

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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### **C-Peptide Treatment Normalizes Reduced Glomerular Na<sup>+</sup>,K<sup>+</sup> 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<sup>+</sup>,K<sup>+</sup> ATPase activity in rats with streptozotocin-induced diabetes mellitus. Diabetic rats were treated with C-peptide (2 × 75 nmol/day). Na<sup>+</sup>,K<sup>+</sup> ATPase activity was measured in isolated glomeruli by means of [<sup>32</sup>P]ATP hydrolysis. Na<sup>+</sup>,K<sup>+</sup> ATPase activity was significantly reduced in the untreated diabetic rats (227 ± 50 nmol P<sub>i</sub>/mg protein/h) compared to controls (996 ± 55 nmol P<sub>i</sub>/mg protein/h). C-peptide treatment significantly increased glomerular Na<sup>+</sup>,K<sup>+</sup> ATPase activity (843 ± 50 nmol P<sub>i</sub>/mg protein/h), but did not abolish hyperglycemia and kidney hypertrophy in the diabetic rat. There was no statistical difference in the glomerular Na<sup>+</sup>,K<sup>+</sup> ATPase activity between the C-peptide-treated diabetic and control rats.

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

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### **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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### **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

and below the cut-off of 6.0 U/ml in adults. In contrast, the prevalence of IA-2 antibodies did not differ between these two cohorts. Thus, the age-independent 97.5th centile for IA-2 antibodies was 0.975 U/ml in the total cohort. No effect of gender was seen for both antibodies. As expected, children with recent-onset diabetes had significantly higher GAD and IA-2 antibody levels than healthy children ( $p < 0.001$ ). If the 97.5th centiles of the reference groups were applied in children with recent-onset diabetes, 43% had elevated levels for both antibodies. This was not the case in any healthy subject (specificity 100%, sensitivity 43%).

These data indicate the importance of establishing age-related reference values for diabetes-related antibodies in the background population before applying them for screening and intervention studies.

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### Does It Make Sense to Screen for Celiac Disease in Children and Adolescents with Type 1 Diabetes?

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Among patients with type 1 diabetes the prevalence of asymptomatic and symptomatic celiac disease (CD) is 1.8–4.0%, about 10× higher than in the general population. CD is often difficult to suspect, because of its mild, unspecific or even absent clinical symptoms. The introduction of a gluten-free diet in a child or adolescent with diabetes is an additional burden and has negative psychological consequences, except for those with clinical symptoms, who are compliant for diet because of the immediate benefit. The most severe complication of untreated CD is an intestinal T-cell lymphoma (enteropathy-associated T-cell lymphoma = EATCL). It is rare and appears mostly in older people: T-cell lymphomas represent 20% of all non-Hodgkin lymphomas, and less than 3% of them are EATCL. The incidence of EATCL in CD patients is about 50× higher than in the general population. The goal of this study was to find out the incidence of EATCL in diabetic patients. We performed a country-wide retrospective survey and, in addition, searched the more accurate regional cancer registry for EATCL between 1988 and 1993. The ascertainment in the regional cancer registry was 95%. The second ascertainment in archives of lymphomas of the local university and the two regional clinics was 100%. All data of malabsorption, CD and other associated diseases were collected. We found 10 cases of EATCL, 5 of them in the regional cancer registry. None of them suffered from diabetes. The mean age of the patients with EATCL was 61.9 (range 43–76), well comparable to the literature. Five of the patients had a long history of malabsorption, 3 of them since childhood. From these results we conclude that it is not realistic and perhaps ethically not acceptable to screen for CD in type 1 diabetes. The risk of noncompliance in diabetes therapy and the deterioration of metabolic control – especially in adolescents – by an additional strict dietary regime for a clinically asymptomatic disease might be much higher than the risk of developing EATCL. However, larger, e.g. international, studies would be necessary to verify our data.

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### Link between Incidence of Childhood IDDM and Month of Birth: Illusion or Fact?

