OP 001

Residual beta-cell function at 12 months is predicted more by autoimmune activity than HLA haplotypes

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On behalf of the Hvidøre Study Group on Childhood Diabetes
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Background and aims: To investigate autoimmune activity (ICAs, GADAs, and IA–2As), insulin antibodies and HLA haplotypes as predictors of residual beta cell function during the remission phase.
Material and methods: Clinical data was collected locally from 275 children and adolescents age < 16 years with newly diagnosed type 1 diabetes. HbA1c, immunological samples, HLA typing, stimulated C-peptide levels (Boost test at 1, 6 and 12 months) were analysed centrally.
Results: ICA, GAD and IA2 generally decreased over the 12-month period. One month after diagnosis 90% of the children were positive for at least one of the 3 autoantibodies and 86% after 12 months. Insulin antibody positivity increased from 1 to 6 months and only 1.5% were negative for this antibody at 12 months. At 12 months C-peptide levels were 46% lower ($p < 0.001$) and the HbA1c significantly higher (0.63%, $p < 0.05$) as was daily insulin dosage (0.15 U/kg/24 h, $p < 0.002$) in those with 3 autoantibodies. At 6 and 12 months ($p < 0.001$) older children (11–16 yrs) tested more frequently positive for GAD antibodies. High levels of insulin antibodies at 12 months were significantly ($p < 0.001$) associated with a higher dose (0.23 U/kg/24 h) of exogenous insulin. Total number of pancreatic antibodies was not associated with high-risk HLA haplotypes.
Conclusion: Positivity for 3 pancreatic islet cell autoantibodies at 12 months was associated with poor beta-cell function and high levels of insulin antibodies were associated with increased daily insulin requirement. There seemed no association between HLA risk haplotypes and residual beta-cell function at 12 months after diagnosis.

OP 002

The Glu23lys variant of the ATP sensitive K^+ (K_{ATP}) channel subunit is related to glycaemic control during the remission phase of young people with newly diagnosed type 1 diabetes

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Introduction: Together with SUR1 the Kir6.2 constitute an ATP-sensitive potassium channel involved in the regulation of glucose sensing activities in pancreatic beta cells, GLP-1 secreting L cells in the distal gut and in neurones of appetite-regulating centers of the brain. The common Glu23Lys variant of Kir6.2 is overactive and less sensitive to inhibition by ATP resulting in impaired insulin secretion during an oral glucose tolerance test and susceptibility to type 2 diabetes. The aim was to investigate the impact of the Glu23Lys on the β-cell function, on the L-cell function (GLP-1 secretion) and glycaemic control during remission of 275 children and adolescents less than 16 years with newly diagnosed type I diabetes.
Methodology: HbA1c was measured centrally and stimulated C-peptide and GLP-1 (Boost) test was performed at 1, 6 and 12 months after diagnosis. DNA was extracted for analysis of the Glu23Lys variant of the Kir6.2.
Results: Statistical analyses with repeated measurement models showed that carriers of the Glu23Lys variant had a tendency towards a reduced stimulated serum GLP-1 level (coefficient 0.11, $p = 0.09$) while the stimulated serum C-peptide level was unchanged ($p = 0.85$) compared to non carriers. HbA_{1c}, adjusted for insulin dosage and body weight, was significantly ($p = 0.03$) higher during the 12 months period for those carrying the variant (coefficient 0.42).
Conclusion: The study suggests that the Glu123Lys might impede glycaemic control through a reduced postprandial GLP-1 secretion and relative impairment in neuronal regulation of appetite/satiation. The Glu23Lys variant of Kir6.2 does not have an impact on residual beta-cell function during remission of type 1 diabetes.

OP 003

Annual incidence and clinical characteristics of type 2 diabetes in school students detected by urine glucose screening in Tokyo

