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Serum Levels of 90K Protein (a Member of SRCR Superfamily Protein) Is Related to Age at Onset of Diabetes in Children

S. Tumini^a, C. Natoli^b, L. Di Ricco^a, N. Tinari^b, S. Iacobelli^b, F. Chiarelli^a

Departments of ^aPediatrics and ^bOncology, University of Chieti, Italy

90K protein (90KP) is a member of a protein superfamily defined by a scavenger receptor cysteine-rich (SRCR) domain which may have a role in host defense; 90KP has also been shown to enhance the in vitro generation of cytotoxic effector cells (NK/LAK) and to indirectly support T-cell costimulation through accessory cell activation, suggesting a role in enhancement of cell-mediated immunity; furthermore, 90KP increases class I expression on cancer cells and might help make those cells more susceptible to cytotoxic T-cell or LAK-mediated cytotoxicity. Serum levels of 90KP were measured by ELISA in 60 diabetic children aged less than 18 years (12.6 ± 3.2 years) with duration of disease <10 years (4.3 ± 2.2 years). There was no correlation between glycemic control, insulin requirement and serum 90KP levels. 90KP levels were negatively correlated with age of patients ($p < 0.02$). At variance, in the multiple regression analysis only onset of diabetes (12.2 ± 3.5 years) had an independent significant relationship with serum 90KP levels ($p < 0.01$), while age and duration of disease did not show any significant influence (multiple $r = 0.33$; adjusted $r^2 = 0.10$). 90KP, a non-HLA-related factor, may play a role in modulation of intensity and time of autoimmune β -cellular destruction in type 1 diabetes mellitus.

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Celiac Disease and Thyroid Disease in Children with Diabetes mellitus Type 1 after Starting a Screening Programme

W.M. van Waarde, C. Rouwé, R.J. Odink

Department of Pediatrics, University Hospital Groningen, The Netherlands

Introduction: In patients with diabetes type 1 (DM), there is an increased incidence of celiac disease (CD) and thyroid disease (TD), compared to the general population. CD and the early phase of TD is often accompanied by few or no symptoms. A screening programme was started in 1996.

Methods: In the screening programme once a year all children with DM should be investigated. TD by measurement of FT4, TSH and antibodies against thyroid colloid and cytoplasm. IgA- and IgG-antigliadin antibodies and anti-endomysium antibodies to detect CD. In the case of positive antigliadin- and anti-endomysium antibodies, a jejunal biopsy was performed. Since October 1997, we also started with the measurement of IgA to detect patients with IgA deficiency in whom the screening tests are false-negative.

Results: In 69 of a total of 91 patients with DM, the screening programme was done (76%). Of the 69 patients, 67 were screened for CD. Two children had positive antigliadin and anti-endomysium antibodies and showed nearly complete villous atrophy in jejunal

biopsy (3%). One patient with IgA deficiency, weak positive anti-endomysium antibodies, positive IgG-antigliadin antibodies underwent a jejunal biopsy, which showed no signs of CD. Four patients had only positive IgG-antigliadin antibodies. In all 69 patients FT4 and TSH levels were measured. Hypothyroidism was diagnosed in 2 patients (3%). In 38 of the 69 patients antibodies against thyroid colloid and cytoplasm were measured. Six children, including the 2 diagnosed patients, had positive antibodies against thyroid colloid and cytoplasm. Before screening started 1 patient was known to have CD and 2 TD.

Conclusion: Despite a screening programme only 76% of the patient group has been screened until now. This screening programme detected 2 patients with TD and 2 with CD. The frequency of CD in this Dutch population is 4.5% (3 of 67 patients). This is in accordance with the literature. Collaboration with other diabetes centers in the Netherlands may confirm these data.

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Low Serum Levels of Vitamin D and Osteocalcin in Diabetics with Persistent Microalbuminuria

