations in gut permeability, antioxidant capacity and inflammation.

Conclusion: Our data suggest that early metabolic insult(s) may lead to alterations in the immune system making it autoimmunity-prone. The preseroconversion changes support the trigger-booster hypothesis claiming that the processes leading to T1D are triggered by an exogenous factor driven by one or several environmental determinants. Our data further suggest that advanced high-throughput metabolomics methods may markedly antedate and improve accuracy of defining which children will later progress to autoimmunity and T1D.

014

Unchanged clinical picture and beta cell function of diabetic children in the last 25 years.

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Introduction: The incidence of type 1 diabetes in childhood has doubled from 20–40/100 000 children/year the last two decades in Sweden. The reason must be environmental factors, which also might lead to different disease process and manifestation. The insulin regimens have been more intensive.

Aim: To study whether clinical characteristics at onset, duration of partial remission and C-peptide secretion the first years after newly diagnosed diabetes have changed in the last 25 years.

Methodology: All 316 children with type 1 diabetes diagnosed during 1976–2000 in the Linköping area were included. Information about age, gender, duration of symptoms prior to diagnosis, ketoacidosis at diagnosis and HbA1c and insulin therapy at diagnosis and during the first years was collected retrospectively from medical records. Duration of partial clinical remission was defined as the period with insulin dose $< 0, 5$ E/kg. Fasting and stimulated C-peptide secretion was measured regularly during the first 5 years. For the analysis the population was divided in 5 cohorts according to the year of diagnosis.

Results: The clinical characteristics at onset were unchanged as well as the duration of partial remission (median 0.9 years). Insulin therapy changed from s.c insulin at diagnosis and then 1–2 daily doses to i.v insulin and multiple insulin injections from the mid 80s. C-peptide secretion was highest after 3 months and then declined gradually. After 5 years still 33% of the patients had measurable fasting C-peptide, but only 7% > 0.1 nmol/l. The cohort 1996–2000 had higher C-peptide secretion at diagnosis and at 3 months, but after longer follow up there was no difference.

Conclusion: The clinical characteristics at diagnosis, the period of partial remission and magnitude and duration of C-peptide secretion have remained largely unchanged in the last 25 years.

015

Insulin secretion and sensitivity in the prediction of type 1 diabetes among children with signs of beta cell autoimmunity

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Introduction: A reduced first-phase insulin response (FPIR) to intravenous glucose and decreased insulin sensitivity have been reported as predictors of type 1 diabetes (T1D) among first-degree relatives. The value of these markers for prediction of T1D is, however, poorly defined among young children with signs of beta-cell autoimmunity in the general population.

Aims: To assess the predictive role of FPIR and insulin resistance for T1D in genetically susceptible children, who have been recruited from the general population at birth and later seroconverted to positivity for multiple (≥ 2) autoantibodies.

Methodology: An intravenous glucose tolerance test (IVGTT) was performed in 130 children with persistent positivity for at least two

of the four autoantibodies (ICA, IAA, GADA, and IA-2A). The subjects were observed for progression to T1D for a mean of 5.8 years. Plasma glucose concentrations were measured with an enzymatic method, and serum insulin with an enzyme immunoassay. Weight for height was assessed, and FPIR (sum of insulin concentrations at 1 and 3 min), the homeostasis model assessment of insulin resistance (HOMA-IR) and the HOMA-IR/FPIR ratio were calculated.

Results: Forty-one children progressed to T1D and their mean age at diagnosis was 4.5 years (2.1–9.2 years). The mean weight for height at IVGTT was 97.7% (range 88%–133%), and there was no difference between progressors and nonprogressors. Children developing T1D were younger at initial seroconversion (1.5 years vs. 2.2 years; $p = 0.015$), and they presented with multiple autoantibodies earlier (1.6 years vs. 2.5 years; $p = 0.006$) than those remaining nondiabetic. Progressors had lower median FPIR values (27.8 mU/l vs. 47 mU/l; $p < 0.001$), and their HOMA-IR/FPIR ratio was higher (0.027 vs. 0.017; $p < 0.001$). HOMA-IR did not differ between the two groups.

Conclusions: Children developing T1D at a young age have a decreased FPIR but not reduced insulin sensitivity, arguing against a role of insulin resistance as a factor affecting the progression rate to T1D.

O16

Diabetic children with several or high GAD65 antibodies have a different seasonality of month of birth than no or low antibody populations

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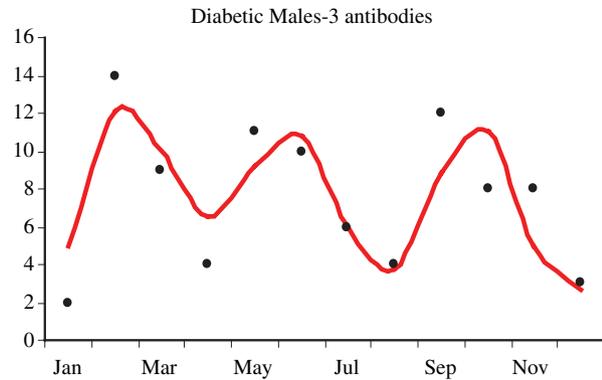
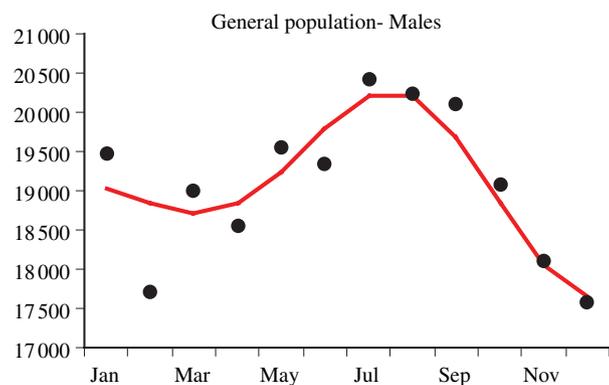
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Background: In previous studies we have reported that children with Type 1 diabetes (T1D)¹ and IAA/GAD positive offsprings of diabetic parents have a different pattern of month of birth (MOB) than the general population or antibody (Ab) negative offsprings².

