

Consensus Guidelines: Reality or Dream?

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Aim of Study: Assess quality of diabetes care defined by consensus guidelines of ISPAD in our area; develop appropriate strategies to improve care.

Design: Retrospective chart review of all individuals with IDDM diagnosis before spring 1997 followed regularly by us (either outpatient clinic or office).

Method: Comparison of number of patients having had: (1) eye exam by ophthalmologist; (2) determination of MAU, and (3) lipids within 1 year among 4 subgroups defined by duration of IDDM (<2 years and having entered puberty or not. HbA1c (monoclonal AB n = 3–6%) was used nearest to June 1997.

Results are expressed as mean \pm SD; t test used to confirm significance.

Results: Group A (prepub. <2 years IDDM), n = 14 (5 females, 9 males), age 7.3 ± 3 years (range 2.8–11.9). Group B (prepub. >2 years IDDM), n = 10 (1 female, 9 males), age 8.4 ± 2.9 years (range 3.8–11.5). Group C (pubertal, <2 years IDDM), n = 10 (6 females, 4 males), age 13.1 ± 1.5 years (range 10.9–15.5). Group D (pubertal, >2 years IDDM), n = 26 (15 females, 11 males), age 13.9 ± 2.8 years (range 10.4–20.8).

	A	B	C	D
Eye exam	9/14	5/10	9/10	21/26
MAU	1/14	4/10	6/10	16/26
Lipids	6/14	6/10	8/10	13/26
HbA1c	7.7+1.3	8.6+1.5	7.4+1.5	8.4+1.2
	**aa) 8.4+0.5	*ab) 7.1+1.5	da) 8.7+1.2	**db) 7.8+1.1

aa) <6 years, n = 6; ab) >6 years, n = 8, da) <15 years, n = 16; db) >15 years, n = 8.

* p < 0.01 A vs. B; ** p < 0.05 C vs. D; aa vs. ab; da vs. db

Conclusions: Although the majority of pubertal patients with longstanding IDDM have had a recent eye exam, screening for MAU as an early marker of kidney involvement needs to be improved as well as detection of dyslipidemias favoring vascular complications. HbA1c is lower in IDDM up to 2 years duration except the very young and improves again in the older adolescents with longstanding IDDM.

Pain Perception and Bleeding in Diabetic Children when Using Different Sizes of Injection Needles

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In this double-blind, randomized, controlled study the aim was to compare pain and bleeding when using different needles. 40 children and adolescents with IDDM aged 8–20 years (mean 15.9) with a diabetes duration of 0–16 years (mean 6.8) participated. The test prod-

ucts were B-D Micro-Fine+ G29 (12.7 \times 0.33 mm) and NovoFine G30 (8 \times 0.30 mm). NovoFine G28 (12 \times 0.36 mm) and a placebo (without needle) were used as reference. The patients received 6 injections (1 in thigh and 1 in abdomen of each needle type) with test media and 2 dummy injections at 2 separate study visits. Pain was recorded on a 10-cm visual analogue scale (VAS) with faces. We found no statistically significant difference in pain perception between the needles but all were clearly separated from placebo (ANOVA p = 0.0001). Abdominal injections were more painful than thigh injections (ANOVA p = 0.0099). Bleeding was less common with the G29 needle than with the G28 needle (Friedman p = 0.028). The frequency of intracutaneous injections was 1.2–5.0% (Friedman p = n.s.). Leakage of insulin was found in 9–18% of abdominal and 19–29% of thigh injections (Friedman p = n.s.). The VAS pain score when taking a blood glucose test was 1.5 ± 1.7 .

Pain perception, VAS score cm (mean \pm SD):

Needle	G28	G29	G30	Placebo
Abdomen	2.7 \pm 2.1	2.6 \pm 1.8	2.8 \pm 1.7	0.3 \pm 0.6
Thigh	2.3 \pm 1.7	2.1 \pm 1.8	2.1 \pm 1.6	0.4 \pm 0.6

In conclusion, we found small pain perceptions with all 3 needles with no difference between the needle types.

Deoxyglucose Uptake in Pancreatic Glands of Diabetic/Nondiabetic NOD and Swiss Mice

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At present no in vivo method is available to represent the insulinitis in patients with IDDM.

