EDITORIAL (SEE KNIP ET AL., P. 1206)

Enhancing the Understanding of Pre-Type 1 Diabetes in the General Population

Type 1 diabetes occurs in ~90% of patients with no family history of the disease. The majority of studies seeking to identify at-risk subjects have been conducted in first-degree relatives who comprise just 10% of all cases of type 1 diabetes but may have a 20-fold increased risk for type 1 diabetes (1). Although the peak incidence occurs at adolescence, there are data to suggest that 5–10% of all adults diagnosed with type 2 diabetes may actually have type 1 diabetes (latent autoimmune diabetes in adults [LADA]). If type 1 diabetes is to be prevented, significantly enhanced understanding of both the mechanisms leading to type 1 diabetes and the natural history of the pre-diabetic period is essential.

Current evidence suggests that type 1 diabetes results from a complex interaction between type 1 diabetes genetic susceptibility (predominantly HLA Class II associations) and environmental exposure(s) leading to a breakdown of tolerance culminating in β-cell autoimmunity and destruction (2). In the process leading to overt type 1 diabetes, both T and B lymphocytes are activated. B-lymphocyte activation is characterized by the emergence of cytoplasmic islet cell autoantibodies (ICAs) and one or more autoantibodies against the β-cell–specific autoantigen insulin, glutamate decarboxylase, the IA-2 protein tyrosine phosphatase, or the zinc transporter ZnT8 (IAA, GADA, IA-2A, and ZnT8A, respectively). For the most part, IAA, GADA, IA-2A, and ZnT8A have replaced ICA, which is measured using indirect immunofluorescence that requires a subjective evaluation of the fluorescence intensity. The IAA, GADA, IA-2A, and ZnT8A analyses require only small amounts of serum (5–20 μl in most assays) and are thus well suited for large-scale studies comprising both infants and small children. Serum samples can be safely stored at −20°C for years before the measurement of the autoantibodies is undertaken, and the samples usually also tolerate repeated freeze-thaw cycles without alterations in the measured concentrations. Analyses of T-cell function—both regulatory (tolerance) and effector (β-cell killing)—are highly demanding and poorly reproducible between most laboratories. Most assays require large volumes of freshly drawn blood, are labor-intensive, and have limited, if any, predictive ability on their own. In general, when autoantibodies are present in combination, at higher titers, at a younger age, and with high-risk HLA genes, the predictability of the disease in relatives is well over 50% in a 5-year period (3,4).

Defining individuals at risk for type 1 diabetes is crucial for both understanding the etiopathogenesis of the disease as well as instituting preventative strategies. Two approaches exist *1*) primary autoantibody screening followed by quantification of risk by further autoantibody, genetic, and metabolic testing, and *2*) primary genetic screening (e.g., of newborns using cord blood or dried blood spots) with determination of high-risk HLA (DR/DQ) gene alleles and subsequent quantification of risk by further autoantibody and metabolic testing. Depending on the circumstances, both approaches have their advantages and disadvantages (5).

The value of diabetes-associated autoantibodies in the prediction of clinical type 1 diabetes has been firmly documented in the first-degree relatives of type 1 diabetes probands of subjects affected with the disease, as well as in subjects in the general population who develop type 1 diabetes. However, the time of life when the disease actually begins, and the inductive events that trigger this process, have remained elusive. The earlier German BABYDIAB study, Finnish Diabetes Prediction and Prevention (DIPP) study, Denver Study of Diabetes in the Young (DAISY) as well as the Florida-Georgia Prospective Assessment of Newborns for Diabetes Autoimmunity (PANDA) study have screened newborns for genetic risk and followed those with increased diabetes susceptibility at frequent intervals from birth onward in an attempt to identify potential environmental factors that contribute to the development of autoimmunity and subsequent diabetes. However, these studies were limited mostly by insufficient power resulting from the relatively small numbers of patients followed. Five years ago, The Environmental Determinants of Diabetes in the Young (TEDDY) multinational study began enrolling newborns with HLA-conferred type 1 diabetes susceptibility both from the general population of newborns and from newborns with affected first-degree relatives (6). The TEDDY study has now completed screening with nearly 8,000 infants enrolled.

