Can We Predict Type 1 Diabetes in the General Population?

Diabetes-associated autoantibodies have been shown to be useful in the assessment of diabetes risk among first-degree relatives of subjects with type 1 diabetes (1–3), whereas their predictive characteristics are poorly defined in the general population, from which ~90% of the newly diagnosed patients are derived (4). In a simulation study based on the combination of cross-sectional data from children with newly diagnosed type 1 diabetes and unaffected schoolchildren, Bingley et al. (5) reported earlier that positivity for multiple diabetes-associated autoantibodies was associated with reasonable sensitivity and a relatively high positive predictive value for clinical disease in schoolchildren. In this issue of *Diabetes Care*, LaGasse et al. (6) confirm the utility of disease-associated autoantibodies in the prediction of type 1 diabetes in the general population, represented by 4,505 schoolchildren from Washington state aged 12–18 years at initial sampling. The authors conclude that teens with at least two defined autoantibodies, i.e., antibodies to insulin, the 65-kDa isoform of GAD, and/or to the protein tyrosine phosphatase-related IA-2/islet cell autoantibody (ICA)-512 molecule, are characterized by a high risk of progression to overt diabetes, and that a screening strategy based on the analysis of insulin autoantibodies and GAD and IA-2 antibodies is highly successful in the assessment of type 1 diabetes risk in adolescents.

The conclusions are based on information obtained by recontacting 3,000 of the aforementioned 4,505 schoolchildren (67%) 6–11 years later, with a median interval of 8 years. All but 4 of the 141 children who initially tested positive for at least one autoantibody were reached. Six subjects presented with type 1 diabetes within a median interval of 2.8 years after the initial test, and all of them initially tested positive for multiple (≥2) defined autoantibodies. Altogether, there were 12 individuals with multiple autoantibodies in their initial sample. Accordingly, positivity for multiple autoantibodies had a

sensitivity of 100% (95% CI 58–100) and a positive predictive value of 50% (25–75) for type 1 diabetes. These predictive characteristics are impressive and actually of the same magnitude as those reported in first-degree relatives (1–3), but one has to remember that they are based on a low number of progressors, as reflected by their wide CIs.

The study by LaGasse et al. has its limitations. One is that only 67% of the initially antibody-negative children were recontacted, leaving possible progression to clinical diabetes open in one-third of the subjects. The argument stressed by the authors that none of the 2,863 initially antibody-negative subjects who were recontacted presented with type 1 diabetes does not exclude the possibility of disease progression in some of the remaining 1,502 individuals. The median age of the schoolchildren at initial sampling was 14 years, whereas the cumulative incidence of type 1 diabetes by age 14 is more than half of that by age 30. Accordingly, a screening program starting at age 14 will miss more than half of those who progress to clinical diabetes because that proportion has already presented with overt diabetes before that age. This fact raises several issues. For example, when should screening for individuals at risk for type 1 diabetes be initiated in the general population, and what would be the optimal screening strategy for the identification of at-risk individuals as early as possible to facilitate intervention in the early stage of preclinical type 1 diabetes? In this context, one has to emphasize that the availability of a proven effective intervention modality that can be clinically applied is an absolute prerequisite for starting general screening aimed at identifying high-risk individuals. So far, no such intervention modality is available, and accordingly, screening of the general population for the risk of type 1 diabetes has to be restricted to well-conceived research projects.

Because a series of intervention studies aimed at the prevention of type 1 dia-

betes is currently underway, the issues mentioned above should be considered and studied to prepare for a working screening strategy that can be extensively applied as soon as the first effective preventive treatment can be introduced into clinical practice. One may argue that screening for individuals at increased risk for type 1 diabetes should be started as early as possible, because early intervention can be expected to be more effective than treatment in late preclinical type 1 diabetes. One practical consideration is that diabetes-associated antibodies are transferred from the maternal circulation to the newborn infant (7). Approximately 3% of pregnant nondiabetic Finnish women have been observed to test positive for at least one diabetes-associated autoantibody (8). Such antibodies are eliminated from the circulation of the infant by the age of 15 months at the latest. Based on these observations, autoantibodies detected in a child aged 1.5 years or older most likely represent de novo synthesized autoantibodies. Thus, one could recommend that an appropriate age for the initiation of autoantibody screening would be 1.5 years, especially because very few individuals are diagnosed with type 1 diabetes before the age of 2 years (9). The prevalence of diabetes-associated autoantibodies seems to increase as a function of age at least up to the age of 6 years (10), and accordingly, autoantibody screening must be repeated sequentially. As of yet, information on the appearance of diabetes-associated autoantibodies in relation to age is limited in the general population; therefore, no evidence-based recommendation can be given for the optimal schedule of a screening program. A possible approach could be to repeat the antibody tests at the ages of 3, 5, 7, and 10 years after the initial screening at the age of 1.5–2 years.

Which autoantibodies should be analyzed in a screening program? This is a controversial issue. Some argue that initial screening for GAD and IA-2 antibodies is sufficient, followed by a second step

comprising the analysis of ICAs and insulin autoantibodies (IAAs) to increase the positive predictive value (5,11). Others, such as LaGasse et al., favor the use of the antibodies to the three biochemically characterized autoantigens in type 1 diabetes (2), whereas some recommend that ICAs should still be included and counted as a fourth antibody specificity (3). It is well documented that GAD and IA-2 antibodies contribute to the immunofluorescence detected by classical ICA. In most ICA-positive samples, the staining is, however, not completely inhibited by preincubation with GAD and IA-2 antibodies (12), demonstrating that the ICA immunofluorescence is in addition caused by some other yet unidentified antigen(s). The inclusion of IAAs into the screening battery is particularly important in young children, as it has been repeatedly shown that IAAs are the first or among the first antibodies to appear in young children under prospective observation (10,13,14).

Another open issue is whether the screening program should include initial genetic testing to limit the population that should be followed by repeated autoantibody screening. By typing for HLA DQB1 genes, one can cut the at-risk group to be followed down to 13–15% of the total population and still target 70–80% of future subjects with type 1 diabetes (15). A cost analysis clearly showed that a screening strategy based on initial HLA genotyping and subsequent autoantibody testing in those identified to be at increased genetic risk is cost-effective compared with an approach based on sequential autoantibody tests in the whole population (16). The only drawback of initial genotyping is that one will miss those progressors who lack increased HLA-conferred genetic susceptibility to type 1 diabetes, comprising 5–15% of patients with newly diagnosed type 1 diabetes, the proportion being higher in those diagnosed after the age of 20 (17). In the study by LaGasse et al., five of the six progressors carried HLA-defined genetic predisposition to type 1 diabetes.

Despite its limitations and low statistical power, the study by LaGasse et al. opens up promising prospects for the prediction of type 1 diabetes in the general population. The report confirms that the experience gained in the assessment of risk for type 1 diabetes in first-degree relatives and based on the use of multiple autoantibodies can be by and large applied to the general population. Supplementary data will be provided by prospective population-based studies starting in young children (18) or even at birth (10).

MIKAEL KNIP, MD, PHD

From the Hospital for Children and Adolescents, Hucs, Finland.
Address correspondence to Mikael Knip, Hospital for Children and Adolescents, P.O. Box 281, Hucs FIN-00029, Finland. E-mail: mikael.knip@hus.fi.

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