A. Verrotti^a, F. Basciani^a, M. Catino^a, G. Morgese^b, F. Chiarelli^a

Departments of Pediatrics, Universities of ^aChieti and ^bSiena, Italy

Evidence has been accumulating in the last years that abnormalities in calcium metabolism may be present in insulin-dependent diabetes mellitus. In order to clarify if the presence of persistent microalbuminuria (MA) can affect calcium metabolism, we selected 22 diabetic adolescents and young adults with persistent MA and compared them with 24 patients without MA. Mean values of serum calcium, phosphorus and magnesium were similar in diabetics with and without persistent MA and in healthy controls. The mean values of PTH and 25-OHD, 1,25(OH)₂D₃ and osteocalcin (OC) did not differ between diabetics without MA and controls. On the contrary, diabetics with persistent MA had significantly ($p < 0.01$) lower 25-OHD (26.5 ± 5.2 ng/ml) and 1,25(OH)₂D₃ (38.8 ± 8.9 pg/ml) as well as OC levels (9.81 ± 2.54 ng/ml) than controls (38.1 ± 4.97 ng/ml, 40.7 ± 6.4 pg/ml and 14.5 ± 3.2 ng/ml, respectively) and subjects with normoalbuminuria (35.0 ± 4.5 ng/ml, 38.8 ± 8.9 pg/ml and 16.50 ± 5.80 ng/ml). Regression analysis showed a significant correlation between intact PTH and 1,25(OH)₂D₃ ($p < 0.01$) and between 1,25(OH)₂D₃ and OC ($p < 0.001$); there was no significant correlation between the 25-OHD and 1,25(OH)₂D₃ concentrations in either group of diabetics.

In conclusion, abnormalities of bone remodelling markers such as 25-OHD, 1,25(OH)₂D₃ and OC are present in diabetic adolescents and young adults with early nephropathy and these abnormalities are independent from the quality of metabolic control.

Adequate Nutrient Intakes in Young Children with IDDM Having Low Intake of Fat

S.M. Virtanen, K. Ylönen, L. Räsänen, H.K. Åkerblom

Division of Nutrition and the Children's Hospital, University of Helsinki, Finland

Experts in pediatrics and nutrition have expressed concern about adequacy of essential nutrient intakes of young children with very low intake of fat. For example, in British recommendations for children with IDDM, the use of skimmed milk is not recommended to children under 5 years of age. We compared the intakes of energy and 37 nutrients between fat intake tertiles among young Finnish children with IDDM (<6 years of age at diagnosis) 3 months and 2 years after diagnosis. Of the 39 children invited, 38 participated in the study at 3 months and 33 were followed until 2 years after diagnosis. On average, the children with IDDM received 26% and 30% of energy from fat 3 months and 2 years after diagnosis, respectively. At 3 months, the intakes of energy, selenium and cholesterol were lowest ($p < 0.05$) in the lowest tertile (fat intake <23% of energy) compared with the middle (23–27%) and highest fat intake tertiles ($\geq 28\%$). Also the intakes of saturated, monounsaturated, polyunsaturated and essential fatty acids were lowest ($p < 0.05$) in children belonging to the lowest fat intake tertile. Two years after the diagnosis, only the intakes of fatty acids and cholesterol differed between the fat intake tertiles (<27%, 27–32% vs. $\geq 33\%$ of energy). However, both 3 months and 2 years after diagnosis the intakes of most vitamins and minerals studied and of essential fatty acids were adequate in all fat intake tertiles. As has been observed in earlier Finnish dietary studies in children, the intakes of vitamin D, chromium and fluorine were lower than recommended in all tertiles. To conclude, low intake of fat was overall associated with adequate intakes of nutrients in young Finnish children with IDDM.

Enhanced in vitro Production of TNF- α and IL-1 in Newly Diagnosed Type 1 Diabetic Patients

L. Vitali^a, M. De Amici^a, G. d'Annunzio^a, A. Alibrandi^a, R. Lorini^b

^aDepartment of Pediatrics, IRCCS Policlinico San Matteo, Pavia; ^bDepartment of Pediatrics, University of Genoa, Istituto G. Gaslini, Genoa, Italy

Recent studies showed that IL-1 may interfere with insulin secretion from pancreatic β -cells and have a direct cytotoxic effect on the islet cells. Moreover, in experimental diabetes, it has been observed that monocytes/macrophages or their products, IL-1 and TNF- α play a primary role in the initiation of insulin-dependent diabetes. The aim of our study was to evaluate the in vitro production of TNF- α and IL-1 in cultures of adherent cells from type 1 diabetic patients. We considered 11 newly diagnosed patients, aged 3–15 years and 13 long-standing patients with a disease duration >5 years, aged 11–21 years; 13 healthy subjects served as controls. Adherent cells were incubated for 24 h. TNF- α and IL-1 levels were determined by immunoradiometric assay (Medgenix). Results were expressed as pg/ml. The spontaneous release of TNF- α and IL-1 was significantly

higher in newly diagnosed (TNF- α median 2,429.2 pg/ml, range 419.52–6,220.5; IL-1 median 2,100 pg/ml, range 334.45–21,457) as compared to long-standing patients (TNF- α median 536.35 pg/ml, range 156.61–3,168, $p = 0.003$; IL-1 median 276.11 pg/ml, range 59.92–6,580, $p = 0.0013$) and controls (TNF- α median 559.52 pg/ml, range 661–3,767.1, $p = 0.007$; IL-1 median 580.43 pg/ml, range 84–9,754.9, $p = 0.018$). The increased in vitro production of TNF- α and IL-1 in newly diagnosed type 1 diabetic patients may reflect an impaired monocyte function in the early phase of type 1 diabetes.