Aim: To investigate the MOB pattern by gender in 462 diabetic children from Sweden in whom the titer of GAD65 was determined and compared to 833 healthy children as well as the MOB pattern in 504 diabetic children in Berlin in whom the titers of IAA, GAD65 and IA2 were compared to the pattern in the general population (n = 446 571).

Method: Rhythmicity of MOB was evaluated by Cosinor analysis.

Results: In both cohorts of children with T1D we found that children with either a high titer of GAD65 (above the 80th percentile) or positivity for 3 anti-beta cell antibodies differed in their pattern of MOB from the healthy population as illustrated in



the figures for the Berlin male subjects and even from T1D children with no or a low titer of Abs.

Conclusions: Our past and present observations support the hypothesis that the autoimmune process leading to childhood T1D is triggered in the perinatal period by virus infections in genetically susceptible individuals.

References:

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O17

Nonalcoholic fatty liver in obese prepubertal children: relation to insulin-resistance

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Nonalcoholic fatty liver disease (NAFLD) represents an emerging clinical concern in the obese paediatric population. While in adults a clear casual association with insulin resistance (IR) has been documented few data are available in the prepubertal age. The aim of this study was to determine whether IR might play a role in the development of NAFLD in this age group. We performed hepatic ultrasound with a convex 5 MHz probe in 66 prepubertal children (36M/30F, mean age of 8.56 ± 2.18 years) with severe obesity (BMI 27.9 ± 2.83). Oral glucose test (1.75 g of glucose/kg of body weight) was performed and the following IR-indexes were calculated: basal insulin, fasting glycemia/fasting insulin (G/I), homeostatic model assessment (HOMA-IR) and whole body insulin sensitivity index (WBISI). Furthermore lipid profile and hepatic function (ALT; AST; gamma GT) were performed in all subjects. According to the presence of NAFLD the patients were divided into two groups (group (1): NAFLD positive and group (2): NAFLD negative). Data were analysed by Mann-Whitney test and by analysis of variance for repeated measurement. ($p < 0.05$). In 36 subjects (22M, 14F) NAFLD was detected, where significantly increased levels of ALT (48.50 ± 28.38 vs. 42.62 ± 23.43, $p = 0.04$) were documented. Group 1 presented significantly increased levels of basal insulin (17.89 ± 13.75 vs. 15.9 ± 14.84, $p = 0.007$) and HOMA-IR (4.09 ± 3.41 vs. 3.33 ± 2.74, $p = 0.009$), while G/I (7.18 ± 5.31 vs. 8.61 ± 5.59, $p = 0.004$), and WBISI (3.92 ± 2.12 vs. 5.20 ± 3.09, $p = 0.001$) were significantly reduced. Furthermore, analysis of variance revealed higher insulin levels during OGTT when compared to nonNAFLD subjects ($p = 0.004$) while no difference was detected in blood glucose excursion ($p = 0.05$). These data demonstrate that already in prepubertal children with severe obesity, hyperinsulinemia/IR seems to play a pivotal role in the development of NAFLD. Children with IR should undergo ultrasound examination in order to not underestimate the presence of this condition.

018

Polycystic ovary morphology (PCOM) and syndrome (PCOS) in women with type 1 diabetes mellitus (DM1) is associated with intensive insulin treatment

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Introduction: Recently the criteria for the diagnosis of PCOS have been modified.

Aim: The purpose of this study was to determine the frequency of PCOS and PCOM in women with DM1 and evaluate its potential association with intensive insulin treatment.

Methods: We evaluated the presence of PCOS and PCOM using the new Rotterdam criteria. All the postpubertal women with DM1 (n = 42, age: 23.4 ± 1.1 year) attending our hospital were invited to participate and compared to healthy women (n:38, age: 26.3±1.2 yr) with regular menses and without a history of hyperandrogenism.

Results: Hirsutism was present in 28.6% and 0% of DM1 and C, respectively (p < 0.001). Biochemical hyperandrogenism was present in 23.8% and 7.9% of DM1 and C, respectively. DM1 women had higher levels of testosterone, androstenedione, larger ovarian volume, and follicle number by ovary and higher prevalence of PCOM and PCOS than C (Table). The proportion of women using intensive insulin treatment was higher in women with PCOM/PCOS (p < 0.05). Intensive treatment was a significant factor related to presence of PCOM/PCOS in DM1 women (p < 0.05)

	DM1	C
Intensive insulin treatment (%)	24 (57.1)	
Testosterone (ng/dl)	61.5 ± 36.0	49.5 ± 2.0 ^a
Androstenedione (ng/ml)	1.8 ± 0.1	1.4 ± 0.0 ^a
Ovarian volume (ml)	9.3 ± 0.6	7.1 ± 0.4 ^a
Follicle number (n)	10.0 ± 0.8	6.9 ± 0.5 ^a
PCO morphology (%)	23(54.8)	5(13.2) ^b
PCOS (%)	17(40.5)	1(2.6) ^c

^ap < 0.0001, ^bp < 0.001, ^cp < 0.0001

Conclusions: A high frequency of hyperandrogenism, PCOM and PCOS is observed in DM1, which appears to be associated with intensive insulin treatment. (FONDECYT grant 1050452)

019

Insulin resistance and whole body energy homeostasis in obese adolescents with fatty liver disease

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Introduction: Obese adolescents are at risk of developing nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes.

Aims: Measure non-invasively the intra-hepatic fat (IHF) content of obese adolescents, to ascertain whether is associated with abnormal whole body energy homeostasis and insulin resistance.