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To test the hypothesis that the initiation of the autoimmune process of childhood IDDM in genetically susceptible subjects is started in the perinatal period by a viral infection transmitted by the mother, we studied the existence of seasonal variations in the month of birth of several cohorts of patients. Population groups with high or low IDDM incidence were analyzed separately by ANOVA and COSINOR. In Israel, we included 1,045 of 1,188 patients from the whole-country registry (years 1980–1993) – Ashkenazi Jews (incidence 10/10<sup>5</sup>), Yemenite Jews (incidence 18/10<sup>5</sup>) and Arabs (incidence 2.9/10<sup>5</sup>). In Shanghai (incidence <1/10<sup>5</sup>) a hospital cohort of 136 children (0.7–15 years) was studied. In the Jewish population in Israel, Ashkenazi or Yemenite, a significantly ( $p < 0.001$ ) higher number of children with IDDM were born during April to June, the least during January to March. Onset of disease in the same cohort showed an inverse trend ( $p < 0.01$ ). There was no seasonal variation in onset of disease in the Arab and Chinese children nor in the normal live births of Jews and Arabs in Israel during a 14-year period. More Arab children who developed IDDM were born during January–March ( $p < 0.05$ ). In other months, there were no significant differences, nor were any observed in Chinese children. Our present and previous data clearly show a different temporal relationship in the month of birth and month of onset of childhood IDDM in populations with a high or low incidence. The increased incidence of IDDM in children born in spring fits a viral infection in the first part of pregnancy. The viral epidemics occur in autumn and early winter, corresponding to the increase in month of onset. The lack of stable seasonality in the low incidence population is possibly due to immunization against viral pathogens both in first-child-afflicted families (China) or large families (Arabs).

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### High GAD Antibody Positivity in Singapore IDDM Children

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It was previously reported that GAD was 39% positive and ICA 20% positive in Chinese youth onset (<30 years) IDDM [Thai AC, Ng WY, Loke KY, Lee WRW, Lui KF, Cheah JS: Anti-GAD antibodies in Chinese patients with youth and adult onset IDDM & NIDDM. *Diabetologia* 1997;430:1425–1430]. A total of 24 Singaporean IDDM children age 2–12 years were tested using a RIA for recombinant human GAD-65 antibody kit (RSR Limited, Cardiff, UK) (local normal 0.32–0.7), and for islet cell antibodies (Indirect IF, Euroimmune Laboratorium, Germany). Out of 17 children newly diagnosed (<12 months duration in 1997) to have IDDM at the

KKH, 4 were negative for both ICA and GAD antibodies. There were 12 positive for GAD, of whom 8 were positive for both GAD and ICA and 5 were GAD-positive only. One child was positive for ICA alone. Of 7 children diagnosed to have IDDM between 1993 and 1996 and retested in 1997, 6 were positive for GAD, of whom one was weakly positive for ICA. Thus 70% of a group of newly diagnosed (<12 months) IDDM children in Singapore were positive for GAD alone, 53% were positive for ICA alone, and 76% were positive for either GAD or ICA, while 85% of a group of 7 childhood IDDM patients diagnosed 1–4 years ago were positive for GAD. 10 of the 12 GAD-positive recent-onset diabetics were Chinese, while 4 out of the 7 children with longer duration of diabetes were Chinese. We conclude that GAD antibody and ICA antibodies are frequently positive in recently diagnosed IDDM children in Singapore, as in their Caucasian counterparts.

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### Hypoglycemia and Its Nutritional Aspects in Diabetic Adolescents

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**Introduction:** The aim of this study was to assess the nutritional state and food intake of young adolescents with IDDM and its relation with hypoglycemia.

**Patients and Methods:** 35 adolescents with IDDM (16 males, 19 females) aged 12–18; diabetes duration  $5.57 \pm 3.8$ ; insulin dose  $0.8 \pm 0.25$  U/kg/day, mean HbA1c  $8.28 \pm 1.89$ . Study duration 2 months. MGB (monitoring blood glucose) performed >2 times/day. Food records and diet questionnaire were made.