Treatment with Insulin Lispro (LysB₂₈ProB₂₉) in Adolescents with Diabetes Type 1

R.B. Wąsikowa, A. Basiak, K. Dolata

Department of Endocrinology for Children and Adolescents, University of Medicine, Wrocław, Poland

The aim of our present study was to examine if therapy with a short-acting insulin analogue Lispro in adolescents improves postprandial blood glucose control and reduces the frequency of hypoglycemic episodes. The investigations began on 1.1.95 and included up to now 76 adolescent patients, mean age 16.3 ± 1.6 . Insulin Lispro was injected immediately before each meal. In all the patients the basal level was obtained with 1–2 daily doses of NPH insulin. Measurements included self-control of daily blood glucose levels, HbA_{1c}, frequency of hypoglycemic episodes, BMI and insulin requirement. A special questionnaire was also prepared where the patient answered if the treatment with Lispro is much more comfortable, more comfortable, without any difference, or worsened.

Results: Treatment with Lispro reduced postprandial blood glucose levels as well as hypoglycemic episodes and provided better long-term glucose control.

Conclusion: The ability to give insulin Lispro immediately before a meal allows a greater flexibility of life style, a better compensation of the disease, and greater compliance in pediatric patients with type 1 diabetes.

Diabetes in First- and Second-Degree Relatives of Patients with Type 1 Diabetes in Two Polish Regions in the Years 1993–1997

R.B. Wąsikowa^a, J. Bieniasz^a, M. Dziatkowiak^b, M. Ciechanowska^b

^aDepartment of Endocrinology for Children and Adolescents, University of Medicine, Wrocław; ^bPolish-American Institution for Children, Collegium Medicum UJ, Cracow, Poland

The aim of our present study was to evaluate the frequency of diabetes in relatives of diabetic children and adolescents. Our registration started 01.01.1993. The registration included all newly diagnosed diabetics aged 0–19 years in the region of Cracow and Wrocław. A special questionnaire was performed which included the age of patients at the time of diagnosis, sex, first- and second-degree relatives, diabetes type 1 or type 2 in relatives, age at diagnosis. Ascer-

tained was an incidence of type 1 as well as type 2 diabetes. The total number of relatives of 174 patients in the years 1993–1997 was 64, 11 with type 1 and 56 with type 2 diabetes. Interesting is the high number of diabetes type 2 in the families of our patients. All those with diabetes type 2 were second-degree relatives (except 2), i.e. grandparents. The remaining 2 were siblings of the mothers of our diabetic children. Among the 11 type 1 diabetics, 6 were fathers, 3 brothers of the fathers, and 2 siblings.

Conclusion: In the families of diabetic children and adolescents observed the relatives had type 1 and type 2 diabetes with a dominance of type 2.

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IA-2 Autoantibodies: A Useful Complement to GAD₆₅ Autoantibodies for the Classification and Prediction of Diabetes

I. Weets^a, K. Decochez^a, F. Winnock^a, P. Goubert^a, H. Dorchy^b, J. De Schepper^c, C.L. Vandewalle^a, D.G. Pipeleers^a, F.K. Gorus^a, the Belgian Diabetes Registry^d

^aDepartment of Metabolism and Endocrinology, Diabetes Research Center, VUB; ^bDiabetology Clinic of the Hôpital Universitaire des Enfants Reine Fabiola, ^cDepartment of Pediatrics, AZ-VUB, and ^dBDR, Brussels, Belgium