Methods: Swiss mice as well as nondiabetic/diabetic (insulin-treated, blood glucose <250 mg/dl) NOD mice were injected either with 125 μ Ci 2-F-18 deoxyglucose (FDG), a substance for positron emission tomography (PET), or, for autoradiography, with 25 μ Ci 2-[¹⁴C(U)]-deoxyglucose (DG). 30 min post-FDG liver, pancreas, muscle and fat pads were removed, weighed and the radioactivity determined by γ -counting. Results (median, 25th and 75th percentiles) are expressed as cpm/mg tissue per cpm/mg liver. In addition, 1 h post-DG pancreatic tissue of 2 diabetic NOD and 2 Swiss mice were excised and autoradiographed. Slices of each pancreas were stained with HE.

Results: FDG uptake by muscle: 0.3–0.5–0.8 (23) and fat: 0.1–0.2–0.7 (18) was similar in all mice and lower when compared to liver uptake. The table shows the results for the pancreas:

	Pancreas/liver ratios		
	25%	Median	75%
NOD, diabetic (15)	2.3	3.0	9.0
NOD, nondiabetic (8)	0.4	0.7	0.9
Swiss albino (8)	0.4	0.5	0.6

Islets of diabetic, but not of nondiabetic NOD or Swiss mice were infiltrated with lymphocytes.

Autoradiography: In controls and one NOD with no inflammatory cells in the examined sections labelling was almost evenly distributed. In contrast, pancreatic sections of the 2nd NOD mouse exhibited clear-cut differences in the distribution of radioactivity. Labelling was found to be extremely high over lymphocytes located in the center of almost completely destroyed islets, while labelling of islets encapsulated by lymphocytes was identical to that over exocrine pancreas.

Conclusion: Uptake of deoxyglucose by the pancreas of diabetic NOD mice with insulinitis was markedly augmented compared with nondiabetic NOD or Swiss mice. PET may turn out to be a method to detect insulinitis in IDDM.

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32

Self-Efficacy, Problem-Solving and Knowledge as Predictors of Glycaemic Control in Young People with Type 1 Diabetes: A Cross-Sectional and Longitudinal Study

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Self-efficacy in diabetes care (perceived competence in diabetes self management) has been found to be predictive of better adherence to management regimens (e.g. insulin therapy, diet) of type 1 diabetes. This study examined whether self-efficacy in diabetes care in young people is associated with better glycaemic control. As part of a longitudinal intervention study, 91 Caucasian subjects (mean age 17 years, range 12–25; mean duration 13 years, range 1–13; M = 46) were assessed on self-efficacy in diabetes care (SED); diabetes knowledge; problem-solving (examining overall problem-solving ability and specific problem-solving skills); and barriers to adherence. Glycaemic control was assessed by calculating mean glycated haemoglobin (HbA_{1c}%) for the year preceding the baseline assessment: <8% was accepted as good overall glycaemic control. SED was associated with HbA_{1c} ($r = -0.23$; $p = 0.05$) and the specific skill of rational problem-solving ($r = -0.22$; $p = 0.05$). A high SED was associated with overall ability to solve problems ($r = 0.35$; $p = 0.01$) and low barriers to adherence ($r = -0.27$; $p = 0.01$). Those with good glycaemic control had higher SED (57.2 vs. 41.0; $p = 0.007$) but no more knowledge than those with poorer control. Measures were repeated at 1 year. Longitudinal data allows further examination of the nature of cross-sectional associations and predictors of psychosocial glycaemic control. A person's self-efficacy can be enhanced through strategies of care and education, specific problem-solving skills can be rehearsed and encouraged. We believe the management of young people with type 1 diabetes should fully incorporate such goals.

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33

Diabetes mellitus in Children Aged 0–36 Months

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Objective: To analyse cases of diabetes diagnosed in infancy (0–12 months) and in young children aged 13–36 months.

Methods: We studied 40 cases of diabetes in children from 3 diabetic centres: Katowice, Wrocław (Poland) and Kosice (Slovakia) divided into three age groups: group I – 7 children with diabetes diagnosed in infancy; group II – 15 children with diabetes diagnosed between 13 and 24 months of age; group III – 18 children with diabetes diagnosed between 25 and 36 months of age. We analysed gestational age, birthweight, sequence of pregnancies, pregnancy and perinatal problems, age of parents, breast-feeding period, IDDM and NIDDM history in first- and second-degree relatives, symptoms of onset of diabetes and mean glycohemoglobin HbA_{1c} in the first years of disease.