**Results:** The 57.1% of adolescents (n = 20) had several degrees of slight or medium hypoglycemia, nobody had severe hypoglycemia at the time of this study. The BMI was normal (p10–p75) in 88.5% of the adolescents, only 8.7% was > p 90 (females). Those adolescents with hypoglycemia were in a lower percentile of BMI than the ones without (p < 0.02). There was a statistically significant negative correlation between adipose-muscular index and hypoglycemia incidence (F = -2,97, p < 0.005). **Hypoglycemia and dietary management:** The caloric intake was superior in girls, with a greater percentage of lipids than in boys ( $2,129 \pm 766$  vs.  $1,861 \pm 510$  cal) (p = 0.18). The basic caloric intake was slightly lower in adolescents with hypoglycemia than in those without but there were no statistical differences ( $1,898.03 \pm 555$  vs.  $2,123.25 \pm 769$  cal/day) (p = 0.4). No relationship was found between the greater number of cases of hypoglycemia and distribution or proportion of the basic nutrients.

**Conclusions:** (1) The presence of hypoglycemia was related with a lower BMI and with a negative correlation of the adipose-muscular index; (2) no relationship was found between dietary management and hypoglycemia.

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### Incidence and Prevalence of MODY: A Multicentre Italian Study

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During childhood, incidental hyperglycaemia can lead to a diagnosis of maturity-onset diabetes of the young (MODY). To assess the incidence and the prevalence of MODY among subjects investigated for incidental hyperglycaemia, a questionnaire was distributed to 28 Italian Pediatric Centers in order to report year-by-year (from 1992 to 1997): (1) the number of subjects screened for incidental hyperglycaemia; (2) the number of subjects with clinical diagnosis of MODY, including familial type 2 diabetes (consistent with an autosomal-dominant inheritance) and absence of type 1 diabetes autoimmunity; (3) the number of subjects analysed for MODY genes. Among 652 subjects with incidental hyperglycaemia, we found 180 subjects with clinical diagnosis of MODY, therefore the prevalence was 27.6%. Genetic analysis was performed in 58 subjects: mutations in the glucokinase gene on chromosome 7p (MODY-2) were found in 34 subjects and mutations in the HNF-1 $\alpha$  gene on chromosome 12q (MODY-3) in 5. National cumulative incidence of MODY was 0.13 new cases per person-years. No difference was found between Northern, Central and Southern Italy, where the cumulative incidence was 0.16, 0.14 and 0.11 new cases per person-year, respectively. An increased prevalence of MODY was observed from 1992 to 1997, probably due to the greater attention of paediatricians to this disease. Our results underline the importance to investigate children with incidental hyperglycaemia and familial type 2 diabetes, in order to make an early diagnosis of MODY.

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### Accuracy of Pen Injectors vs. Insulin Syringes in Children with Type 1 Diabetes mellitus

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The accuracy of insulin delivery to children has rarely been assessed in clinical practice. We compared the accuracy of pen injection devices and insulin syringes in the hands of children with type 1 diabetes mellitus and the hands of parents who routinely dispense and administer insulin to their infants and young children. Forty-eight subjects were instructed to measure out their morning insulin

doses 3 times from vials and/or cartridges containing saline mixed with small amounts of [ $^{14}\text{C}$ ]glucose (solution used as regular insulin), and [ $^3\text{H}$ ]glucose (solution used as NPH). Subjects regularly using a pen device ( $n = 24$ ) were asked to make measurements using both the pen and the syringes. For patients on an insulin mixture, the solution containing [ $^3\text{H}$ ]glucose was sampled to determine the amount of contamination with [ $^{14}\text{C}$ ]glucose. The absolute error in drawing up doses of regular insulin smaller than 5 units was  $4.9 \pm 1.6\%$  using the pen devices and  $12.3 \pm 2.6\%$  using the insulin syringes ( $p < 0.01$ ). However, both devices were comparable for regular insulin doses greater than 5 units ( $2.2 \pm 0.4\%$  vs.  $2.9 \pm 0.5\%$  for pen and syringe, respectively). The accuracy in drawing up NPH doses was similar for small and large insulin doses (mean percent error of  $5.7 \pm 0.9$  and  $5 \pm 1.2\%$  for insulin doses  $\leq 5$  or  $>5$  units, respectively). Children with diabetes were as accurate as their caregivers in drawing up the insulin in doses less than 5 units (mean percent error of  $11.6 \pm 4.2$  for parents vs.  $14.5 \pm 5.4\%$  for children). Only 1 patient contaminated the NPH vial with regular insulin. We conclude that pen devices are more accurate than insulin syringes at low insulin doses and that regular insulin, which is drawn up first, is less accurately delivered than NPH when an insulin mixture is used.