The protein tyrosine phosphatase IA-2 has been identified as an autoantigen that is recognized by immunoglobulins of patients with type 1 (insulin-dependent) diabetes mellitus (IDDM). Using a liquid-phase radiobinding assay, we determined IA-2 autoantibodies (IA-2-A) in sera from 608 recent-onset (0–7 days of insulin treatment) IDDM patients and 703 nondiabetic control subjects age 0–39 years. IA-2-A were detected in 56% of the patients and 0.6% of control subjects. Their prevalence in patients was lower than that of islet cell autoantibodies (ICA: 72%) or glutamic acid decarboxylase (M_r 65 kD) autoantibodies (GADA; 79%) but higher than that of insulin autoantibodies (IAA; 46%). In contrast to GADA, but similar to ICA and IAA, IA-2-A were more frequent under age 20 years (70%) than between age 20 and 40 years (42%; $p < 0.001$). In the whole IDDM group, 90% of patients were positive for at least one of the three molecular assays (IAA, IA-2-A or GADA), which is higher than the positivity for the ICA assay (72%). Only 1% was negative in the molecular assays and positive in the ICA assay. IA-2-A levels were positively correlated with ICA titers ($p < 0.001$) and HLA DQ A1*0301–DQ B1*0302 ($p < 0.003$) by multivariate analysis. In a group of 480 nondiabetic siblings (age 0–39 years) of IDDM patients only 10 were IA-2-A-positive at initial screening (2%). All ten were under age 20 years, positive for at least another autoantibody type and for DQ A1*0301–DQ B1*0302 and thus at very high risk to develop IDDM during the next 5 years. Five of these 10 subjects developed IDDM 5–26 months after initial testing. The positive predictive value of IA-2-A (50%) was higher than that of ICA, GADA or IAA, alone or in combination ($\leq 33\%$) but these calculations are restricted by the relatively short observation period and the small number of cases. In conclusion, IA-2-A show a high diagnostic specificity for IDDM and are predictive markers of impending diabetes in siblings of patients. In combination with other molecular antibody assays such as IAA and GADA they may replace ICA testing in the future.

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Impaired Production of Interferon- α in Whole Blood Cultures from Children with Type 1 Diabetes mellitus

J. Weill^a, D. Chehadeh^b, D. Hober^b, L. Andreoletti^b, C. Stuckens^a, M. Cartigny^a, P. Watré^b

^aEndocrinologie Pédiatrique, Hôpital Jeanne-de-Flandre, et

^bLaboratoire de Virologie, Institut Genrez-Rieux, CHU, Lille, France

Insulin-dependent diabetes mellitus (IDDM) is one of the most common and chronic endocrine disorders of children and young adults. Although autoimmunity and genetic predisposition are recognized as major factors, epidemiologic evidence and studies have supported a role of viruses in some cases. Because interferon- α (IFN- α) plays a role in the defense mechanism against viral infection, we have determined the profile of IFN- α producing capacity of children with IDDM. IFN- α production induced by Sendai virus in vitro was measured by biological assay in whole blood culture from 14 newly diagnosed IDDM children and from 8 children in the course of IDDM, with or without metabolic decompensation. The comparison group was 10 healthy children without any viral infection or metabolic disease. An impaired IFN- α -producing capacity was found in 5 of 14 (36%) newly diagnosed IDDM children (mean value \pm SD was 29 ± 20 IU/ml, $p = 0.002$, $n = 5$ vs. controls: 185 ± 88 IU/ml, $n = 10$), and in 6 of 8 (75%) children in the course of IDDM (32 ± 18 IU/ml, $p = 0.001$, $n = 6$ vs. controls). Four of 5 children with impaired IFN- α producing capacity at the onset of IDDM and 1 of 6 in the course of IDDM had metabolic decompensation. These results display a defect of IFN- α production in certain IDDM patients that may increase the susceptibility to viral infection which is likely to play a role in the pathogenesis of the disease.

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Has the Eating Behavior of Children and Adolescents with Type 1 Diabetes Changed? Results of an Anonymous Questionnaire 1987 and 1997

S. Wiegand, I. Enders, G. Heide, T. Danne

Charité Children's Hospital, Humboldt University, Berlin, Germany

Increased use of flexible insulin regimens and a liberalization of dietary recommendations has not changed the average glycemic control in our clinic during the past decade. The present study investigated the potential impact of these factors on the patients' attitudes regarding their diet. The same anonymous questionnaire (multiple choice, open questions, rating scales; 40 items overall) on the individual problems with dietary recommendations was mailed in 1987 and in 1997 to all current patients of our diabetes outpatient clinic (1987: $n = 208$; 1997: $n = 362$).