Results: All children were born in term with normal birthweight except 4 children with intrauterine dystrophy from group I. Age of parents was similar for all children and so was the duration of breast-feeding (4–6 months). Group I consisted mostly of children of I pregnancy without the presence of family history of diabetes. Group II, III were mostly from following pregnancies and had family history of diabetes presence – 26.7% (II), 44.4% (III) adequately. Group I infants often had no ketonuria during diagnosis (5 cases). Ketonuria was present in all children from groups II and III. Mean HbA_{1c} was similar in all groups' children during first years of diabetes.

Conclusions: (1) Prenatal parameters do not make any difference between children with diabetes diagnosed in 13–36 months of age and healthy children. (2) Intrauterine dystrophy occurs in half children with diabetes diagnosed in infancy. (3) Children with diabetes diagnosed in infancy mostly have negative ketonuria in onset of disease.

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34

Birthweight, Parents' Age, Sequence of Children in Family in Newly Diagnosed IDDM Children in the Period 1989–1996 in Upper Silesia, Poland

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The aim of the research was to analyse birthweight, parents' age, sequence of children in family in the group of 459 IDDM children. The subjects (208 girls, 251 boys) were aged 0–14 years, diagnosed as diabetic between 1989 and 1996 in the Upper Silesia region, Poland. All of them were born between 1976 and 1995 (with average number of all children born per year exceeding 65,000 in the region). Incidence of IDDM is 6.7/100,000 for this region, for children from this age group. The average birthweight of IDDM children is 3,271.7 g (95% CI 3,224.7–3,318.7, birthweight median 3,350 g); mother's age 26.45 years (95% CI 25.98–26.93, median 25), father's age 28.95

years (95% CI 28.45–29.45, median 29). Most of the children's birthweight fell into the 3,000–3,999 g group (66.16% of the entire population) and the majority of mothers were 20–29 years old (68.66%). As far as fathers are concerned, their age distribution was slightly different and generally they were older than the mothers. Most of them were 24–33 years old (67.71%). Furthermore, the sequence of the children in the family was taken into account. Obtained data showed that in most cases the IDDM children were either first (223 cases – 49.01%) or second (165 cases – 36.26%) in the family, with quartile range 1–2. We also observed that there were no significant differences in the birthweight cdf ($p < 0.05$); however, these differences appear in parents' age and birth sequence cdfs. It has also been established that the higher risk is associated with high birthweight ($>4,000$ OR = 1.192) it was not observed for small one ($<2,500$ OR = 1.01). Mothers' age seems to be also a risk factor (>35 OR = 1.193). Father's age cannot be associated with increasing risk, however it seems that lower age is protective against IDDM (>40 OR = 0.98, >35 OR = 0.86, <26 OR = 0.74).

Conclusions: Mothers' age seems to affect the risk of IDDM development. Moreover, so does high birthweight despite that its distribution function does not significantly differ for IDDM and all children.

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35

Genetics of Diabetic Retinopathy: Differences in Those Diagnosed Before 5 Years of Age

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To investigate potential genetic risk factors for early diabetic retinopathy, five candidate polymorphisms were examined in genomic DNA from 195 adolescents with IDDM. Retinopathy status was determined from stereoscopic fundal photography. Three proposed polymorphisms have been implicated in macrovascular disease in adults both with and without diabetes: MTHFR (methylenetetrahydrofolate reductase), and paroxonase1 (PON1) at 192 and 54. The other two polymorphisms are novel and found in the promoter and the intron region of the aldose reductase gene (AR). The MTHFR and PON1 192 mutations were not associated with retinopathy. The L/L genotype of PON1 Leu-Met 54 increased the risk for retinopathy (OR 2.89 [CI 1.48–5.66]) as did the intronic BB of the AR (OR 5.03 [CI 1.73–14.57]). The polymorphism CC of the AR promoter also increased the risk of retinopathy (OR 9.12 [2.48–33.52]). The effect of duration was smaller (OR 1.20 [1.09–1.31]). In the subgroup of adolescents diagnosed after 5 years, no genotype was significantly associated with retinopathy after allowing for diabetes duration. In those diagnosed before 5 years of age, diabetes duration was not significant in the model after allowing for the effect of the two genotypes. The BB genotype increased the risk eightfold (OR 8.29 [1.43–48.03]), the L/L increased the risk sixfold (OR: 6.28 [1.54–25.63]), and the CC increased the risk sevenfold (OR: 7.20 [1.28–40.36]). Three candidate polymorphisms were associated with an increased risk for diabetic retinopathy in adolescents. The risk profile was only evident in those diagnosed before age 5 years.