Almost without exception, the ongoing early type 1 diabetes prediction and prevention studies recruit subjects at birth or within the first few months of life and aim to follow the children until at least 10 to 15 years of age. Due to the highly variable incidence numbers in different European and U.S. populations, the cost-efficiency of the recruitment strategy may differ markedly in different corners of the world. To optimize the strategy for the long-term assessment of type 1 diabetes risk, the information obtained in the birth-onset studies must to be connected to, and correlated with, information obtained by following the cohorts through the years of puberty and early adulthood. The data from the studies with enrollment at birth strongly suggest that early seroconversion to autoantibody positivity provides a high risk for progressing to clinical type 1 diabetes at a young age, but clearly, some exceptions exist. Although positivity for a single autoantibody often indicates only minor or no increase in risk, the risk may by high if samples are collected at frequent intervals in which seroconversion to two or more autoantibodies occurs over time. As none of the prediction-oriented studies with onset at birth has continued long enough for a large cohort to reach puberty and young adulthood, little is known of the predictive characteristics and fate of the autoantibodies in this age-group.

To date only a few long-term population–based studies have primarily tested the predictive ability of autoantibody positivity in the general population (7–10).

In this issue of *Diabetes Care*, Knip et al. (11) have utilized serum samples collected 6 years apart in the Cardiovascular Risk in Young Finns (LASERI) study. The authors have sought to test the predictive ability of GADA and IA-2A measurements in the general population by examining the development of clinical diabetes in the cohort for up to 27 years. As part of their study, they evaluated the 6-year rates of seroconversion to GADA and IA-2A positivity and whether these autoantibodies persist or disappear during follow-up. The first samples were collected in 1980 from a general population cohort comprising ~3,500 children ages 3, 6, 9, 12, 15, and 18 years. In 1986, new samples were obtained from ~2,400 of the children tested in 1980 whose ages then ranged from 9 to 24 years. GADA and IA-2A were measured in all the available samples and, if positive for either one of these two autoantibodies, the two samples from that individual were then tested for ICA and IAA. The end point of the study was progression to clinical type 1 diabetes by the end of the year 2007.

Although the absolute number of children who had seroconverted to GADA or IA-2A positivity before 1980 were understandably low (34 for GADA and 22 for IA-2A), and the number of children who seroconverted to GADA or IA-2A positivity during the following 6 years (by the year 1986) were even lower (9 and 4, respectively), the data supported the conclusion that a one-time screening for GADA and IA-2A in the general childhood population in Finland would identify ~60% of those who would develop type 1 diabetes over the next 27 years, and those individuals who had both autoantibodies were at an extremely high risk for type 1 diabetes. The authors also determined that autoantibodies continue to both emerge and disappear during and after puberty. However, the autoantibodies disappear predominantly from subjects who are positive for only one autoantibody.

Unfortunately, since the risk in the general population is low, even a small false-positive rate will identify many subjects who will never develop the disease (Bayes Theorem). Screening with and finding two or more antibodies increases the positive predictive value but reduces sensitivity and markedly increases cost. This notion is supported by Knip et al. in their study, which also followed patients over a longer period of time as compared with previous studies. The combined sensitivity of 61% for GADA and/or IA-2A in the prediction of type 1 diabetes demonstrates that other markers of islet autoimmunity may be important (e.g., ICA, ZnT8A, and in children, IAA). In clinical practice if one were to seek markers used to predict type 1 diabetes, GADA and IA-2A testing alone would have an unacceptably low sensitivity.

Although the study provides valuable information, some questions remain. Most subjects who developed autoantibodies or were autoantibody positive in the 1980 or 1986 blood draw were prepubertal or pubertal. Any events occurring before 3 years of age are unknown. In contrast, since 18 years was the upper age recruited, there are no data about seroconversion in older subjects. It is not known in patients with LADA or adult type 1 diabetes whether the appearance of autoantibodies may occur later. Another drawback in this study is the absence of genetic information concerning the study subjects. Hopefully such data and an analysis of type 1 diabetes–related risk factors will be made available soon. As the cohort grows older, it will be interesting to follow the appearance and disappearance of autoantibodies and the progression to disease. Despite emerging technologies such as metabolomics, gene expression profiling, and pathway analyses (12), autoantibodies will most likely remain one of the most broadly utilized predictors of type 1 diabetes.

The greatest single barrier toward wide-scale population screening and prevention of the disease is the hitherto lack of an effective intervention. It is clear that screening for type 1 diabetes risk in the general population still should only be conducted in the context of defined research questions.

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