Methodology: IHF content, energy homeostasis, insulin sensitivity and body composition were measured using localized hepatic

¹H-MRS, indirect calorimetry, a 3-h OGTT-derived surrogate index (WBISI), and DXA respectively, in 54 obese adolescents (24F/30M, age: 13 ± 2 years, BMI >99th percentile for their age and sex).

Results: NAFLD (defined as IHF content >5% wet weight) was found in 16 individuals (30%) in association with higher alanineaminotransferase (p < 0.006), HbA1c (p = 0.021) and lower HDL-chol (p < 0.05). Individuals with NAFLD had higher fasting plasma glucose (89 ± 8 vs. 83 ± 9 mg/dl; p = 0.01) and a mild impairment of WBISI (2.7 ± 1. vs. 3.4 ± 1.3; p = 0.05) in comparison with those with normal IHF content; parameters of insulin secretion (Φ and Φ_{30}) were unaffected. In spite of a higher resting energy expenditure (REE; p = 0.043), their reliance on fat oxidation in the fasting state was lower (respiratory quotient 0.83 ± 0.08 vs. 0.77 ± 0.05; p < 0.01) and their ability to switch to carbohydrate oxidation during the oral glucose challenge was impaired (p < 0.05) in comparison with those with normal IHF content.

Conclusions: NAFLD is common in childhood obesity and is associated with inappropriate fasting and oral glucose-challenge whole body substrates oxidation; in addition, mild abnormalities of glucose homeostasis and whole body insulin resistance were detected in these youngsters.

020

Vascular endothelial and smooth muscle function relate to BMI and glucose in normal children and those with obesity or type 1 diabetes

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Background: Endothelial dysfunction is a critical precursor of atherosclerosis, and precedes development of vascular complications in diabetes. Vascular smooth muscle dysfunction occurs independently of endothelial dysfunction.

Objective: To evaluate vascular endothelial and smooth muscle function using flow mediated dilatation (FMD) and glyceryl trinitrate mediated dilatation (GTN) in obese and non-obese children in comparison to children with type 1 diabetes (T1DM).

Subjects/Methods: A total of 270 children (140 males, age 13.7 ± 2.8 years), including 58 obese children (BMI z-score > +1.7), 53 non-obese children and 159 children with T1DM were studied. Vascular function (FMD and GTN), body mass index (BMI) z-score, BP, glucose, HbA1c, lipids, folate status, total homocysteine and high sensitive CRP were measured.

Results: FMD and GTN were significantly lower in obese compared to nonobese subjects (p < 0.001, p < 0.001), and were similarly reduced in obese and T1DM subjects (p = 0.22, p = 0.28). In all non-diabetic subjects (obese and nonobese, n = 111) both FMD and GTN were significantly and independently related to BMI z-score (r = -0.28, p = 0.003; β = -0.36, p < 0.001) and weight z-score (r = -0.52, p = < 0.001; β = -0.31, p = 0.002). FMD related independently to total cholesterol (β = -0.22, p = 0.02). GTN related to glucose within the normal range (r = -0.34, p = 0.001). In the whole group (n = 270), FMD related to HbA1c (r = -0.15, p = 0.01) and GTN related to fasting glucose (r = -0.18, p = 0.004) and HbA1c (r = -0.23, p < 0.001).

Conclusions: Obese children and children with T1DM have a similar degree of vascular dysfunction. BMI and weight adjusted for age and sex are major determinants of endothelial and smooth

muscle function in obese and nonobese children. Smooth muscle function is related to glucose and insulin within the normal range in non-diabetic children. Vascular endothelial and smooth muscle function also relate to glucose homeostasis in a large group including healthy children, obese children and children with T1DM.

O21

Experience with continuous subcutaneous insulin injection (CSII) in 245 children and adolescents with type 1 diabetes mellitus (T1D) in a large paediatric diabetes centre

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Introduction: CSII is used more frequently for the treatment of type 1 diabetes mellitus in some paediatric diabetes centres but long-term results in large patient groups are lacking.

Aim: To analyze over a period of 5 years the experience of one paediatric centre using a standardized concept of insulin pump therapy.

Methodology: A total of 245 children and adolescents (50% male) with T1D started CSII from 2001 to 2005. At the beginning of CSII the median age was 11.5 years (from 0–20 years) and the T1D-duration was 3.1 years (from 0–17 years). Indications for CSII were: high HbA1c (n = 26; 11%), recurrent hypoglycaemic events (n = 79; 32%), dawn phenomenon (n = 72, 30%), flexibility of life (n = 55; 22%), and needle phobia (n = 13; 5%). For the beginning and training of the insulin pump therapy the patients were in hospital for an average time of 4.8 days. HbA1c was measured with DCA 2000 (Bayer, normal range 4.3–5.7%).

Results: During follow-up (1.5 years (0.1–4.8 years)) only nine of 245 patients stopped CSII. In the whole group the HbA1c was 7.4% (5.4–14.7%) before CSII, 7.5% (5.4–14.0%) after 6 months and 7.6% (5.5–11.8%) at the last outpatient visit. Patients with a high HbA1c as reason for CSII improved significantly: 8.9% (7.4–14.0%), vs. 8.1% (6.9–14.0%) vs. 8.5% (6.6–11.8%), $p < 0.001$; the others did not have a significant change in HbA1c. The body mass index did not change in the whole group (BMI-SDS before CSII: 0.55 ± 0.81 , last visit: 0.61 ± 0.80).

Conclusion: In experienced diabetes centres, CSII is an important therapeutic option for paediatric patients, even for those in poor glycaemic control. CSII does not provide a risk for overweight.

O22

Insulin pump therapy enables better metabolic control in patients with type I diabetes with eating disorders

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Eating disorders (ED) and their subthreshold variants are relatively common among adolescent females with type I diabetes. They are associated with poor metabolic control and earlier-than-expected onset of diabetes related complications. Adolescent girls with diabetes frequently use deliberate insulin omission to achieve weight control or weight loss.

