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A long and winding road to understand latent autoimmune diabetes in adults

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Latent autoimmune diabetes in adults (LADA) describes a subgroup of patients who develop phenotypic type 2 diabetes (T2D) but with markers of islet autoimmunity. It is under debate whether LADA is a subtype of type 1 diabetes (T1D) or a unique disease. LADA comprises about 1.5% to 14.2% in phenotypic T2D depending on ethnicity. It is the most common form of autoimmune diabetes diagnosed in adults, with 3.3- to 12.2-fold higher prevalence than that of adult-onset T1D.[1] LADA has similar pathogenesis as classic insulin-dependent diabetes mellitus, which is contributed to simultaneously by environmental factors and genetic susceptibility. It is characterized by autoimmune and slow progressive damage in islet β cells. As an important subtype of diabetes, LADA should be recognized, understood, and managed appropriately in clinical practice. Up to now, an increasing number of researches worldwide have depicted and updated the naming, diagnostic criteria, clinical features, pathogenesis, and treatment of LADA. There is a long and winding road to understand LADA. Here, we will discuss the expanding understanding of LADA and update the latest evidence on LADA.

Controversial Nomenclature, Diagnostic Criteria, and Classification

LADA has been known for more than 40 years. The first identification of the LADA phenotype has been made in 1976 by Irvine *et al* who described a group of phenotypic T2D patients with the presence of islet cell antibodies and insulin dependency. Ten years later in 1986, Groop *et al* further reported the clinical features and treatment needs of this type of diabetes. He devoted much of his job to this new phenotype and was considered the father of LADA.[2] The term "LADA" had been used by Leif *et al* in 1986 then, in 1993, by Tuomi from the Leif Groop team.[2] Alternative and controversial terms for this phenotype have been suggested in the past years, including "slowly progressive insulin-dependent T1D", "non-insulin requiring autoimmune diabetes", "type 1.5 diabetes", "adult-onset autoimmune diabetes", "slowly progressive T1D", and so on. All these terms were used to describe patients who initially were thought to be T2D but had evidence of pancreatic autoantibodies.

The most widely used diagnostic criteria for LADA was established by the Immunology of Diabetes Society (IDS) in 2005[3] as follows: (1) adult age at onset of diabetes; (2) the presence of circulating islet autoantibodies; and (3) lack of a requirement for insulin for at least 6 months after diagnosis. The criteria describe the key characteristics and the heterogeneity of LADA. However, the LADA definition is still a matter of debate. For example, adult age, often defined as >35 years, is an arbitrary limit. In IDS criteria, the operational minimal age is 30 years, but in the Chinese Expert Consensus on Diagnosis of LADA in 2012,[4] the adult age is greater than 18 years, which allows for a wider screen for islet-autoantibody-positive adults with diabetes; Moreover, the early use of insulin treatment, the false positivity and transient positivity of autoantibodies are also obstacles to define LADA. Hence, the 2020 international consensus on LADA highlighted that all these clinical characteristics help to identify LADA but could not categorically define LADA.[5]

There is still debate on whether LADA is a unique disease or a subtype of T1D. According to the 1999 WHO and 2020 ADA recommendations for the classification of diabetes, LADA is classified as T1D,[6,7] but in the latest 2019 WHO classification of diabetes, LADA is referred to as "slowly evolving, immune-mediated diabetes of adults" and is classified as "hybrid forms of diabetes". Some scholars believed that this type of diabetes should be renamed the term "intermediary diabetes mellitus" that can truly reflect the essence of this phenotype.[2] More high-quality evidence is in need to understand LADA and promote the precise classification of diabetes.

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Heterogeneous Clinical Features

LADA has the common, but not identical, features of both T1D and T2D. Mounting evidence indicates that diabetes is a continuous spectrum, from T1D to T2D, and LADA is the between.[8] The clinical features of LADA patients are more like those of T2D than T1D. In LADA China Study, compared to the patients with typical T1D, LADA patients were older, had higher body mass index (BMI), higher C peptide levels, and were not in urgent need of insulin at onset.[9] Compared to T1D, LADA patients were more likely to present T2D-like features, such as overweight or obesity, metabolic syndrome, and insulin resistance-related systemic inflammation.[10] However, LADA patients also differ from those with non-autoimmune T2D, since they are younger, have lower BMI, and lower C peptide levels. LADA patients are also prone to have other autoimmune disorders, such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease.

