Early determinants of type 1 diabetes: experience from the BABYDIAB and BABYDIET studies\textsuperscript{1–4}

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ABSTRACT

Type 1 diabetes is an immune-mediated disorder that results from progressive destruction of the islet β cells. A genetic susceptibility for the development of islet autoimmunity and type 1 diabetes is well documented, and an environmental influence is assumed. Prospective studies from birth have shown that islet autoimmunity occurs very early in life, which implies that fetal or postnatal environmental factors may program the development of islet autoimmunity. In this overview, results from the BABYDIAB study, a prospective study from birth on the natural history of type 1 diabetes, and the BABYDIET study, a dietary intervention study, are discussed with a focus on the role of a diabetes environment in utero and the role of early gluten exposure on islet autoimmunity risk in children. Am J Clin Nutr doi: 10.3945/ajcn.110.000646.

INTRODUCTION

Type 1 diabetes, a chronic inflammatory disease caused by a selective destruction of the β cells of the pancreas, which produce insulin, is one of the most common and serious chronic diseases in children (1, 2). A recently published review reported an overall annual increase of 3.9% in the incidence of childhood type 1 diabetes in Europe and predicted that the incidence rate in children aged <5 y will double between 2005 and 2020 (3).

Type 1 diabetes is preceded by a preclinical phase characterized by autoimmunity against pancreatic islets (4). A genetic susceptibility for the development of islet autoimmunity and type 1 diabetes is well documented, and an environmental influence is assumed (5). Over the last 20 y several groups have initiated prospective studies from birth that investigated the development of islet autoimmunity and diabetes (6–9). These studies provide an opportunity to investigate when islet autoimmunity does initiate, if there is a time window when islet autoimmunity is frequent, and what environmental exposures are frequent around that time. Findings from these studies have significantly contributed to our current understanding of the pathogenesis of childhood diabetes.

Genetic factors that influence the development of islet autoimmunity and type 1 diabetes

Children with a first-degree relative with type 1 diabetes have a >10-fold-higher risk of the development of type 1 diabetes and this risk increases further if both parents are affected. Genetic variability in the human leukocyte antigen (HLA) region explains \textasciitilde50% of the familiar clustering (10); other genes provide more modest contributions to the risk (11, 12). The concordance of type 1 diabetes between monozygotic twins is up to 65%, whereas between dizygotic twins it is only 10% (13). Although such differences in the concordance rates between identical and nonidentical twins clearly underline the effect of genes on the development of type 1 diabetes, they also show that genetic susceptibility alone cannot be the ultimate cause for the disease and that environmental factors seem to modify the risk of islet autoimmunity and type 1 diabetes.

Initiation of islet autoimmunity

Prospective studies from birth have shown that islet autoimmunity occurs very early in life. Approximately 4% of offspring of parents with type 1 diabetes in the BABYDIAB study and \textasciimath�6% of genetically at-risk infants from the general population in the Finnish Diabetes Prediction and Prevention (DIPP) study developed islet autoantibodies by age 2 y (14, 15). The BABYDIAB study also shows that the incidence of islet autoantibodies, defined as cases per 100/y, is highest between 9 mo and 2 y of age (16). Children who develop autoantibodies within the first 2 y of life are those who most often develop multiple islet autoantibodies and progress to type 1 diabetes in childhood (14). These findings imply that fetal or postnatal environmental factors may program the development of islet autoimmunity. Candidate environmental factors that are suspected to influence the risk of islet autoimmunity in genetically susceptible individuals are factors associated with maternal type 1 diabetes and early dietary factors.

The role of a diabetes environment in utero on islet autoimmunity risk in offspring

Recent studies have shown that the offspring of mothers with type 1 diabetes have a decreased risk of the development of islet

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autoimmunity and type 1 diabetes compared with the offspring of fathers with type 1 diabetes (16–19). Results from the prospective BABYDIAB study showed that the lower incidence of islet autoimmunity in the offspring of mothers with type 1 diabetes compared with the offspring of fathers with type 1 diabetes was most marked at 9 mo of age (16). These results indicate that a type 1 diabetes environment in utero may affect the development of islet autoimmunity in the offspring. Perinatal factors that are affected by maternal type 1 diabetes are birth weight, gestational age, perterm delivery, cesarean delivery, Appgar score, and maternal age at delivery (16). Of these factors, birth weight was significantly associated with islet autoantibody risk: compared with children whose birth weight was in the middle tertile (3250-3700 g), the frequency of islet autoantibodies was reduced in children whose birth weight was in the lower or upper tertile of the study group [adjusted hazard ratio (HR): 0.43, P = 0.009 and HR: 0.42, P = 0.007, respectively]. Furthermore, an association between maternal glycated hemoglobin (Hb A1c) and risk of islet autoimmunity could be identified. Compared with children born to mothers with near-normal Hb A1c (<5.7%), islet autoantibody risk in children was significantly reduced if mothers had a moderately elevated Hb A1c of 5.7–7% (adjusted HR: 0.35; P = 0.03) and increased if mothers had HbA1c values >7% (adjusted HR: 2.8, P = 0.03).