We compared body mass index (BMI), glycemic control, retinopathy and urinary albumin excretion in 42 diabetic patients with

ED (three anorexia nervosa, seven bulimia nervosa, 32 ED not otherwise specified or subthreshold ED) during multiple daily injection treatment and after switch to insulin pump therapy. At the beginning of multiple daily injection treatment, the mean age of the patients was 12.6 ± 1.9 years and duration of diabetes 3.5 ± 3.1 years, the mean age at the switch to the insulin pump therapy was 15.1 ± 2.2 years and diabetes duration 5.9 ± 4.0 years. The changes in body weight was expressed as BMI standard deviation score (BMI SDS) and glycemic control as HbA1c. Two-tailed, paired t test was used for statistical analysis. BMI SDS increase was significantly higher during multiple injection regime ($p < 0.01$) compared to insulin pump therapy. The mean value of HbA1c remained stable during multiple injection treatment, and significantly decreased during insulin pump therapy ($p < 0.05$), the mean HbA1c values at the beginning of insulin pump therapy being $9.3 \pm 1.8\%$ and at the end of the study $8.5 \pm 1.5\%$. Insulin pump therapy enables better metabolic control in diabetic patients with eating disorders compared to multiple daily injections regime.

O23

To compare metabolic control and quality of life (QoL) of SCII with multiple daily injections (MDI) in children/adolescents at onset of T1DM.

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Introduction: Continuous subcutaneous insulin infusion (SCII) by pump is a well-established therapy in both adults and children with type 1 diabetes mellitus (T1DM). However, little is known about the advantages/disadvantages with SCII in children/adolescents from the onset of their T1DM.

Aims: To compare metabolic control and quality of life (QoL) of SCII with multiple daily injections (MDI) in children/adolescents at onset of T1DM.

Methodology: A total of 72 children/adolescents (7–17 years of age) were enrolled in an open, randomised, parallel, multi-centre study from nine hospitals. Half of the patients were treated with conventional MDI (long-acting insulin twice daily and short-acting insulin 3–4 times a day) by pen, the other half received SCII. The patients were followed for 24 months with clinical visits at the entry of the study and after 1, 6 and 12 and 24 months. During these visits samples were taken for analyses of metabolic control (HbA1c), C-peptide and growth factor markers (IGF-1, IGF1BP-1, IGF1BP-3). In addition, during each visit the patients/parents answered a questionnaire about their quality of life (DSTQ) and insulin doses, weight and length measurements were registered. Furthermore, severe episodes of hypoglycaemia and ketoacidosis as well as technical problems with the insulin pen/pump were registered.

Results: Preliminary results show no significant differences in metabolic control or length of remission phase (C-peptide) between the groups. QoL was significantly improved in the group treated with SCII ($p \leq 0.01$ at all screening visits). No episodes of ketoacidosis were found and only a few cases with severe hypoglycaemia were reported and there was no difference between the groups.

Conclusion: SCII treatment proved to be a safe therapy in children/adolescents followed for 24 months after onset of DM1. QoL was better in the SCII group compared with the MDI group. No difference with regard to metabolic control was found between the groups.

024

First user experience with an integrated insulin pump and real-time continuous glucose monitoring system in paediatric and young adult patients with type 1 diabetes

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Aim: To assess the effectiveness of the training for a novel integrated insulin pump and real-time continuous glucose monitoring system and the experience with this system in patients with type 1 diabetes (T1D).

Methodology: A prospective, multi-center user evaluation was conducted in 38 paediatric and adult patients. Patients were trained on a system including an insulin pump combined with a real-time display of interstitial glucose values and low/high alert for preset glucose levels (Paradigm[®] Real-Time, Medtronic MiniMed, USA). The system was used under normal life conditions during 1 month. Patients rated training materials and product features using two structured questionnaires (7-point Likert scale: 1 – disagree/not at all to 7 – strongly agree/very useful).

Results: A total of 35 patients (12 male, age 18.7 ± 13.3 years, T1D duration 7.2 ± 6.6 years, pump duration 1.9 ± 2.5 years, mean ± SD) completed the one-month evaluation. Reasons for drop-out were technical pump failure, sensor setting problem, and noncompliance in three patients. No severe adverse event was reported. Training material was rated effective in 97% of patients with an average rating of 5.6. Patient ratings were high for overall acceptance of the system (6.0), ease of use (5.8), usage of alert function (6.5) and helpline support (6.5). Lower ratings were found for comfort of wearing the system (4.3) and having alarms at night (4.2). In terms of diabetes management, 86% of patients assessed that the system will change the way they manage their disease. The users rated the value of the information given by the system as 6.3. They assessed that the system will improve their diabetes control (6.2), although they made few therapeutic changes based on the system information (3.7) during 1 month.

Conclusions: Most patients rated the education, support and the experience with the integrated system very favourably. Further investigational studies are needed to evaluate the metabolic benefit of this new treatment system.

025

The role of cytokines in type 1 diabetes prediction

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Background: Reliable prediction is a prerequisite for developing and testing prevention strategies for type 1 diabetes(T1D). It is unknown if cytokine levels at time of birth can predict development of T1D.

Aims: To determine levels of cytokines and other inflammatory markers at time of birth in a large unselected population-based case-control population of newborns using Dried Blood Spots (DBS) at day 5 and test the hypothesis that levels of inflammatory markers at birth predict T1D. Samples: DBS of 2086 Danish T1D patients from the birth cohorts of 1981–2002, and two controls per patient were selected. Patient and control samples were matched by

place and date of birth. The samples had been stored for 3–24 years at –25ordm; at Statens Serum Institut, Denmark.