The respondents (71% in 1987, 62% in 1997) were representative for the whole group regarding age, sex, diabetes duration and metabolic control. The frequency of patients with multiple injection therapy was higher in 1997 (59%) than in 1987 ($p < 0.001$). Weighing of the food was reported less in 1997 (31 vs. 59%; $p < 0.001$). Although a

flexible adaptation of the insulin dose to changing carbohydrate contents of the meal was practiced significantly more often by the 1997 patients (74 vs. 47%; $p < 0.001$), surprisingly, no change was observed in the frequency of patients reporting substantial problems with the adherence to the dietary recommendations (19 vs. 18%). Interestingly, adherence of the other family members to the patients' dietary recommendations was reported even less in the current survey (31 vs. 57%; $p < 0.001$). Correspondingly, the frequency of daily family quarrels regarding the diabetes diet was increased in the 1997 survey (15 vs. 5%; $p < 0.001$). Regular consumption of dextrose-containing sweets was rare in 1987 but frequent in 1997 (20 vs. 85%; $p < 0.001$). Nevertheless, the percentage of patients regarding themselves as outsiders compared to their peers due to their diet was reduced only slightly in the recent analysis (42 vs. 52%; n.s.). As in the previous survey, the adherence to the dietary recommendations decreased with age, while sex, insulin regimen and social class showed no influence.

During the last decade no major change in the subjective daily stress caused by our dietary recommendations has occurred.

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Serum Antioxidant Status and Oxidized LDL in Well-Controlled Young Type 1 Diabetic Patients with and without Subclinical Complications

D. Willems^a, H. Dorchy^b, D. Dufrasne^a

^aDepartment of Clinical Chemistry, Brugmann University Hospital, and ^bDiabetology Clinic, Children's University Hospital Queen Fabiola, Brussels, Belgium

It has been suggested that oxidative stress may play an important role in the pathogenesis of diabetic complications because hyperglycemia may cause increased production of free radicals. However, studies on the antioxidant status of young type 1 diabetic patients are very scarce as well as the relationships of oxidative stress and the presence of subclinical complications. Therefore, we decided to evaluate autoantibodies against LDL (o-LAB) and antioxidant status in relationship with glycated hemoglobin levels (HbA1c), lipoproteins and subclinical complications (retinopathy, neuropathy, nephropathy). The study included 110 young type 1 diabetic patients with a median age of 15 years and a median diabetes duration of 5 years. The mean \pm SEM of HbA1c levels was $7.1 \pm 0.2\%$. Subclinical complications were detected in 26 patients. Total antioxidant status, vitamin A or E were not decreased in our patients and no significant differences were noted between the different subgroups of patients classified according to their subclinical complications. HbA1c levels were not related to antioxidants. Autoantibodies against LDL lipoproteins decreased with age and diabetes duration, as reported in healthy non-diabetic subjects.

In conclusion, in our diabetic patients with a more or less good diabetic control, increased lipid peroxidation or reduced lipid antioxidant defense could not be demonstrated, even in the patients with subclinical complications.

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Healthy Food Choice in Young People with Type 1 Diabetes

A. Wilson^a, L. Howells^a, M. Johnston^b, R. Newton^c, S. Greene^a

^aChild Health, University of Dundee; ^bSchool of Psychology, University of St. Andrews; ^cDepartment of Medicine, Ninewells Hospital and Medical School, Dundee, UK

Diet is an important component of the management of type 1 diabetes. Dietary recommendations support the eating of a healthy mix of foods by limiting the intake of fatty and sugary foods and eating appropriate amounts of fibre, fruit and vegetables. Despite the importance of dietary management many patients deviate from the recommended guidelines. As part of a larger longitudinal intervention study the dietary habits of 58 subjects (mean age 16.8 years, range 12.2–27.4; mean duration 7.5 years, 1.0–19.3; $M = 27$) were related to measures of psychological factors, diabetes knowledge and glycaemic control. Dietary habits were assessed by a 3-day diary coded for 'healthy' and 'less healthy' choices. Psychological factors and knowledge were obtained from questionnaires and glycaemic control assessed by HbA1c. Healthy food choices were associated with knowledge about diabetes management and diet in diabetes ($r = 0.43$, $p = 0.001$; $r = 0.26$, $p = 0.05$) but not with HbA1c or psychological factors. Only self-efficacy in diabetes and dietary self-efficacy were associated with HbA1c ($r = -0.24$, $p = 0.02$; $r = -0.36$, $p = 0.0001$). Healthy lifestyle and food choices reduce the risk of cardiovascular disease in later life and improved glycaemic control reduces the risk of long-term diabetes complications. It is therefore desirable to achieve both in young people with diabetes. It appears that a knowledge of diabetic management and diet is important for young people to make healthy food choices, but a belief in their ability to manage their diabetes and diet is necessary to achieve improved glycaemic control. The promotion of strategies to improve self-efficacy and knowledge in young people with diabetes is important.

