Predicting Adult-Onset Autoimmune Diabetes

Clarity From Complexity

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"What is time?" asked Saint Augustine in his *Confessions*, "When someone asks me, I know. But as soon as someone comes to question me on this matter, and I try to explain, I don't know anymore." A physician asked to define an autoimmune disease has a similar sense of frustration. For the perplexed, three features of autoimmune diseases, derived from Witebsky's postulates, might help: *1*) the presence of defined autoantigens and autoantibodies; *2*) passive transfer of T-lymphocytes, which leads to disease development; and *3*) successful immunomodulation of disease (1). Indeed, for type 1 diabetes in humans we know that autoantibodies are common and, alas, also that the second postulate is unethical and the third controversial. In reality, a disease is considered autoimmune when target organ destruction is allied to the presence of disease-specific target organ autoantibodies (2). It is through their clinical phenotype that diseases gain identity; only recently have we used genetic and immune responses to adapt disease names. Therefore, the historical characteristic of severe diabetes as childhood-onset disease was supplanted by insulin-dependent diabetes and with identification of diabetes-associated autoantibodies and genetic susceptibility through the major histocompatibilty complex (MHC) for type 1 diabetes, or more precisely type 1a diabetes, with type 2 diabetes being everything type 1 diabetes was not (2,3).

From the earliest years it was apparent that childhood diabetes was not always insulin dependent and vice versa. A revised classification of type 1 diabetes recognized as much when it excluded the term insulin dependent, thereby also excluding two features, ketoacidosis and insulin therapy, which were previously regarded as categorical features of this disease (3). Further complexity ensued with the recognition that a proportion of patients with ketosis-prone diabetes can stop insulin therapy, whereas 5–10% of adult-onset noninsulin-requiring diabetic patients have diabetes-associated autoantibodies (4,5). Indeed, adult-onset autoimmune diabetes is only one form of a broad spectrum of autoimmune diabetes, whether viewed genetically, immunologically, metabolically, or clinically (Fig. 1). When viewed genetically, MHC susceptibility, typical of autoimmune diabetes, is less striking in adulthood (6). From the immunological perspective, autoimmune diabetes is characterized by autoantibodies, although their number in a given subject declines with increasing age at onset (7). Metabolically, insulin secretory loss, but not insensitivity, is less pronounced in adulthood (8,9). From the clinical aspect, noninsulin-requiring autoimmune diabetes is most prevalent in adulthood (10). Adult autoimmune diabetic patients who are initially noninsulin requiring have latent autoimmune diabetes of adults (LADA), which is latent because without testing for diabetes-associated autoantibodies patients masquerade clinically as having type 2 diabetes (5). Other acronyms include slowly progressing insulin-dependent diabetes (SPIDM) or type 1.5 diabetes. Clinicians, in reality, still use their clinical nose to identify type 1a diabetes without routinely checking for autoantibodies, e.g., those for GAD (GADA). But, in maintaining a clinical rather than an immunogenetic definition, something is lost. It follows that the best way to identify autoimmune diabetes is to assess diabetes-associated autoantibodies, which represent the only relevant categorical trait (3,4,5,10).

Although there is no evidence that autoantibodies cause autoimmune diabetes, they share guilt by association. It follows that: *1*) autoantibodies predict autoimmune diabetes irrespective of the age at which they are detected and *2*) the antigen could be used for immunomodulation therapy to alter the disease process. In this issue of *Diabetes*, Lundgren et al. report firm evidence of the former, allied to recent evidence of the latter (11). Lundgren et al. confirm and extend an earlier study by showing that GADA, in a large cohort (initially 4,976 subjects were screened) of adult nondiabetic relatives of type 2 diabetic patients, are significant predictors of diabetes (12). A subgroup of this cohort was followed for 8 years: 252 subjects with GADA and 2,511 subjects without GADA. If GADA truly predicted diabetes, then every nondiseased subject with the autoantibody would eventually develop the disease (high positive predictive value); however, that value, albeit highly significant, was only 14%. Because this cohort was enriched for GADA positivity, even that predictive figure is exaggerated. Nevertheless, several additional factors could have increased the predictive power. First, limited specificity of the GADA assay means that ≥50 patients had false-positive GADA. Given such a large cohort, the assay specificity in recent years fell to 91%. Repeat testing and testing for multiple antibodies would have limited false positivity. Indeed, the predictive power was increased in those who sero-converted, or had high titer GADA. Second, addition of genetic and metabolic biomarkers, the latter tested prospectively, would increase predictive power similar to that for children at risk (8,13). Of note, many individuals with diabetes-associated autoantibodies do not develop diabetes, especially when identified at an older age. In this case,