Methods: Cytokines (IL1b, IFN γ , TNFa, TGFb, IL4, IL6, IL8, IL10, IL12), MBL, CrP, TREM1, Adiponectin and Leptin were measured by use of the flowmetric Luminex[®] xMAP technology. Samples were analyzed simultaneously for all markers. Analysis has been performed and evaluated in the first 2780 samples. Cases and matched controls were run together. GADA and IA-2A autoantibodies in combination were measured by standard radiobinding assay on DBS eluates.

Results: Proportional Hazard Regression model in patients compared to their matched controls showed Hazard Ratios (HR) 1.108 [confidence interval (CI) = 1.034–1.186, p < 0.0035] and 1.402 (CI = 1.033–1.901, p < 0.03) for every increase with 10 pg/ml of IL4 and for every 10-fold increase of IL4 (= log10), respectively. HR for possibly interacting cytokines was 1.136 (CI = 1.024–1.261, p < 0.017) and 1.299 (CI = 1.044–1.616, p < 0.019) for log10 (IL4*IL10) and log10 (IL4*IL12), respectively. No differences were detected between cases and controls for any of the other inflammatory markers. In cases positive for GADA, IA–2A, or both, HR for log10 (IL4) was 5.475 (CI = 2.841–10.55, p < 0.0001), compared to HR = 1.366 (CI = 1.001–1.863, p < 0.049) for log10 (IL4) in patients compared to controls negative for islet-autoantibodies.

Conclusion: Elevated IL4 levels at the time of birth are a prediction marker of T1D diagnosed before 24 years of age, particularly in subjects who have islet-autoantibodies against GADA, IA-2A, or both.

026

Postprandial glucose and GLP-1 stimulates glucagon release in patients with new onset type 1 diabetes 12 months after diagnosis

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Background and aims: Recently it was demonstrated in rat alpha-cells that glucose, arginine and tolbutamide stimulated glucagon release. In humans glucagon secretion in response to these agents is suppressed by intra-islet release of insulin. Similarly, pharmacological concentrations of GLP-1 also suppress endogenous glucagon levels. The aim of the present study was to investigate the relationship between postprandial glucose, and endogenous GLP-1/GIP and glucagon release in insulin deficient children during the first 12 months after diagnosis of type 1 diabetes. Furthermore we investigated the co-localization of Kir6.2 and SUR1 proteins with glucagon in human islets.

Materials and methods: A total of 257 children and adolescents aged < 16 years from 22 centres in 18 countries. A 90-min Boost-test was carried out at 1, 6, and 12 months after diagnosis. Immunohistochemistry was performed on formalin fixed material. Human pancreatic tissue (n = 6) was archival material.

Results: Multiple regression and compound symmetric repeated measurement models showed that postprandial glucagon increased over 1–12 months (p = 0.005) independent of age, gender,

stimulated C-peptide, GIP, but highly dependent on the rise in postprandial glucose ($p = 0.0003$) and GLP-1 ($p = 0.0003$). However, if the same analysis was run for the corresponding visits 1, 6 and 12 months alone there was no statistical significant influence of postprandial glucose ($p = 0.55$) and GLP-1 ($p = 0.21$) on the glucagon level after 1 month while the effect was significant after six ($p = 0.004$ for both) and 12 months (postprandial glucose $p = 0.03$, GLP-1 $p = 0.009$). Immunohistochemistry confirmed the co-expression of Kir6.2 and SUR1 proteins in glucagon immunoreactive cells.

Conclusion: The positive effect of glucose and GLP-1 on the alpha cells is secondary to insulin deficiency and highlights the primary importance of intra-islet paracrine signalling in the regulation of glucagon release. The presence of Kir6.2/SUR1 on alpha-cells suggests that sulfonylurea administered at bedtime to C-peptide negative T1D patients might prevent episodes with nocturnal hypoglycaemia.

O27

Gestational infections may enhance the increased relative birthweight in children with diabetes high risk HLA

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Introduction: Children with type 1 diabetes (T1D) high risk HLA have increased risk for high relative birthweight (HrBW).

Aims: We tested if: (i) mothers reporting gestational infections give birth to children with HrBW; (ii) gestational infections affect the association between HLA and HrBW; (iii) the previously reported reduction in HrBW by islet autoantibodies is explained by gestational infections.

Methodology: HLA-genotypes were determined in dried blood spots of cord blood in the population-based Diabetes Prediction in Skåne (DiPiS) study. Children born preterm and to mothers with diabetes or gestational diabetes were excluded. GAD65Ab, IA-2Ab and IAA was analysed by radioligand binding assays. BW adjusted for gestational age was divided into quartiles. Upper quartile was defined as HrBW. In questionnaires, mothers reported fever, gastroenteritis or both during pregnancy.

Results: 14.4% of the 19 756 mothers reported fever or gastroenteritis during pregnancy; 1.7% in more than one trimester. Children whose mothers reported infections had increased risk for HrBW ($p = 0.0003$), particularly with negative cord blood autoantibodies and infections in more than one trimester (OR 1.51 (1.19–1.91), $p < 0.001$). Infections during several trimesters aggravated the effect on HrBW by T1D high risk HLA-DQ2/8 (4.71 (1.60–13.8), $p = 0.005$). However, neither fever nor gastroenteritis explained all effect between HLA and HrBW. The decrease in HrBW with cord blood autoantibodies was only observed in newborns whose mother reported infections (OR 0.34 (0.19–0.59), $p < 0.0005$). HLA and autoantibodies related independently to HrBW when infections were reported.

Conclusion: This study revealed that (i) children have increased HrBW when born to mothers reporting fever and/or gastroenteritis during pregnancy; (ii) reported infections aggravate the previously reported association between T1D high risk HLA and HrBW and (iii) autoantibodies in cord blood decreases the risk for HrBW when infections are reported. These data suggest an interaction between HLA, gestational infections, islet autoantibodies and fetal growth.