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2q Chromosome Polymorphic Sites in Polish Children Suffering from Type 1 Diabetes

W.H. Witas, W. Młynarski, R. Sychowski, A. Młynarska, J. Bodalski

Molecular Biology Unit, 2nd Clinic of Children Diseases, Medical University of Lodz, Poland

Three independent loci (IDDM7, IDDM12, IDDM13) on the 2q chromosome are suggested as associated with type 1 diabetes. Besides, novel polymorphic sites in IL-1 genes cluster and *CTLA-4* gene promotor were found recently. 98 patients suffering from type 1 diabetes (IDDM) and 108 healthy controls were examined. The substitution at -1903 position T \rightarrow C (*Alu I*), +5810 G \rightarrow A (*Ita I*) within intron 4 and +5887 C \rightarrow T (*Taq I*) within exon 5 of the *IL-1B* gene as well as T \rightarrow C substitution at +8006 within exon 2 (*Msp I*) and T \rightarrow C transition at +11100 within exon 4 (*Ita I*) in the *IL-1RN* gene were analyzed by the RFLP-PCR technique. Additionally, the polymorphism of tandem repeats (VNTR) within intron 2 of the *IL-1RN* gene was identified according to the size of PCR products. The C \rightarrow T *Mse I* transition located at position -318 and transition A \rightarrow G *Ita I* at

position 49 of exon 1 of the *CTLA-4* gene were also analyzed. The corrected χ^2 statistical analysis of IL-1 gene cluster polymorphisms did not reveal significant differences between the IDDM group and the healthy controls. 20.5% (genotype CT) and 0.8% (genotype TT) of 108 controls (allele T frequency 0.111) as well as 17.5% (CT) and 1% (TT) of 98 diabetic patients (allele T frequency 0.096) exhibited *MseI* polymorphism with no significant differences. Heterozygous *ItaI* polymorphism (AG genotype) was identified in 49.5% and homozygous one (GG) in 23.8% of diabetic patients (G allele frequency 0.434). In contrast, 51.6 and 7.3% of control subjects exhibited the polymorphism, respectively (G allele frequency 0.332). Frequencies of homozygous GG and G-positive (GG+GA) genotypes are significantly elevated among the IDDM group ($p = 0.001$ and $p = 0.03$, respectively). The obtained results suggest the possible association of type 1 diabetes in a Polish population only with the *CTLA-4* gene polymorphism in the +49 position, which may be involved in *CTLA-4* molecule expression. In consequence, T-cell activation in autoimmune diabetes may be altered.

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Evaluation of Frequency of Occurrence of Insulin Autoantibodies, Antibodies against Glutamic Acid Decarboxylase and Islet Cell-Surface Antigen in Children of Mothers with Diabetes mellitus Type 1

M. Zawodniak-Szałapska, E. Głowačka, B. Lauk-Puchała, H. Tchórzewski, M. Szalecki

Diabetes Care Unit, Department of Clinical Immunology, Research Institute of Polish Mother's Memorial Hospital, Łódź, Poland

The risk of developing diabetes mellitus type 1 (DM type 1) increases in children of diabetic mothers. Studies of the natural history of β -cell autoimmunity have suggested that the autoimmune process begins predominantly before the age of 6 years. The autoantibodies are important markers of the autoimmune process of DM type 1, because they are present in individuals with early diagnosed DM type 1, and their presence increases the risk of developing the disease. 97 children of mothers with DM type 1 (60 girls and 37 boys, aged 3–14) and 35 nondiabetic healthy children were examined. Anti-GAD antibody levels were measured by ELISA, applying biotinylated rh GAD₆₅ and streptavidin-weighted plates, and using a commercially available Boehringer's Diaplets anti-GAD Kit. IAA were detected by ELISA. ICA were measured by the ENDIT Programme. IAA were found in 5 children. ICA were detected in 2 children. Anti-GAD were found in 4 children. No autoantibodies were detected in the control group. The frequency of occurrence of anti-GAD, IAA, or ICA equalled 10.2%. One of the ICA-positive children developed DM type 1, and one has been treated with nicotinamide. The other 9 children have shown no clinical symptoms of DM type 1. None of the autoantibody-positive children had been breastfed. Children of mothers with DM type 1 should undergo primary diabetes prevention.