LADA has much more heterogeneous clinical features than the above. Different titers of glutamic acid decarboxylase antibody (GADA) can help identify patients with different clinical characteristics. Typically, those with high GADA titer are younger with lower BMI, lower frequency of metabolic syndrome, worse hemoglobin A1c (HbA1c), lower C-peptide levels, and higher positive rates of other islet autoantibodies.[11] Patients with high GADA titer had poorer beta cell functions and less diabetic complications or risk of complications compared to LADA patients with low GADA titer. In conclusion, LADA patients with high GADA titer resembles T1D more closely; alternatively, those with low GADA titer resembles T2D patients in metabolic presentation and beta cell function during follow-up.[11]

Notably, the GADA titer of LADA had ethnic differences. Asian LADA patients had a lower proportion of high GADA titer than that in Caucasians.[12] LADA China study suggested 74% of Chinese patients were in the low GADA titers,[9] while this proportion in the NIRAD study was 49% in Italian.[13] The varied GADA titer may be the result of genetic differences among ethnics.[14] Notably, the GADA varied in different disease duration. After diagnosis, 81% to 97.9% of LADA patients remained GADA positive for 6 to 12 years.[1] High GADA titer is more likely to persist, whereas low GADA titer is more likely seroconverted to negativity. The heterogeneity of LADA patients is also related to the number of antibodies. The multiple positive islet autoantibodies were also associated with a high GADA titer and a faster decline of islet function.[15]

In addition to GADA titer, GADA epitopes are also associated with LADA heterogeneity. The LADA subjects with middle and COOH-terminal epitopes of GADA were younger, lower serum C-peptide level and the requirement for insulin therapy, more increased risk of thyroid autoimmunity, and higher GADA titer compared to NH2-terminally reactive GADA.[16] Besides, onset age is also associated with the heterogeneity of LADA. A recent study identified a distinct phenotype of elderly LADA, which differed phenotypically and genetically from young LADA, but has a clinical and genetic profile more similar to that of elderly T2D.[17] These observations demonstrated that LADA presents great clinical heterogeneity.

Complicated Genetic Background

Though it has been shown that genes predisposing to T1D or T2D present in contributing to LADA concurrently, the main susceptible genes of LADA may be closer to those of T1D.[18] A recent study constructed genetic risk scores (GRS) from T1D- and T2D-implicated single-nucleotide polymorphisms in large LADA samples, where they found that T1D GRS can better distinguish LADA from controls than T2D GRS, suggesting LADA might genetically be closer to T1D.[19] The genome-wide association study of LADA showed that the top significant gene signals in LADA were all T1D-associated, and a genetic correlation with T2D-associated risk loci was weakening, supporting that LADA is genetically closer to T1D than to T2D.[18]

Human leukocyte antigen (HLA), especially HLA class II genes, represents the genomic regions most strongly associated with genetic susceptibility to LADA.[20] HLA class II genotype DR3/DR4 is permissive for LADA in individuals of Caucasian origin while the DR9/DR9 genotype is specific only to subjects of East Asian ancestry.[14] Similarities and differences in the architecture of HLA-conferred susceptibility to LADA between Chinese and Caucasians have been summarized in detail in the literature.[14]

Several non-HLA genes related to T1D also account for genetic susceptibility to LADA. Insulin gene, protein tyrosine phosphatase non-receptor type 22 gene, and transcription factor 7-like 2 gene have also been reported as related to additional genetic risk for LADA, but their effects warrant further investigations across diverse ethnic groups with a larger sample size.