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Objective: To investigate the annual incidence and clinical characteristics of school children with type 2 diabetes among school children detected by urine glucose screening over the past 29 years in Tokyo.
Method: Urine glucose screening to detect diabetes was instituted in 1974 for all school children residing in Tokyo. In total, 8,319,868 (169,706–386,398 annually) school children were examined from 1974 to 2002. Morning urine was used for the analysis and when a student's urine was positive for glucose, an OGTT was carried out to confirm diabetes. All the students with type 2 diabetes detected by urine glucose screening were typically negative for diabetes-related autoantibodies, and they did not need insulin therapy for more than 2 years after the diagnosis.
Results: 232 students were identified to have type 2 diabetes. The overall incidence of type 2 diabetes over the past 29 years was 2.79/100,000/year. The incidence of type 2 diabetes before 1979 was significantly lower than that after 1980 (1.73 vs. 3.13/100,000/year, $p < 0.01$). The incidence of type 2 diabetes was significantly higher for junior high school students compared with primary school children (0.78 vs. 6.4/100,000/year, $p < 0.01$). The overall male-to-female ratio of students with type 2 diabetes was 1.0 : 1.2, but it was 1.0 : 1.6 ($p < 0.05$) in the case of primary school children. 83.4% of the diabetic students were obese, however, non-obese girls with diabetes accounted for 23.0% of the patients, while markedly obese boys accounted for 61.5% of the patients. The frequency of a family history of type 2 diabetes in second- and first- degree relatives was high (56.5%, 39.2%, respectively).

Conclusion: We confirmed that the incidence of young people with type 2 diabetes is increasing in Tokyo. Gender, age and genetic susceptibility may be associated with the occurrence of type 2 diabetes. The increase in the frequency of this disorder seemed to be strongly related to an increasing prevalence of obesity.

OP 004

Adipocytokines and incipient type II diabetes in juvenile obesity

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Introduction: Adipocytokines are centrally involved in metabolic abnormalities of obesity. To elucidate their involvement in very early states of type II diabetes, we measured serum levels of resistin, leptin, leptin receptor, and adiponectin in obese juveniles that were previously found with increased intima media thickness (IMT) of common carotid arteries (CCA) and increased low grade inflammation, and compared them to healthy, normal weighted, juvenile controls.

Methods: Serum/plasma levels of ultra sensitive C-reactive protein (US-CRP), malondialdehyd (MDA), lipid fractions, glucose, homocysteine, resistin, leptin, leptin receptor, and adiponectin were determined by means of ELISA in 199 obese juveniles (BMI-SDS: 6 ± 1.6, age: 13 ± 2.9 years, mean ± SEM) and 203 normal weighted age matched controls. Intima-media thickness (IMT) of both common carotid arteries (CCA) was measured by ultrasonography.

Results: In spite of normal fasting glucose levels and lacking other symptoms of type II diabetes, plasma levels of resistin were significantly positively correlated with US-CRP ($r = 0.42$, $p < 0.0001$) in the obese juveniles. Leptin receptor was markedly decreased in the obese cohort ($p < 0.01$) and correlated negatively with systolic blood pressure ($r = -0.3$, $p < 0.01$) and IMT values ($r = -0.36$, $p < 0.01$). Interestingly, adiponectin showed the best correlation with the increased IMT ($r = -0.46$, $p < 0.0001$) suggesting a protective function of high levels for the vessel wall. Obese probands with markedly decreased adiponectin showed increased MDA levels indicating oxidative stress associated with low adiponectin. HDL-cholesterol correlated positively with adiponectin ($r = 0.33$, $p < 0.002$). Resistin did not correlate with lipid fractions.

Conclusion: Our data clearly indicate the close relationship between incipient insulin resistance, as detected by increased resistin, and low grade inflammation in juvenile obesity. This very early state of type II diabetes is already associated with preatherosclerotic symptoms such as an increased IMT of CCA. Furthermore, adiponectin may be protective against early vascular alterations.

OP 005

Results and lessons from continuous glucose monitoring in a large cohort of children with type-1 diabetes

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Introduction: The evaluation of glycemic control in children with type-1 diabetes beyond honeymoon period is very challenging for both, patients and diabetologists. Continuous glucose monitoring system (CGMS) provides the opportunity for close insight into metabolic control of a whole day, and therefore, may lead to more individual tailoring of insulin therapy.

Methodology: Ambulatory CGMS, standardized self-monitoring blood glucose (SMBG), and HbA1c measurements were performed in 145 patients with type-1 diabetes (64 boys, 81 girls; median age 13.3 [2–20] years, diabetes duration 4.5 [1–17] years). Clinical parameter and data of insulin therapy were analyzed. Eighty-two patients were treated with multiple daily injections, 63 patients with insulin pump. Average glucose concentration/24 h, separately for day- (7–22 h) and night-time (22–7 h), 1 h pre and 3 h post meal, as well as number of excursions, duration and area under the curve of glucose values above 180 mg/dl and below 70 mg/dl were calculated from CGMS data.