O28

Mortality of patients with early onset type 2 diabetes in Japan

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Background and Aims: According to a recent study based on the results of school health checkups involving urinalysis in urban areas in Japan, the number of patients with early-onset type 2 diabetes (E-T2D) has gradually increased, as reported for the number of patients with adult-onset T2D. In a survey in which diabetic complications were matched to the duration of disease, we previously reported that nephropathy in those with E-T2D was more advanced than in those with early-onset type 1 diabetes (E-T1D). The above results suggest that the prognosis of E-T2D is poorer than that of E-T1D, in whom the standardized mortality ratio (SMR) was already reported to be 2.8. The aim of this study is to investigate the mortality and the causes of death in patients with E-T2D.

Patients and Methods: Among 927 patients with E-T2D who consulted our center between January 1, 1980 and December 31, 1990 (age at detection: less than 30 years), the subjects were 642 patients who were treated at our center for 1 year or more. The survival status by January 1, 2001 was investigated. The end-point was determined using questionnaires mailed to attending physicians or through telephone interviews with patients or their families.

Results: There were no differences of baseline characteristics between the subjects ($n = 642$, 358 males and 284 females, age at detection and duration at start of follow-up in the center; 0–9/10–19/20–29 ages = 2/201/439 and $19 \pm 8.8/6.7 \pm 8.4/7.2 \pm 8.2$, respectively) and the patients treated less than 1 year ($n = 285$, 173 males and 112 females, age at detection and duration at start of follow-up in the center; 0–9/10–19/20–29 ages = 0/77/208 and $0/6.8 \pm 8.6/7.4 \pm 8.8$, respectively). The completeness of this study was 84.4% (542/642). Fifty-one patients had died. The mortality ratio (/1000 person-year) was 6.7 and the standardized mortality ratio (SMR) in the subjects was 3.7 (95% CI; 2.2–4.5). The cumulative 10-year and 20-year survival rates from the follow-up period after the initial consultation in our center were 95.7% and 79.5%, respectively. Approximately 33% of the deceased patients died of major vascular disorders (CVD 17.6%; IHD 15.7%), although 67.5% of the patients had end-stage renal disease and received dialysis treatment before dying.

Conclusion: The follow-up rate was lower than that in a survey involving patients with E-T1D in our center, though, the frequency of major vascular disorders as the cause of death was more frequent than that in the survey of E-T1D. This was possibly because the age at detection and that during follow-up in the subjects were older than those in the E-T1D in our center and dialysis treatment was effective for survival but did not prevent the major vascular disorders.

O29

Reduction of post-prandial glucose excursions during closed-loop (CL) feedback-controlled insulin delivery with a manual priming bolus

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Introduction: The most immediately applicable β -cell replacement therapy for children with type 1 diabetes (T1D) is a CL system

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incorporating external glucose sensors and insulin pumps. The Medtronic MiniMed ePID® System combines an external pump and sensor with the ePID variable infusion rate algorithm designed to emulate the physiological insulin delivery characteristics of the β -cell. However, delays in insulin absorption associated with the subcutaneous route of insulin delivery inevitably lead to large post-prandial glucose excursions.

Aims: We hypothesized that the introduction of small manual pre-meal 'priming' boluses would greatly reduce post-prandial excursions in youth with T1D undergoing CL control.

Methods: Twelve adolescents with T1D (age 15.9 ± 1.7 year, A1C $7.1 \pm 0.9\%$), were admitted to the Yale CRC for 36 h of CL control; six were on complete CL control, and six received 'hybrid' CL with small priming pre-meal boluses at a dose to cover no more than 50% of the carbohydrate content of the meal. Target glucose levels were 100 mg/dl from 6AM–10PM and 120 mg/dl from 10PM–6AM. Reference venous glucose levels were obtained q30–60 min.

Results: Mean (95% confidence interval) glucose levels were 156 (149–163) mg/dl in the CL group vs. 135 (129–141) mg/dl in the hybrid group ($p < 0.0001$); night-time (10PM–6AM) glucose levels averaged 109 (87–131) mg/dl in the CL group vs. 114 (98–131) mg/dl in the hybrid group ($p = ns$). Peak post-prandial glucose levels averaged 232 (208–256) mg/dl in the CL group, compared with 191 (168–215) mg/dl in the hybrid group ($p < 0.02$).

Conclusions: CL glucose control using an external sensor and insulin pump provides a means to achieve near normal glucose concentrations in youth with T1DM during the overnight period. The addition of small manual 'priming' bolus doses of insulin, given 10–15 min before a meal, overcomes the delays inherent in subcutaneous insulin absorption and markedly improves post-prandial glycemic excursions.

030

Swedish National Recommendation: Pumps for Toddlers!

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Introduction: The National Swedish Guidelines for the treatment of diabetes in children and adolescents are available since 1982 and have been updated several times since then. These guidelines are generally accepted. Since 2004 there is included national recommendations on insulin pump treatment. Small children are suggested for sc insulin pump treatment from diagnosis.

Aim: To retrospectively evaluate the outcome of and compliance to the relatively new regimen with insulin pump treatment of the smallest children directly from diagnosis.

Methodology: All 33 children diagnosed with T1DM at our clinic and born year 2000 or later were included. Data were collected from the local registry, that covers all patients and outpatient visits.

Results: The mean HbA1c-value of all of the children since diagnosis was 6.1% (7.2% DCCT standard), mean age 3.2 years (1.1–6.1), mean insulin dose 0.7 U/kg (0.32–1.1), BMI 16.7 (SDS-0.01), mean duration 0.9 years (0.3–3.3). 11/33 children had insulin pump therapy. The others were put on multiple injections, (2)-5/ daily. Children diagnosed 2004 and later were mainly on pump from diagnosis, some of them with insulin diluted to 10 U/ml. No child or parent refused this treatment after introduction. After diagnosis none of the patients had experienced DKA or severe HG. No signs of growth disturbances or psychomotor retardation were shown.

Conclusion: Treatment of the youngest patients is demanding in time, effort and economy. Essentially normoglycaemia without severe episodes of hypoglycaemia is urgent and possible to attain with modern technology. National and international guidelines are of importance for future health economy.

