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EDITORIAL

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The Evolution of Type 1 Diabetes

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TYPE 1 DIABETES (T1D) OCCURS IN INDIVIDUALS WITH a genetic predisposition to the disease, predominantly from a human leukocyte antigen (HLA)-related immunogenotype that accounts for approximately 60% of the genetic influence. In these individuals who are genetically at risk, an environmental trigger is thought to initiate an immune response targeting the insulin-secreting pancreatic islet β cells.[1,2] The initial immune response also may engender secondary and tertiary immune responses that contribute to the impairment of β-cell function and destruction of β cells.[3] The rate of development of T1D varies, probably related to non-HLA genetic factors and additional environmental factors beyond the triggering exposure.[4]

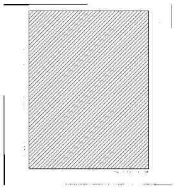
The initial laboratory manifestation of β-cell injury is seroconversion, the appearance of diabetes-related autoantibodies. These autoantibodies likely do not mediate β-cell injury but rather are markers of such injury. With progressive impairment of β-cell function, metabolic abnormalities become measurable, initially either as loss of early insulin response to intravenous glucose[5] or as reduced β-cell sensitivity to glucose resulting in decreased insulin secretion.[6] Subsequently, glucose abnormalities manifest as dysglycemia, either impaired fasting glucose (plasma glucose concentration of 100-125 mg/dL) impaired glucose tolerance (2-hour plasma glucose concentration of 140-199 mg/dL following an oral glucose test), or indeterminate glucose tolerance (plasma glucose concentration of >200 mg/dL at 30, 60, or 90 minutes following an oral glucose test).[7]

Eventually, overt diabetes presents with glucose concentrations meeting current criteria, fasting plasma glucose concentration of >126 mg/dL or 2-hour plasma glucose concentration of >200 mg/dL.[8] At the point of development of overt diabetes there is still evidence of persistent β-cell function shown through measurement of C-peptide. C-peptide is a component of the insulin precursor molecule proinsulin, which is secreted by β cells on an equimolar basis as insulin but is not contained in commercial insulin preparations, thus allowing measurement of β-cell function even in patients treated with insulin. After diagnosis of T1D, however, there is a progressive decline in C-peptide as β-cell function becomes more impaired or absent.[9] Nonetheless, even many years after diagnosis, some patients with T1D may have low detectable levels of C-peptide.[10]

Since the sequence of events leading to T1D involves immunogenotypes detectable at birth or in infancy, several groups have followed birth cohorts with the genetic risk. Working together, Ziegler and colleagues[11] analyzing cohorts in Colorado, Finland, and Germany report in this issue of *JAMA* the risk of progression to T1D from the time of seroconversion by measuring detectable diabetes autoantibodies. Remarkably, the results are similar in all 3 cohorts. Among 585 children who developed 2 or more diabetes-related autoantibodies, nearly 70% (280 of 401 available for follow-up) had developed T1D within 10 years, and 84% (299 of 355 available for follow-up) had developed T1D within 15 years. This is the first report of a longitudinal cohort followed from infancy through the development of T1D. Because the participants were recruited from both the general population (in Colorado and Finland) and offspring of parents with T1D (in Germany), the similar findings take on added significance, suggesting that the same sequence of events occurs in individuals with so-called sporadic T1D and in relatives of individuals with T1D.

The findings in this report raise additional questions. The basis for the differential progression to T1D according to the type of single autoantibody and the pattern of multiple autoantibodies should be explored. Also, the nearly 2-fold higher prevalence of HLA *DR3/DR4-DQ8* in participants with multiple autoantibodies (n=331) than in those with a single autoantibody, and the similar prevalence between participants with a single autoantibody and those with no autoantibodies need to be better understood. In addition, would the identification of those with higher titers provide even a greater likelihood of progression to T1D?

