

## Celiac Disease in Children and Adolescents With Type I Diabetes: Importance of Hypoglycemia

This article explores the association of celiac disease and type 1 diabetes mellitus in a retrospective case-controlled study. Patients with type 1 diabetes mellitus were screened for celiac disease by measurements of both serum immunoglobulin (Ig)A antiendomysial (EMA) and anti gliadin (AGA) antibody levels. The diagnosis of celiac disease was confirmed by small-bowel biopsy when testing for EMA and/or AGA antibodies was positive. Patients were matched for age, sex, and duration of disease for the 18 months before and after the diagnosis of celiac disease. Metabolic control was assessed by hemoglobin A<sub>1c</sub>, frequency of hypoglycemia, and total insulin requirements for the 18 months before and after the diagnosis of celiac disease.

There were 20 patients of 434 with type 1 diabetes who had celiac disease. None of them had symptoms or signs typical of this disease. However, during the 6 months before and after diagnosis of celiac disease, these patients had more hypoglycemic episodes than the controls: 4.5 vs 2 severe episodes with a progressive reduction in insulin requirement of 0.6 vs 0.9  $\mu$ /kg/d. The introduction of a gluten-free diet led to normalization of the intestinal mucosa and reduced the frequency of hypoglycemia in the celiac disease patients. The prevalence of celiac disease in this population of type 1 diabetes mellitus was 4.6%. All 414 control patients had negative tests for EMA and AGA antibodies. The authors concluded that underlying celiac disease should be suspected in patients with diabetes mellitus presenting with symptomatic hypoglycemia.

Mohn A, et al. *J Pediatr Gastroenterol Nutr* 2001;32:37-40.

**Editor's comment:** The association between celiac disease and type 1 diabetes has long been known. The coexistence of these 2 entities appears to be due to a common genetic predisposition attributed to the presence of the locus human leukocyte antigen (HLA) DR3. This report, as well as other studies using serologic data, describe a celiac disease prevalence of 5% to 7% in patients with type 1 diabetes mellitus. Often these patients do not present with any symptoms of overt malabsorption. However, as the authors point out, the occurrence of hypoglycemia in a child with diabetes mellitus should lead to screening for celiac disease. Measurements of EMA or AGA antibodies should be obtained, and, if positive, a confirmatory small-bowel biopsy should be performed even in patients who appear to be asymptomatic. These patients may have malabsorption of a sufficient degree to interfere with carbohydrate absorption with a resultant increased risk for hypoglycemia. It should be kept in mind that the prevalence of celiac disease in normal children might be about 1% (Pediatrics 2001;107:42-45), whereas in type 1 diabetes patients the prevalence is at least 4 times higher. Thus, we should proactively consider routine screening for this disease in type 1 diabetes patients, just as we screen for other diseases (eg, hypothyroidism).

Fima Lifshitz, MD

## Obesity, Increased Linear Growth, and Risk of Type I Diabetes in Children

Hyponen and associates report for the Childhood Diabetes Study Group in Finland on their evaluation of the effect of obesity and linear growth on the risk of developing type 1 diabetes during childhood. All children under the age of 15 years who had type 1 diabetes diagnosed between September 1986 and September 1989 were invited to participate in the study. All the study participants were tested for antibodies associated with diabetes. Ninety-eight percent were found to be positive for at least 1 type of antibody, confirming that they had autoimmune type 1 diabetes. Age- and sex-matched nondiabetic control children were randomly selected from the Finnish National Population Registry. Neonatal data and sociodemographic data were collected using structured questionnaires. An equal proportion of the diabetic and control children lived in rural areas. Information regarding height and weight was obtained from well baby clinics and school healthcare units for the 586 children with diabetes and for the 571 controls. Heights were available for both parents for the majority of study subjects. Relative weight calculated as "weight in relation to mean weight for height" and relative height as "a deviation of height in SD scores" were computed using the Finnish growth standards. Statistical analysis was based on relative weight and relative height in relation to age. Three age groups were studied: 2 weeks to 1.9 years, 2 to 9.9 years, and 10 years and older.

Neither the mean relative weight nor the relative height at birth differed between the diabetic and control subjects. But both boys

and girls who developed type 1 diabetes weighed more than the control children from infancy onward. There was a significant difference between the diabetic and control boys with regard to relative height from early infancy on. Among the girls, this significant difference was present until 10 years of age. Unfortunately, there were only limited data available for girls after the age of 10 years. Adjustments for neonatal and sociodemographic characteristics, or target heights, did not affect the results of this study. Both *higher relative weight* and *greater relative height* were associated with an increased risk of developing type 1 diabetes, and the magnitude of the effect was somewhat greater with respect to relative weight in infancy and early childhood. The effect of relative height remained constant throughout all ages.

