LADA: Time for a New Definition

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In this issue of *Diabetes*, Zhou et al. (1) report on the prevalence and characteristics of latent autoimmune diabetes in adults (LADA) in China. Findings from this study underscore the profound need for a new definition of LADA.

LADA, a slowly progressive form of autoimmune diabetes that develops in adults and does not require insulin therapy for some time after diagnosis, was first described over 25 years ago (2). Subsequently, clinical, metabolic, immunological, and genetic characteristics that are unique to LADA have been identified (3–6). For example, relative to patients with type 1 diabetes (T1D), those with LADA are more likely to be obese and have other elements of the metabolic syndrome. They are also more likely to retain greater β-cell function, express a single autoantibody (particularly GAD65) and certain GAD65 epitopes (7), and carry the transcription factor 7-like 2 (*TCF7L2*) gene polymorphism, which is strongly associated with type 2 diabetes (T2D) (8). However, the rationale for the strict criteria that are most often used to define LADA, including age >30 years at diagnosis and insulin independence for at least 6 months after diagnosis (5), have been questioned repeatedly (9–13). Furthermore, there is substantial heterogeneity in LADA, with some cases closely resembling T1D (e.g., low BMI, association with other autoimmune diseases), and others that share many features with T2D (14–16). Many authors and clinicians question the evidence base for defining LADA as a distinct entity and propose instead that LADA and childhood-onset T1D are opposing ends of the same continuum of autoimmune diabetes.

The multicenter study by Zhou et al. evaluated 4,880 subjects in China with diabetes diagnosed at age >30 years, enrolled within 1 year of diagnosis, and who did not develop diabetic ketoacidosis or insulin dependence for at least 6 months after diagnosis. LADA was diagnosed in 5.9% of these patients based on GAD65 autoantibody positivity, and the rest were classified as T2D. In the south of China, compared with the north, LADA was more prevalent and was characterized by higher GAD65 titers and lower frequency of both metabolic syndrome and obesity. Relative to LADA patients with low GAD65 titers, those with high GAD65 titers were younger, had lower BMI, lower β-cell function, and higher frequency of T1D-associated HLA haplotypes. Thus, consistent with previous studies (14,15), LADA with high GAD65 titers resembled T1D in the current report.

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The authors are to be commended for accomplishing a 100% rate of GAD65 autoantibody testing, 6-month assessment visit, and GAD65 autoantibody assay reproducibility in their remarkably large study. Comparisons of characteristics between Chinese LADA patients and those in other countries are difficult to interpret because of differences in methods of ascertainment, subject selection, and laboratory techniques. Nonetheless, an intriguing implication of the study is that, while the frequency of childhood and adult onset T1D is similar in countries with high incidence of T1D (17), in China, where the incidence is low, LADA may be the most common form of autoimmune diabetes. However, this interpretation requires confirmation of the autoimmune nature of the cases identified as LADA, which may be challenging, as we will discuss.

This study highlights two critical issues in the current definition of LADA (5). One of them is reflected by the authors' observation that patients with LADA and low GAD65 titers were not different from T2D patients in sex, age at diagnosis, HbA_{1c}, β-cell function reserve, or components of the metabolic syndrome. On the other hand, all of those features were different in LADA with high GAD65 titers and T2D (1). One possible interpretation is that the pathogenesis of diabetes with low GAD65 titers is not truly different from that of T2D. Single autoantibody expression, particularly low titers, lacks predictive value for progression to T1D (18). GAD65 autoantibodies are particularly prone to this "biological false positivity" (G. Eisenbarth, personal communication), and their expression in healthy subjects has been reported more frequently than other autoantibodies (19). In the study by Zhou et al. (as in any other study on autoimmune diabetes), analysis of additional anti-islet autoantibodies would have been of interest. It is likely that higher number of positive autoantibodies would have correlated with higher titers of GAD65 autoantibodies. Therefore, single autoantibody positivity at low titers may not be sufficient evidence that β-cell autoimmunity plays a significant role in the pathogenesis of diabetes, and, thus, it may not appropriately classify diabetes as autoimmune, be it LADA or childhood onset.

A second key issue is the failure of the existing LADA criteria to capture a pathogenic mechanism requiring specific preventive and therapeutic approaches. Both criteria of diagnosis in adulthood and transient insulin independence attempt to reflect slowly progressing β-cell loss. However, it is insulin resistance, which does not significantly contribute to most cases of autoimmune T1D, that plays a unique pathogenic role in slow-onset autoimmune diabetes. Furthermore, the risk of metabolic syndrome and cardiovascular complications in patients with insulin resistance turns the latter into an essential therapeutic target. Diabetes results from insulin production not meeting the demands posed by insulin resistance. In patients with protracted autoimmune destruction of β-cells, clinical diabetes may manifest itself when insulin resistance renders insufficient their dwindled insulin secretion capacity (Fig. 1). This hypothesis is supported by observations

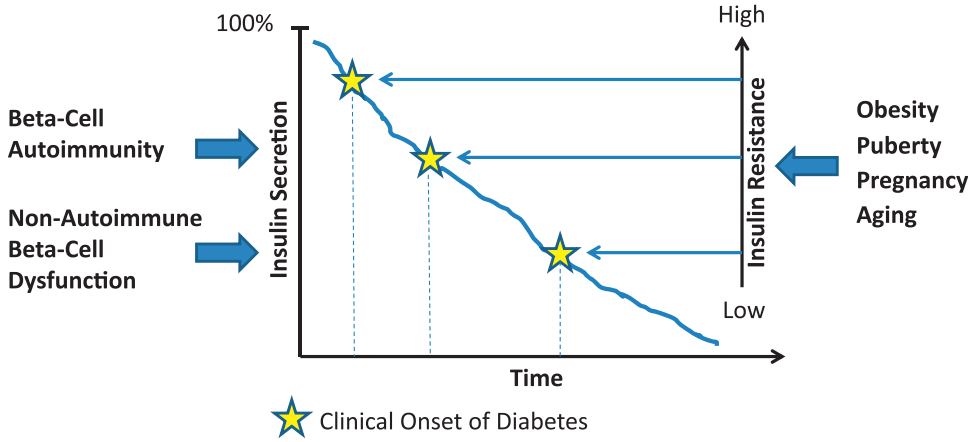

FIG. 1. Model of progression to diabetes determined by insulin secretion and insulin resistance. Clinical diabetes manifests when anti-islet autoimmunity (in T1D) or nonautoimmune β-cell dysfunction (in T2D) decrease insulin secretory capacity below a threshold determined by insulin resistance, which can vary from low (in T1D) to high (in T2D). Although not illustrated in this figure, variation in the rate of insulin secretion decrease also determines time to progression to diabetes. In LADA, as opposed to T1D and T2D, three mechanisms, namely, anti-islet autoimmunity, nonautoimmune β-cell dysfunction, and elevated insulin resistance, likely contribute to disease.

that β-cell function is greater in LADA than in T1D patients, as well as in obese relative to lean children at the onset of T1D (20). Defining a distinct entity with a double component of β-cell autoimmunity and insulin resistance would facilitate identification of patients—children or adults—who may benefit from addressing both aspects of their diabetes.

In summary, the definition of LADA is unsatisfactory in many respects, some of which are highlighted in the study by Zhou et al. Cases without biologically significant β-cell autoimmunity can be classified as LADA. The present diagnostic criteria do identify some patients with slowly progressive β-cell destruction but leave out many more, including young adults and adolescents. Furthermore, the current description of LADA fails to capture insulin resistance, a unique pathogenic mechanism and a therapeutic target in this form of autoimmune diabetes. It is time for a new definition of LADA.

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