Much attention in recent years has focused on whether T1D can be prevented.[12] To that end, studies have been conducted in individuals with the genetic risk alone (primary prevention) and in individuals who have autoantibodies (secondary prevention). Although no study has of yet convincingly demonstrated delay or prevention of T1D, some evidence suggests this may be possible. Primary prevention studies have shown the potential to delay the appearance of autoantibodies by varying infant formula used at the time of weaning from breast milk, either by eliminating cow's milk and instead using a formula with casein hydrolysate[13] or by removing bovine insulin from the formula.[14] It is unknown whether such actions will delay progression to T1D, but an international effort—the National Institute of Child Health and Human Development–sponsored Trial to Reduce Insulin-Dependent Diabetes Mellitus in the Genetically At-Risk (TRIGR) study—is under way to test the casein hydrolysate formula, with results expected in 2017.[15]



See also p 2473.

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A number of secondary prevention studies have been conducted. In the Diabetes Prevention Trial-Type 1 oral insulin study, although the results were negative overall, a post-hoc analysis suggested that individuals with higher titers of insulin autoantibodies at baseline may have a 4.5-year,[16] or even 10-year,[17] delay in the development of T1D. Such potentially promising observations have led to an additional international trial of oral insulin among relatives of individuals with T1D, being conducted by the Type 1 Diabetes TrialNet.[18] In the United States, screening for autoantibodies can be conducted in any physician's office or even online, with the consent of potential research participants.[19] Relatives with a positive screening result are offered the opportunity to have their risk further characterized with the potential to participate in 1 of several secondary prevention studies depending on their eligibility.

The longitudinal demonstration in the report by Ziegler et al[11] of progression to T1D in the vast majority of individuals with diabetes autoantibodies highlights the need for development of effective prevention strategies. The findings also raise the question of whether there should be routine screening at birth for T1D genetic risk, with potential enrollment into primary prevention trials. In theory, this might involve either vaccination with diabetes autoantigens (such as proinsulin peptides)[20] or with a vaccine directed against enteroviruses, if evidence becomes convincing that there are specific enteroviruses that serve as the environmental triggers.[4] The Environmental Determinants of Diabetes in Youth (TEDDY) study is pursuing the identification of environmental factors involved in the evolution of T1D.[21]

The nearly inevitable progression of individuals from seropositivity to T1D in the current report by Ziegler et al also 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.[8] 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.[22,23] This would allow potential intervention with immunomodulatory therapies directed at preservation of β-cell function measured by C-peptide.[24] Data from the Diabetes Control and Complications Trial (DCCT) have demonstrated that preservation of C-peptide results in reduced risk of severe hypoglycemia and of progression of retinopathy and nephropathy.[25] Ongoing efforts in TrialNet and in the Immune Tolerance Network (ITN), among others, are directed toward developing safe and effective immunomodulatory therapies. These approaches may work better in preserving β-cell function if there is more function to preserve. Only with continued rigorous research investigations along with sustained funding and support will efforts to advance the science necessary to prevent T1D be successful.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Skyler is chairman and Dr Sosenko is associate chairman of the Type 1 Diabetes TrialNet clinical trials network, supported by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. Dr Skyler also reported serving as a board member for Amylin Pharmaceuticals, Dexcom, Moerae Matrix, and Paean Therapeutics; consulting for BD Technologies, Boehringer-Ingelheim, Bristol-Myers Squibb, Cebix, DiaVacs, Elcelyx, Exsulin, Gilead, Halozyme Therapeutics, Ideal Life, Intarcia Therapeutics, MannKind, Mellitech, Merck, Orgenesis, Sanofi, Sekris Biomedical, Takeda, Valeritas, and Viacyte; receiving grants from Halozyme Therapeutics, Intuity Medical, Mesoblast, and Osiris Therapeutics; receiving payment for lectures from Novo-Nordisk and Sanofi; receiving royalties for editing a book from Springer; and holding stock in Amylin Pharmaceuticals, Dexcom, Ideal Life, Moerae Matrix, Opko Health, Patton Medical Devices, and Tandem Diabetes Care.

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