Results: In the total group, both, CGMS average glucose/24 h ($r = 0.42$) and SMBG values ($r = 0.43$) correlated with HbA1c ($p < 0.001$) as well as day- ($r = 0.37$) and night-time ($r = 0.30$) glucose average ($p < 0.001$). Hyperglycemic parameters like AUC and time above 180 mg/dl correlated significantly with HbA1c ($r = 0.44$ and $p = 0.36$, $p < 0.001$), while AUC ($r = -0.19$, $p = 0.003$) and time ($r = -0.27$, $p < 0.001$) below 70 mg/dl showed inverse but lower correlation. Glucose average/24 h was equally influenced by pre- and postprandial glucose values ($r = 0.78$ and $r = 0.79$, $p < 0.001$). Apart from age and basal/prandial insulin ratio, AUC above 180 mg/dl was the most predictive independent factor of HbA1c in multivariate analysis (r-square = 0.322, $p < 0.001$).

Conclusion: As compared with SMBG, CGMS data provide a more detailed insight into the intra-day course of glycemic control. Particularly, hyperglycemic parameters like AUC above 180 mg/dl have an independent influence on HbA1c values. Moreover, pre- and postprandial glucose levels seem to be equally relevant for glycemic control.

OP 006

Activating mutations in the gene encoding the ATP sensitive potassium (K_{ATP}) channel subunit KIR6.2 causing permanent diabetes mellitus and developmental delay: a novel syndrome?

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Introduction: Permanent neonatal diabetes mellitus (PNDM) is a rare disorder of heterogeneous aetiology. Activating mutations in the *KCNJ11* gene encoding the Kir6.2 subunit of ATP-sensitive potassium channel (K_{ATP}) were recently described as one of the causes of PNDM. As *KCNJ11* is expressed in muscle, brain and heart as well as beta-cells there could be diverse phenotypic expressions. Most patients with *KCNJ11* mutations have no extra-pancreatic features and respond to sulphonylureas.

Patients: We present three cases with PNDM caused by the heterozygous mutations in *KCNJ11*: V59G, Q52R and I296L with very similar neurological features. Apart from insulin-dependent PNDM and low birth weight, all had a marked developmental delay, muscle weakness and epilepsy, which did not result from diabetes and/or its treatment. Their physical appearance is characterized by a prominent metopic suture, down turned mouth and bilateral ptosis. Two patients had limb contractures which were also seen at birth. The patient with the most severe motor delay died at the age of 1.2 year; the other two are 5 and 17 years old. In contrast to the non-neurological cases, they did not secrete insulin acutely in response to tolbutamide. Similarly, we observe no change either in insulin requirement, diabetes control or neurological/developmental status 6 months after adding sulphonylurea to insulin therapy while non neurological patients have frequently been able to discontinue insulin.

Conclusion: In conclusion, a subgroup of subjects with severe neurological disturbances can be differentiated among patients with PNDM caused by activating mutations in the *KCNJ11* gene. The similarity in clinical pattern, physical appearance and lack of response to sulphonylureas suggest a novel discrete syndrome that may represent

functionally more severe activating mutations of *KCNJ11* that do not respond to sulphonylureas.

OP 007

Analysis of somatic development in paediatric patients with type 1 diabetes mellitus

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Background and aims: National statistics show development of serious complications and delay in physical development in children 5 years from the date of diagnosis. The purpose of this study is to assess changes in the glycemic control of children and young people with type 1 DM in relation with duration of treatment.

Patients and methods: 53 children (18 boys and 35 girls) with type 1DM, aged between 3 and 20 years (mean 13 ± 1.48 years) with duration of diabetes 1–19 years (mean 4.8 ± 2.6 years) were estimated. All patients had bad metabolic control of diabetes (HbA1c-mean 11.45 ± 1.3%) and high variability of blood glucose levels. Glycaemic control was assessed by HbA1c measurements, all were initially assessed for physical and sexual development (Tanner charts), body mass, insulin dosage and complications. Children and parents participated in education program with often regular follow-up clinic contact, because they did not have home self-monitoring and they have blood glucose measurements only on admission. Most of the patients were start treated by intensive insulin therapy and mean daily doses of insulin were increased during treatment. Standing height and weight were recorded every two months. Height measurements were normalized for age and sex by converting them to Standard Deviation Score (SDS).

Results: After 6 months all main clinical and general health parameters were improved.

	Dose	HbA1c	BMI	SDS height	SDS weight
First admission	0.65	12.3	15.9	–1.69	15.8
After 6 months	1.2	9.1	17.5	–0.83	17.5

We concluded that in children with diabetes mellitus deficit of height and weight depends on insulin doses and metabolic control, duration of diabetes.