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36

Patient Acceptance and Use of an Emergency Telephone Hotline Service in Pediatric Diabetes Care

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Families of children and adolescents with type 1 diabetes have to deal with imminent acute complications of the disease. We have therefore introduced a 24-hour 7-day a week telephone hotline service in March 1996 and have asked whether this emergency hotline as part of our diabetes care approach was accepted and used by our patients and their families.

120 phone calls were analyzed in a prospective and structured survey. Calling time, date, and reason for using the telephone hotline were recorded as we documented name, frequency of calling and diabetes-related data. Diabetes care is provided at our institution for 240 children and adolescents, mean age 12.2 years (range 1.8–20), mean duration of diabetes 5 years (range 1 month to 13 years). Mean HbA_{1c} is 7.48% (range 4.8–14.7). The mean age of the patients who used the hotline was 8.2 years (range 2.7–19). Thus, this age was significantly ($p < 0.001$, Student's *t* test) lower than the age in the total population of all patients cared for at our institution. Mean duration of diabetes was 31 months (range 1–152), with 49 of the calls being received from children under 12 months. Mean HbA_{1c} of the patients using the telephone hotline was 7.65% (range 5.8–13.2). The main reasons for calling were insulin dosage (35%), hypoglycemias (23%) and insulin dosage with gastroenteritis (10%) and hyperglycemia (10%).

Conclusion: An emergency telephone hotline for pediatric patients is a service that is accepted and regularly used. Our experience over the recorded period suggests that the service prevented hospital admission in several instances.

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37

Insulin-Dependent Diabetes and Chronic Active Hepatitis in a Nine-Year-Old Boy: An Indication to Cyclosporine

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Insulin-dependent diabetes mellitus (IDDM) in children is an autoimmune process as shown by the presence of islet cell antibodies before and after the beginning of the disease, and the high incidence of some predisposing HLA antigens. The association of IDDM to other autoimmune endocrinopathies is frequent. The following case is rare because diabetes is associated with chronic active hepatitis. Ihab is a 9-year-old boy whose first symptoms were: polyarthrititis, frequent bloody stools, weight loss, and recent polyuria-polydipsia. He was admitted to the hospital. The first biologic screening showed elevated blood sugar (32 mmol/l), elevated AST (1,257), glucosuria and cetonuria. Viral serologies of hepatitis were negative (A, B, C, CMV). The anti-organ autoantibodies including anti-Lkml were negative. Protein electrophoresis and immunoelectrophoresis were

normal. Abdominal ultrasound was normal. Duodenal and rectal biopsies were normal. The latter findings ruled out inflammatory bowel disease. Hepatic needle biopsy showed chronic active hepatitis with beginning of cirrhosis. HLA study showed absence of A1, B8, DR3, DR4. The diagnosis of diabetes mellitus associated to active chronic hepatitis was then confirmed. Insulin regimen was started with a mixture of regular and intermediate-acting insulin (1 IU/kg/day). Azathioprine (Immurel: 2 mg/kg/day) was also started for his chronic hepatitis instead of cortisone because of diabetes. One month later hepatic enzymes are still very high; cyclosporine (7 mg/kg/day) was started at 14 mg/kg/day and then decreased to 12 mg/kg/day. Cyclosporine level was kept within the therapeutic margin. Biologic hepatic tests improved after 13 months of immunosuppressive therapy.

Last blood test showed AST (80 IU) and normal creatinine and cyclosporinemia. We also note a decrease in HbA1c from 12.7 to 6% and in insulin doses from 1 to 0.5 IU/kg/day.