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### Long-Term Follow-Up of Siblings of Type 1 Diabetic Children Initially Evaluated for Islet Cell Antibodies (ICA) and HLA Haplotypes

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During the period 1981–1989, 179 siblings of Caucasian children with type 1 diabetes were screened for ICA by indirect immunofluorescence using type O human pancreas and were HLA typed for HLA A, B, C, DR by the microlymphocytotoxicity technique. Most were followed once or twice yearly for up to 12 years (mean 3.75 years) for ICA status and diabetes concordance (C) and all but 15 were recontacted after 8–16 years for C by history.

**Results:** Six siblings were initially ICA-positive (3.3%) and remained ICA-positive with five becoming C after 8 months to 12 years. One ICA-positive sibling remains nonconcordant (NC) after 12 years (ICA-positive 6 times). One ICA-negative sibling became C after 3 years, remaining ICA-negative in 4 specimens pre-C, at C and 6 months post-C. Of 122 ICA-negative siblings followed at least 2 years with serial ICA, 5 converted to ICA after 2–6 years (2–10 prior negative specimens) and have remained positive for 3–13 years, but none is yet C. [3 converters were entered into the ENDIT study (ICA positivity confirmed).] Two other initially ICA-negative siblings were found ICA-positive but NC after long lapses in follow-up. Five of the original 6 ICA-positive siblings were DR3, DR4, as were 4 of the 7 converters ( $p = 0.01$ ). Five of the original 6 were HLA identical to probands whereas 6 of 7 converters were haploidentical ( $p = 0.001$ ).

**Conclusions:** Long-term follow-up confirms that ICA positivity is associated with a high probability of C but interval to C varies considerably. HLA DR3, DR4 haplotypes confer susceptibility to develop ICA, with siblings HLA identical to probands becoming positive earlier than those not HLA identical.

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### Prevalence of Atopy in Children with Diabetes mellitus Type 1

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**Background:** Atopy is characterized by a chronic inflammatory reaction that is predominantly of a Th2-cell type. Diabetes mellitus type I (DM) is Th1-cell-dominated. We hypothesized that the prevalence of atopy may be lower in children with DM, since Th1 and Th2 cells reciprocally counteract each other as is reported for rheumatic arthritis and multiple sclerosis.

**Objective:** To compare the prevalence of atopic disease between children with DM and age-matched controls.

**Methods:** All Dutch pediatricians invited the parents of children with DM (younger than 18 years of age) to complete the ISAAC questionnaire on the prevalence of atopy. A cross-sectional survey (ISAAC II study) was used as a control group. Asthma was defined as the presence of symptoms and/or a doctor's diagnosis. Eczema and hay fever were defined as the presence of symptoms and a doctor's diagnosis, to differentiate from swimmer's eczema and common cold, respectively. The differences between the two groups were tested by using the  $\chi^2$  test.

**Results:** We received 555 questionnaires, which is estimated to be 15% of the total number of Dutch children with DM. The control group consisted of 604 children. The questionnaires of 254 DM patients were age-matched with the controls. The prevalence of asthma was 17.8% in DM patients compared with 25% in controls ( $p < 0.01$ ). Eczema was reported to be present in 7.7% of DM patients compared with 13.4% of controls ( $p < 0.01$ ). In contrast, hay fever was significantly more reported in DM patients compared with controls: 7.2 and 3.9%, respectively ( $p < 0.001$ ).

**Conclusion:** In this study, the lower prevalence of asthma and eczema in DM patients compared with controls is consistent with the Th1/Th2 concept. Neither symptoms nor diagnosis of asthma, rhinitis or eczema were found in 82.2, 76.8 and 76.4% of children with DM compared to 72.4, 64.6 and 71.5% of controls.

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### Beta-Cell Autoimmunity at Birth and Early Onset Insulin-Dependent Diabetes mellitus

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Recent reports suggest that beta-cell autoimmunity could start early in infancy and sometimes in pregnancy. Antibodies to glutamic acid decarboxylase (GAD) and to protein tyrosine phosphatase (IA-2) are useful markers of prediabetes in family members and in the general population and are present in about 5% of relatives of type 1 diabetic patients. GAD and IA-2 antibodies can be measured by