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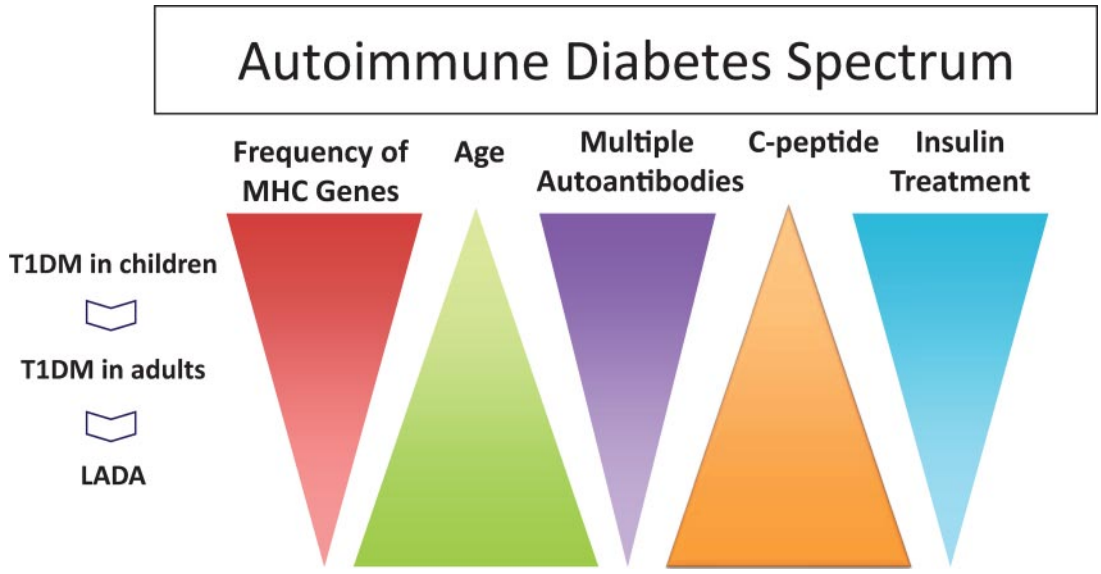

FIG. 1. The spectrum of autoimmune diabetes extends across all ages and varies with age at diagnosis. Older patients are more likely to have appreciable C-peptide but less likely to have high-risk MHC genes, have multiple autoantibodies, and require insulin treatment. T1DM, type 1 diabetes.

they reflect islet cell antibodies detected in first-degree relatives of type 1 diabetic patients in whom older age is also associated with lower risk of progression to diabetes (14). Further, in line with the proposal that adult-onset autoimmune diabetes is usually noninsulin requiring, all but 3 of 36 patients who developed diabetes had a non–insulin-dependent phenotype 1 year postdiagnosis, i.e., they had LADA (11).

The purpose of prediction is prevention. Given that the predictive power of GADA for diabetes in children now extends to adults, albeit less impressively, can we prevent autoimmune diabetes? Certainly, we can modify the disease process in established diabetes, as illustrated by recent studies using alum-formulated GAD. Two injections of GAD, given 30 days apart to GADA-positive childhood-onset and adult-onset autoimmune diabetic patients, affected serum C-peptide levels after 2 and 5 years, respectively (15,16). It was no less remarkable that the effect was modest than that there was any effect. Alum-formulated GAD, among other approaches, is now to be given in the pre-diabetic period, when we anticipate it would have a substantially greater impact. There was a time when predicting autoimmune diabetes was beyond our imagination. However, the change in disease definition, in association with the identification of disease-associated autoantibodies, has brought diabetes prediction within our grasp. For the perplexed, clarity has come from complexity and, with it, the real potential of disease prevention.

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