Conclusion: In a diabetic child, cyclosporine induced a remission of chronic active hepatitis after 13 months. Cyclosporine is not usually the first drug of choice in this disease, but association to diabetes and noncompliance of the family to its treatment are the main reasons for that choice.

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38

Endogenous Cyclosporine-Like Factors in the Blood of Children with IDDM

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In the blood serum of persons not treated with drugs the occurrence of endogenous drug-like factors can be found. In our previous clinical observations we estimated the occurrence of digoxin-, theophylline-, phenytoin- and quinidine-like factors in the blood of healthy subjects. Now we take our consideration into cyclosporine which was used in many clinical trials with the aim of provoking a remission in IDDM. Great toxicity of cyclosporine caused its break. In our present study we estimated the occurrence of cyclosporine-like factors in healthy subjects and in children with IDDM. The observations were carried out in 85 healthy children and in 145 new cases of IDDM aged 6–15 years not receiving any treatment before or during the test was studied. We also observed the blood of cyclosporine in children with IDDM during the remission. The examinations were carried out with the use of the fluorescence-polarization-immunoassay (FPIA)-TDX Abbott. The presence of endogenous cyclosporine-like factors in blood serum was found in healthy children in 91.4% and in children with IDDM in 90.8%. The mean values of the cyclosporine-like factors were as follows: in healthy children 12.13 ± 5.18 ng/ml and in children with IDDM 17.98 ± 4.12 ng/ml in the first days of the onset of diabetes. In the remission period, however, the level was 33.42 ± 6.12 ng/ml and after the end of the remission 20.18 ± 5.80 ng/ml. The concentration of cyclosporine during the remission is statistically significantly higher ($p < 0.05$). Our findings suggest that the occurrence in blood serum endogenous cyclosporine-like factors regulates the functional state of the immunological sys-

tem and is produced by the organism according to its needs. The higher level of cyclosporine in the remission period of IDDM can be the expression of the fight of the human organism against the antigens which destroy the beta cells. Perhaps in the future stimulation of the endogenous cyclosporine factors could be used to evoke a remission.

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39

Electrophysiological Evaluation of Neuropathy in Children with IDDM

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The object of this study was to compare the efficacy of two different electrophysiological methods to evaluate diabetic neuropathy. In addition to conventional motor and sensory nerve conduction studies, infra fascicular microneurography was performed in the median nerve. A tungsten microelectrode was inserted into the median nerve trunk at the elbow, and a compound nerve action potential (CNAP) was recorded with supramaximal electrical stimulation at the wrist. We studied 30 patients with IDDM (12 boys 14.8 ± 4.1 years and 18 girls 14.8 ± 3.9 years, mean \pm SD) with a duration of disease of 7.3 ± 3.9 (mean \pm SD) years. No patients had symptomatic neuropathy. Informed consent was obtained from all patients. In the median nerve conduction studies, none of the patients had any abnormality, but 36% showed abnormalities in the amplitude of CNAP. In particular, 50% of long-term patients (over 10 years) showed a CNAP with low amplitude. The decrease in CNAP amplitude had a tendency to correlate with duration of diabetes and long-term poor metabolic control.

These data suggest that microneurography is useful for the detection of relatively early stages of diabetic neuropathy.

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40

Incidence of Insulin-Dependent Diabetes mellitus in Children under 4 Years of Age in the Republic of Macedonia

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Republic of Macedonia is a cold spot considering the IDDM incidence in childhood. The overall IDDM incidence in children up to 15 years of age has remained low during the last 10 years (1.84–4.11/100,000 children/year). However, the incidence in the youngest group has not been evaluated. The aim of this study is to determine and follow over time the IDDM incidence in children under 4 years of age in this low-incidence population. Registration of all newly diagnosed children with diabetes was performed at the Pediatric Clinic as a central institution for diabetes treatment in children. The overall incidence in the 0- to 4-year age group was 1.53 on average. The lowest incidence was 0.64 per 100,000 (in 1990) and the highest 2.66 per 100,000 (in 1992). The average incidence for this period of

time was higher for girls (1.80 per 100,000) than for boys (1.27 per 100,000); however, the difference did not reach statistical significance. There is a slight increase of males below 4 years with diabetes during the last 5 years, but not as important as data in some other studies.