031

Adolescent girls with T1DM, does combination treatment with flutamide and metformin make a difference?

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Hyperandrogenism, oligomenorrhoea and excess weight gain often beset young women with type 1 diabetes (T1DM). This triad of symptoms is frequently attributed to the unphysiological administration of subcutaneous insulin.

We have looked at the prevalence of these problems in the first phase of a multicentre European pilot study. Thirty-six young women with T1DM (median (range)) age: 16.6 (13.5–22.5) year were screened in the follicular phase of their menstrual cycle. Mean (sd) of age at diagnosis: 8.7 (3.6) year, duration of T1DM 7.9 (4.0) year, HbA1c 8.75 (1.25) %, daily insulin dose 0.95 (0.34) u/kg/d. Hyperandrogenism, defined by a Free Androgen Index (FAI) >4.5, was observed in 48% of subjects. Data were compared to a group of healthy controls of similar ages participating in a trial of women's health (Table):

	A4	95% CI	FAI	95% CI	Waistcirc,cm	95% CI	BMISDS
T1DM	10.5	9.1–12.0	4.1	3.2–5.3	74.1	72.4–75.9	1.40
Control	9.1	8.5–9.8	3.3	3.0–3.6	70.8	69.2–72.4	0.29
P	0.03	ns	0.04	0.001			

Subjects with an FAI > 4.5 or a testosterone > 1.38 nmol/ml were invited to participate in the second phase of the study; a double blind randomised placebo controlled treatment arm exploring the effects of a combined preparation of flutamide (62.5 mg/day) and metformin (1275 mg/day), (Flumet). To date 12 have been treated (six with Flumet). Three subjects on placebo have not finished the study and one withdrew before treatment commenced. Preliminary results in six subjects who have completed 6 months treatment with Flumet are reported: Mean decreases were observed: BMISDS of 0.86, HbA1c of 0.67%, testosterone of 0.72 nmol/l, insulin dose 0.1 u/kg/d. No change was seen in waist circumference. These pilot data suggest that treatment with Flumet might confer positive effects on body composition and hyperandrogenism in young women with T1DM.

032

Efficacy and safety of bedtime insulin detemir (IDET) vs. insulin semilente (SEM) in children, adolescents, and young adults with type 1 diabetes (T1D) - a randomised, open-label, cross-over study

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Background: Semilente (SEM) is an amorphous, porcine insulin zinc suspension with an intermediate duration of action. It has been used frequently for the treatment of Dawn-phenomenon in paediatric patients. The new long-acting insulin analogue detemir (IDET) may be an alternative.

Aim: To compare the efficacy (fasting plasma glucose (FPG)) and safety of insulin detemir and SEM administered at bedtime.

Methodology: Open-label, randomised, cross-over trial with a duration of each period being 16 weeks including a 4 weeks

titration phase; thus, each subject participated in the trial for 32 weeks. 68 patients (35 IDET-SEM; 33 SEM-IDET; age: 14.0 ± 2.7 years, T1D duration: 6.1 ± 3.6 years) were evaluated in the intent-to-treat set. All previously administered daytime insulins remained unchanged.

Results: No difference was found for the mean absolute change in FPG values adjusted for baseline values (ANCOVA model: 10.54 mg/dl for IDET compared to 26.76 mg/dl for SEM (P -value = 0.2688)). Mean values for HbA_{1c}% at the end of the treatment period for both IDET (7.9 ± 1.4) and SEM (7.8 ± 1.3), indicated a slight increase from baseline ($7.4 \pm 1.1\%$ and $7.6 \pm 1.0\%$, respectively). The mean absolute change in HbA_{1c} values at 16 weeks adjusted for baseline values was 0.29 for IDET compared to 0.14 for SEM ($p = 0.2442$). The daily dose pooled across both treatment sequences was higher for IDET (0.27 ± 0.11 U/kg vs. 0.16 ± 0.05 IU/kg). Nevertheless, the incidence of major hypoglycaemic episodes (0.3 vs. 0.9 per subject-year, $P = 0.039$) and nocturnal hypoglycaemic episodes was lower for the IDET treatment (3.4 vs. 7.6 episodes per subject-year, $P < 0.0001$).

Conclusion: The effectiveness of IDET and SEM administered at bedtime are comparable in controlling FPG. Although the average dose for IDET was higher than for SEM, results from the safety evaluation suggest that paediatric patients treated with IDET have a lesser risk of developing major and nocturnal hypoglycaemic episodes.

O33

Externalising behaviour problems at diagnosis a risk factor for poor outcome in young people with type 1 diabetes.

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There is evidence that psychological problems are increased in children with type 1 diabetes (T1DM) and are often associated with poor metabolic control of the illness. It is important to identify children at risk for this dual morbidity early in the course of the illness if intervention is to be effective.

Aim: This study examined continuity of internalising (e.g. depression, anxiety, social withdrawal) and externalising (e.g. delinquency, aggression) behaviour problems in a sample of young people with T1DM studied prospectively from diagnosis 12–15 years previously.

Methods: Young people with T1DM ($N = 78$, current mean age 21.1 years, $SD 3.9$) were assessed at diagnosis using the parent reported *Child Behavior Checklist* (Achenbach, 1991) and again 12–15 years later on the *Youth Self Report* (Achenbach, 1991) or the *Young Adult Self Report* (Achenbach, 1997).

Results: Regression models indicate that externalising behaviour problems at diagnosis of T1DM were significantly associated with both internalising (standardised coefficient $\beta = 0.379$, $t = 2.82$, $p < 0.01$) and externalising (standardised coefficient $\beta = 0.438$, $t = 3.30$, $p < 0.01$) behaviour problems 12–15 years after disease onset. There was no relationship between internalising behaviour problems at diagnosis and internalising or externalising symptoms 12–15 years after disease onset.

