Markers of beta-cell dysfunction associated with high rate of progression to type 1 diabetes

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The majority of children at risk of type 1 diabetes who developed 2 or more diabetes-related autoantibodies developed type 1 diabetes within 15 years, findings that highlight the need for research into finding interventions to stop the development of multiple islet autoantibodies, according to a study in the June 19 issue of *JAMA*.

"Type 1 diabetes is a chronic autoimmune disease that often manifests during childhood and adolescence. The lifelong requirement for insulin injections and the many complications that follow the diagnosis can be difficult for those affected. Type 1 diabetes usually has a preclinical phase that can be identified by the presence of autoantibodies to antigens of the pancreatic beta cells," according to background information in the article. The rate of progression to diabetes after seroconversion to islet autoantibodies is uncertain.

Anette G. Ziegler, M.D., of Helmholtz Zentrum Munchen, Neuherberg, Germany, and colleagues conducted a study to estimate rates of progression to type 1 diabetes and associated characteristics based on islet autoantibody status. For the study, data were pooled from prospective cohort studies performed in Colorado (recruitment, 1993-2006), Finland (recruitment, 1994-2009), and Germany (recruitment, 1989-2006) examining children genetically at risk for type 1 diabetes for the development of insulin autoantibodies, glutamic acid decarboxylase 65 (GAD65) autoantibodies, insulinoma antigen 2 (IA2)

autoantibodies, and diabetes. Participants were all children recruited and followed up in the 3 studies (Colorado, 1,962; Finland, 8,597; Germany, 2,818). Follow-up assessment in each study was concluded by July 2012.

The researchers found that progression to type 1 diabetes at 10-year follow-up after islet autoantibody seroconversion in 585 children with multiple islet autoantibodies was 69.7 percent, and in 474 children with a single islet autoantibody was 14.5 percent. Risk of diabetes in children who had no islet autoantibodies was 0.4 percent by the age of 15 years.

A total of 355 children (60.7 percent) with multiple islet autoantibodies progressed to diabetes at a median (midpoint) follow-up time after seroconversion of 3.5 years, and a median age of 6.1 years. Progression to diabetes after seroconversion was 43.5 percent at 5-year follow-up, 69.7 percent at the 10-year follow-up, and 84.2 percent at the 15-year follow-up.

Analysis indicated that more rapid progression to diabetes after seroconversion was associated with younger age at seroconversion (younger than age 3 years [10-year risk, 74.9 percent] vs. children 3 years or older [60.9 percent]); and female sex (10-year risk of 74.8 percent for girls vs. 65.7 percent for boys).

"These data show that the detection of multiple islet autoantibodies in children who are genetically at risk marks a preclinical stage of type 1 diabetes. … Thus, the development of multiple islet autoantibodies in children predicts type 1 diabetes," the authors write. "Future prevention studies should focus on this high-risk population."

Jay S. Skyler, M.D., and Jay M. Sosenko, M.D., of the University of Miami Miller School of Medicine, write in an accompanying editorial that the nearly inevitable progression of individuals from seropositivity to type 1 diabetes (T1D) in the current report by Ziegler et al "serves to

raise the question of whether the definition of T1D needs updating, perhaps broadening to include a prediabetic state."

"Current criteria for overt diabetes are based on what is used for type 2 diabetes. Yet the sequence of events in diabetes development suggests it is possible to modify the definition at least to include individuals who are seropositive with either dysglycemia or a high T1D risk score. This would allow potential intervention with immunomodulatory therapies directed at preservation of beta-cell function measured by C-peptide. Data from the Diabetes Control and Complications Trial have demonstrated that preservation of C-peptide results in reduced risk of severe hypoglycemia and of progression of retinopathy and nephropathy."

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