The authors remind us that obesity is a well-known risk factor for type 2 diabetes, and that obesity is an increasing problem in many countries. In Finland, the annual incidence of type 1 diabetes has increased more than 4 times between 1953 and 1998. The role of obesity in this increase is unclear. Unequivocally, the increase in risk of type 1 diabetes for 1 SDS increment in relative height was 20% to 30%. Obesity or relative weight >120% after 3 years of age was associated with a more than 2-fold risk of developing type 1 diabetes. It is known that there is an association between obesity, accelerated height gain, insulin resistance, or enhanced insulin secretion, and significant subsequent enhanced insulin secretion. Hyperinsulinemia is obviously associated with

active beta cells, and active beta cells have been shown to be more susceptible to cytokine-induced damage than resting cells in vitro.

Hyponen E, et al. *Diabetes Care* 2000;23:1755-1760.

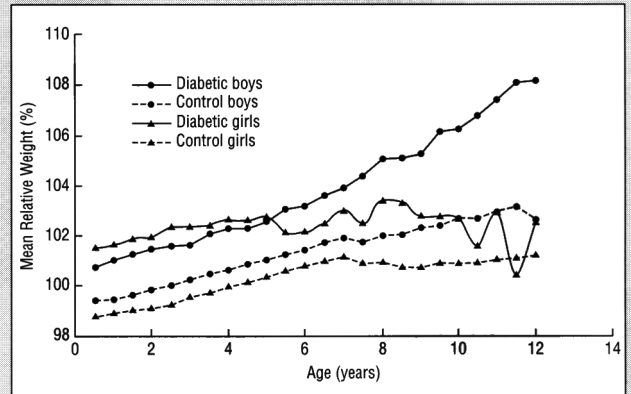
**Editor's comment:** This is a very interesting and important article. The incidence of type 1 diabetes in Finland is exceedingly high, much higher than that in the United States. The association of early childhood obesity and increases in relative height with an increased incidence of type 1 diabetes is significant information and a warning to the pediatric community. Recent reports have documented a significant increase in the incidence of type 2 diabetes among children and adolescents, paralleling the increase in obesity in this group. Hyponen et al's paper is the first to show that an increase in weight also is associated with an increase in type 1 diabetes. The information regarding tall stature is not new, but is consistent with other reports from Europe and the United States.

The Childhood Diabetes Study Group in Finland has presented information that needs to be transmitted to all physicians caring for children. The prevention of childhood obesity may be one of the most important therapeutic activities of pediatricians.

William L. Clarke, MD

Figure

**Cross-Sectioned Mean Relative Weights for Diabetic and Control Groups, Calculated from the Interpolated Values**



Reprinted with permission from Hyponen E, et al. *Diabetes Care* 2000; 23:1755-1760.

## Neonatal Outcome After Preimplantation Genetic Diagnosis by Analysis of the Polar Bodies

New reproductive technologies have increased the options available to couples. Preimplantation genetic diagnosis (PGD) was developed for couples at high genetic risk to avoid establishing pregnancies with genetic diseases. PGD is performed by blastomere biopsy or polar body removal (PBR) for mendelian or chromosomal disorders. Mothers who are heterozygotes for a mutation are good candidates for this procedure. Primordial germ cells will contain 1 chromosome carrying the affected allele and another carrying a normal allele. During meiosis, the oocyte will double its genetic material, yielding 2 chromosomes with normal alleles and 2 that contain the mutant allele. At the conclusion of meiosis I, the oocyte extrudes half of its chromosomes in the form of the first polar body. When the first polar body is removed before fertilization, it can be analyzed for the presence of the normal or mutant allele. Subsequently, fertilization occurs, the oocyte completes a second meiotic division, and then the second polar body is extruded containing 1 set of chromosomes. The second polar body also can be analyzed, and it will usually be identical to the 1 that remains in the egg. If a crossover occurs during meiosis, the first polar body may contain both mutated and normal alleles, in which case it will be necessary to analyze the second polar body to see which allele will be left in the fertilized egg. It is therefore possible to identify embryos developing from oocytes that contain a normal allele and then to transfer the fertilized oocyte back to the mother and establish a pregnancy.

The present study is the follow-up of the first 97 pregnancies that yielded 109 live-births after PGD by PBR and assessment. Ninety-one infants were born where analysis had been done for chromo-

somal disorders, and 18 infants were born where analysis had been done for mendelian disorders (including cystic fibrosis, sickle cell disease, long-chain acyl-CoA dehydrogenase deficiency, and thalassemia). All case analyses also were done postnatally to confirm the prenatal diagnosis. Birth data are available for 98% of the cohort, and developmental assessments are available for 44 children older than 6 months of age (see Table, page 31).

There were 80 singleton pregnancies, 9 twins, and 7 triplets, of which 3 were reduced to twins. One gestation with 5 fetuses

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