Conclusions: The current findings are consistent with the developmental psychopathology literature which suggests that early onset externalising problems persist. If untreated and, over time, generalise to include internalising symptoms in addition to the externalising behaviour problems. These findings have important implications for early intervention. Externalising behaviour problems in young children are easily identifiable and effective treatments are available, particularly if implemented early.

Routine screening for externalising behaviour problems at diagnosis of T1DM will identify children 'at risk' for poor mental and physical health outcomes. Effective interventions can then be implemented to reduce the risk of this dual morbidity.

O34

The impact of hypoglycaemic seizures on central nervous system function in type 1 diabetes

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The impact of hypoglycaemia on the developing brain is a major factor influencing clinical management of type 1 diabetes.

Aim: This study combined neuroimaging and neuropsychological assessment to examine the impact of hypoglycaemic seizures on CNS function in young people with T1DM with normal neuropsychological profiles at diagnosis 12–15 years previously.

Methods: *Subjects* T1DM with a history of one or more hypoglycaemic seizures [H+] ($n = 46$, mean age 19.6 $SD 4.1$); T1DM with no history of hypoglycaemic seizure [H-] ($n = 60$, mean age 21.2 $SD 4.2$) and healthy community controls [C] ($n = 69$, mean age 20.7 $SD 4.1$) There were no group differences on age, or baseline Full Scale IQ (FSIQ) and socioeconomic status assessed on study entry, 12–15 years previously. *Neuropsychological assessment.* Wechsler Abbreviated Scale of General Intelligence. *Neuroimaging* Structural and T2 relaxation measurements were performed at 3T. Proton MRS was recorded from 2 cm isotropic voxels placed bilaterally in the temporal and frontal lobes and basal ganglia. Neuroimaging data were available for H+ $n = 36$; H- $n = 39$; C $n = 50$.

Results: H+ had lower Verbal IQ than H- ($p < 0.05$) and C ($p < 0.01$) and lower FSIQ than C ($p < 0.05$). In basal ganglia, myoinositol (MI) levels were higher in H+ and H- (both $p < 0.05$) than in C, and N-acetylaspartyl (NAA) was lower in H+ than C ($p < 0.01$). In frontal lobes, MI and trimethylamines (TMA) were elevated in H+ and H- (both $p < 0.01$), and NAA was reduced in H+ ($p < 0.01$) relative to C. MI levels in temporal lobes were higher in H+ ($p < 0.01$) and H- ($p < 0.05$) than in C.

Conclusions: Verbal and Full Scale IQ are reduced in H+ relative to H- and C. T1DM with H+ has a greater impact on cognition and metabolite profiles than T1DM alone. Metabolite changes varied by region, and suggest a global increase in glial activity (MI), and frontal lobe membrane turnover (TMA), with neuronal stress (NAA) in basal ganglia and frontal lobe evident in H+ only. These findings suggest that intensified treatment regimens, with their associated increased risk of severe hypoglycaemia, should be introduced with caution in children because of possible risk to CNS function.

O35

KICK-OFF – a structured education program for children.

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Background: KICK-OFF is a novel, structured education programme which has been developed from the adult DAFNE curriculum, with input from children and teachers.

Aims: The pilot study was designed to (i) refine the paediatric curriculum, and (ii) assess its impact on glycaemic control and quality of life (QoL)

Methods: Six pilot courses were held in three UK centres between November, 2004 and March, 2006. Semi-structured interviews and independent course observation were designed to evaluate the

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curriculum. Biomedical (HbA1c, body mass index (BMI), hypoglycaemia) and psychosocial (QoL, self-efficacy, treatment satisfaction, family conflict, parent-child responsibility) outcomes were measured at baseline, 3- and 6-months post-intervention.

Results: Forty-eight children completed a course. Evaluation of the curriculum was very positive. There were significant improvements in QoL (General: child-p = 0.0001, Parent-p = 0.001; Diabetes-specific: child-p = 0.0001, parent-p = 0.005), treatment satisfaction (child-p = 0.002, parent-p = 0.0001), self-efficacy (child-p = 0.0001, parent-ns) and child responsibility for self-care (child-p = 0.001, parent-p = 0.0001). Mean HbA1c, BMI and hypoglycaemia were unchanged. However, those with baseline HbA1c > 9% showed a mean improvement of 0.61% between baseline and 6-months.

Conclusions: Courses were well received, needing minor changes to curriculum format. Initial evaluation found significant improvements in psychosocial outcome, which was maintained at 6-months, and a possible effect on HbA1c, particularly in those with poor baseline control. A randomised controlled trial is indicated.

036

The 730+ Club: Children as an agent for change in the delivery of a paediatric diabetes service.

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Introduction: The measured HbA1c values of children with diabetes varies widely between clinical centres, even in the same geographical location, implying that the service provided by such centres can influence metabolic outcomes.

Aims: We wanted to improve the quality and relevance of a local diabetes service by seeking the independent views of diabetic children.

Methods: Volunteers were sought from children aged between 11 and 16 years attending our hospital based diabetic clinic. Following parental consent, five unrelated children assisted by a trained facilitator undertook a systematic review of the diabetes service. This included interviewing diabetic peers as well as delivering and analysing questionnaires. After the children had prepared an initial report they asked to visit another diabetes centre to compare different systems, and a trip to a Swedish clinic was organised. The final report was submitted at a public meeting

Results: The children identified several areas for improvement. These included the clinic environment and organisation, arrangements for peer support, education and available treatment options. Most of the recommendations were implemented, including changes to the clinic structure and in the provision of an insulin pump service. Over the subsequent 3 years the clinic mean HbA_{1c} fell from 8.55% to 8.08%. We are hoping to repeat the exercise with another group of children in the next 12 months.

Conclusions: Children are more than capable of recognising the limitations of a clinical service and proposing workable solutions. As the principle users of such services, their views should be regularly sought.