In conclusion, IDDM incidence in the very young group of children below 4 years of age is low and stays low over years in the Republic of Macedonia and is comparable with the overall low incidence of IDDM in children with diabetes.

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41

C-Peptide Treatment Normalizes Reduced Glomerular Na⁺,K⁺ ATPase Activity in Streptozotocin Diabetic Rats

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According to the prevailing view in the past C-peptide was considered to be a biologically inert peptide. However, it has been established that C-peptide does in fact exert a restraining influence on glomerular hyperfiltration and diminishes microalbuminuria in type 1 diabetic patients. The aim of the present study was to investigate the effect of C peptide on glomerular Na⁺,K⁺ ATPase activity in rats with streptozotocin-induced diabetes mellitus. Diabetic rats were treated with C-peptide (2 × 75 nmol/day). Na⁺,K⁺ ATPase activity was measured in isolated glomeruli by means of [³²P]ATP hydrolysis. Na⁺,K⁺ ATPase activity was significantly reduced in the untreated diabetic rats (227 ± 50 nmol P_i/mg protein/h) compared to controls (996 ± 55 nmol P_i/mg protein/h). C-peptide treatment significantly increased glomerular Na⁺,K⁺ ATPase activity (843 ± 50 nmol P_i/mg protein/h), but did not abolish hyperglycemia and kidney hypertrophy in the diabetic rat. There was no statistical difference in the glomerular Na⁺,K⁺ ATPase activity between the C-peptide-treated diabetic and control rats.

Conclusions: Diabetes is associated with decreased glomerular Na⁺,K⁺ ATPase activity. C peptide treatment stimulates reduced Na⁺,K⁺ ATPase activity in rats with streptozotocin-induced diabetes.

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42

Characteristics of Very Young Children with Insulin-Dependent Diabetes mellitus (IDDM)

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We analysed the clinical, autoimmune, and genetic characteristics of 36 children diagnosed to have IDDM before 2 years of age, and compared them to 148 children diagnosed between 2.0 and 4.9, and 627 children diagnosed between 5.0 and 14.9 years of age. At diagnosis, the youngest children were more susceptible to diabetic ketoacidosis than children in the other two groups (53, 14 and 22%; $p < 0.001$). Also their median serum C-peptide levels were lower than in the other groups (0.07, 0.14 and 0.17 nmol/l; $p < 0.001$). Children in the youngest age group tested more often positive for insulin autoantibodies (91, 68 and 41%, $p < 0.001$), but not for islet cell antibodies or antibodies against the 65-kD isoform of glutamic acid decarboxylase. They also had higher levels of insulin autoantibodies ($p < 0.001$) and islet cell antibodies ($p < 0.01$). The subjects were divided into four groups based on HLA-DQB1 genotypes: DQB1*0302/0201 (high risk); *0302/x (moderate risk); *0201/y (low risk), and *z/z (decreased risk) x stands for *0302 or a neutral allele and y for *0201 or a neutral allele, whereas z represents alleles other than 0302 or 0201). Children in the youngest age group were under-represented among those with the genotype conferring decreased risk (17, 20 and 27%, $p < 0.05$).

We conclude that children diagnosed with IDDM before 2 years of age are characterised by a more severe metabolic decompensation at diagnosis, signs of an aggressive autoimmune attack and strong genetic disease susceptibility.

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43

Children without Diabetes Have Significantly Higher Levels of GAD Antibodies than Adults

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Recent strategies for assessing the risk of progression to diabetes mellitus among first-degree relatives of patients with diabetes are increasingly based on the determination of antibodies to glutamic acid decarboxylase (GAD) and tyrosine phosphatase IA-2. This study investigated whether there is an influence of age concerning the prevalence of these antibodies in healthy children and adults with no family history of type 1 diabetes. GAD and IA-2 antibodies were measured by radioimmunoassays in sera of 138 healthy children (median age: 9.2 years; range: 1–17) and 100 healthy adult blood donors (age: 37 years, 18–65). They were compared to levels in 150 children with recent-onset diabetes (age at onset: 8.9 years, 1–17). Healthy children had significantly higher levels of GAD antibodies than adults ($p < 0.001$). The 97.5th centile was 9.98 U/ml in children