Another factor associated with maternal type 1 diabetes in utero that may affect the development of islet autoimmunity is the transmission of maternal islet autoantibodies. The influence of maternally transmitted islet autoantibodies on the development of islet autoimmunity and type 1 diabetes has been examined in both animal models and humans. In the nonobese diabetic mouse, removal of maternally transmitted immunoglobulin prevented spontaneous diabetes in offspring mice, which suggests that maternal antibodies present during gestation, which include islet autoantibodies, could be important factors in the pathogenesis of β cell destruction (20). Further studies in mice that looked specifically at whether maternal insulin antibodies influence diabetes development reported controversial findings (21, 22).

In the BABYDIAB study 86% of offspring from mothers with type 1 diabetes had antibodies to exogenously administered insulin at birth, and 66% of offspring had autoantibodies to glutamate-decarboxylase (GADA) and/or autoantibodies to the tyrosine phosphatase–related protein IA-2 (IA-2A) at birth. The presence or absence of maternal insulin antibodies did not affect the risk of development of diabetes-associated autoantibodies and type 1 diabetes in the child, but offspring with GADAs and/or IA-2As at birth had a significantly lower diabetes risk than offspring who were autoantibody negative at birth (23). Therefore, and in contrast to the data from animal studies, these findings in humans do not support the hypothesis that fetal exposure to islet autoantibodies increases diabetes risk, but rather, suggest that fetal exposure to GADA and/or IA-2A may protect from future endogenous islet autoimmunity and type 1 diabetes. This observation is consistent with the overall decreased risk of development of islet autoimmunity and diabetes in offspring of mothers with type 1 diabetes compared with that of offspring of fathers with type 1 diabetes and nondiabetic mothers.

**The role of gluten on islet autoimmunity risk in offspring**

The influence of dietary factors on the development of islet autoimmunity and type 1 diabetes has been studied in both animal models and humans. Results of 2 prospective studies have shown that the risk of development of islet autoimmunity is increased in children who were exposed to cereal proteins (24, 25), and particularly gluten, during the first 3 mo of life compared with children who received gluten between 3 and 6 mo of age (adjusted HR: 5.2, P = 0.003) (24). These results have been confirmed by studies in the nonobese diabetic mouse, which showed that the removal of gluten from the diet can reduce diabetes risk from 88% to 42% (P < 0.005) (26). The observation that patients with type 1 diabetes and their first-degree relatives show an increased prevalence of celiac disease–associated autoimmunity compared with the general population (27–29) further indicates that gluten may play a role not only in the development of celiac disease but also in the development of islet autoimmunity and type 1 diabetes. To test this hypothesis, 2 intervention trials were conducted.

**Elimination of dietary gluten: secondary prevention**

A secondary prevention trial was conducted with the aim of preventing the progression to diabetes and decrease islet autoantibodies in nondiabetic children with islet autoantibodies by the removal of gluten from the diet (30). Seven offspring or siblings of patients with type 1 diabetes were included in this trial. All were <6 y and were persistently positive for more than one islet autoantibody but still had a normal glucose tolerance. In those children who were on a normal diet that contained gluten, gluten was removed from the diet for 12 mo, followed by a normal diet that contained gluten for 12 mo. This dietary intervention did not show any changes in islet autoantibody titers on commencement of the dietary intervention. The antibody variations observed within the 7 relatives at the end of the 12-mo gluten-free diet were similar to the increases and decreases in autoantibody concentrations observed in a matched historical control population, which suggests that the removal of dietary gluten did not modulate the islet autoimmunity within the early preclinical period of type 1 diabetes (30). The onset of diabetes observed in the gluten reexposure period was also consistent with the natural history of the disease in young multiple autoantibody–positive relatives (31). In conclusion, removal of gluten in islet autoantibody–positive children cannot prevent progression to type 1 diabetes.

**BABYDIET: primary prevention**

The BABYDIET study, a primary prevention trial, was initiated to investigate whether delay of the introduction of dietary gluten can prevent the development of islet autoimmunity in newborns with a first-degree relative with type 1 diabetes, who are at genetically high risk of type 1 diabetes (32). Children who participate in BABYDIET are randomly assigned to 1 of 2 dietary intervention groups that introduce cereals that contain gluten either at age 6 mo, as recommended by the German National Committee for the Promotion of Breastfeeding, or at age 12 mo (intervention group). One hundred fifty children have been recruited and followed every 3 mo until the age of 3 y, and will be followed yearly thereafter until the age of 10 y, for the development of islet autoimmunity, type 1 diabetes, and celiac disease–associated autoimmunity. To include 150 newborns in the study, a total of 1168 newborns with a first-degree relative with type 1 diabetes have been HLA screened at birth. Analyses on the effect of a delayed gluten exposure on islet autoimmunity are ongoing and will be published in 2011.
CONCLUSIONS

In conclusion, there is evidence that factors associated with a maternal type 1 diabetes environment in utero reduce islet autoantibody risk during early infancy in the offspring. Although we cannot provide insight into the mechanisms of protection at the moment, it is tempting to interpret the associations of autoantibody transfer, high birth weight, and increased glucose with reduced risk of islet autoimmunity as a reflection of increased immune tolerance to islet antigens during fetal and newborn life. Furthermore, evidence from studies in animals and humans indicates that early exposure to dietary gluten is associated with an increased risk of islet autoimmunity. Therefore, efforts should be made to follow international guidelines that recommend that complementary feeding should not be introduced before 17 wk of age.

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