Multiple Immunological Mechanisms

The autoimmune evidence of LADA includes humoral immune responses, such as the presence of autoantibodies against islet antigens in the circulating blood, and cellular immune responses, such as islet antigen-specific T cells. Currently, the immunological diagnosis of LADA is primarily based on the presence of islet autoantibodies. The main islet autoantibodies include GADA, IA-2A, insulin autoantibody (IAA), and ZnT8A. Recently, TSPAN7A was valid as another new islet autoantibody for use in east Asian populations with LADA.[21] GADA has been recognized as the most sensitive immune index for screening LADA at diagnosis in patients with phenotypic T2D. Other autoantibodies can be used as joint screening indicators to increase the positive prevalence of LADA diagnosis.

The appearance of islet autoantibodies reflects the autoimmune characteristics of LADA but has a limitation in elucidating the pathogenesis. There are some peripheral "sensitized" T lymphocytes, including CD8+ autoreactive T cells, in LADA patients. They produce a variety of cytokines and reproduce their immune response in vitro. For example, there are GAD-responsive Th1 cells and Th1/Th2 ratio imbalance in LADA patients, which is evidence

of cellular autoimmunity in LADA. Apart from this, regulatory T cells (Tregs) are a subset of T cells that inhibit the excessive immune response. LADA patients have a decreased frequency of Tregs and the expression of Treg-related functional molecules. The reduction of Tregs function may be a key reason for autoimmunity in LADA patients. Based on the advance of cellular immunity, Rolandsson and Palmer[22] proposed the concepts of B cell LADA (B-LADA) and T cell LADA (T-LADA). The former is LADA with positive autoantibodies secreted by B lymphocytes, and the latter is LADA with specific islet-autoreactive T lymphocytes.

Human B lymphocytes can be further divided into Marginal zone B cells (MZB), follicular B cells (FoB), and regulatory B cells (Bregs). MZB cells and FoB cells can activate CD4+ T cells, and they are the bridge between innate immunity and adaptive immunity. Bregs inhibit T cell-mediated immune disorders by secreting IL-10 and antigen-restricted methods. It is assumed that the decrease in the frequency of Bregs may impair immune tolerance, and then cause autoimmune destruction of pancreatic β-cells, leading to LADA. The frequency of MZB cells also was negatively correlated with islet function and positively correlated with blood-glucose control.[23] These findings suggest changes in B lymphocyte subsets may have important significance in the occurrence and development of LADA.

Limited Therapeutic Strategy

Evidence has suggested that sulfonylurea may accelerate β cell failure in LADA patients. Therefore, sulfonylureas should be avoided as first-line treatment. However, some widely used oral hypoglycemic agents, such as dipeptidyl-peptidase 4 (DPP-4) inhibitors and thiazolidinediones, showed favorable effects in β cell function preservation for LADA.[24] Sodium-glucose cotransporter 2 inhibitor (SGLT2i) has been recommended as the first-line combined treatment for T2D with heart failure or chronic kidney disease. The thrilling results of DEPICT-1 suggested the efficacy of SGLT2i in glucose control for T1D patients.[25] It would be interesting to see if subjects with LADA, especially those with poor β cell function, could benefit from SGLT2i. Besides conventional oral hypoglycemic agents, Vitamin D, a nonspecific immune regulator, has also been studied in patients with LADA to alleviate immune attack and slow down β cell failure. A recent study confirmed that adding vitamin D3 to the DPP-4 inhibitor had the potential to protect beta-cell function in LADA patients through a multicenter, randomized, nonblinded clinical trial.[26]

LADA patients are characterized by insulin independence at the onset with preserved β cell function. Nevertheless, evidence from small randomized studies consistently suggested that early initiation of insulin therapy was better than conventional oral hypoglycemia agents in metabolic control and β cell function preservation. Glucagon-like peptide-1 receptor (GLP-1R) agonist has received much attention for its benefit for T2D patients with cardiovascular disease. However, the data of GLP-1R agonists to treat LADA is limited. A post-hoc analysis of phase 3 clinical trial of dulaglutide found that the reduction of HbA1c is comparable in subjects with LADA and patients with GADA negative T2D. And LADA patients increased HOMA-B compared to the baseline during 12 months follow-up.[27] However, another observational study suggested a milder glycemic response to exenatide or liraglutide in patients with LADA than that in patients with T2D.[28]

It has been well documented that bariatric surgery is superior to lifestyle and medication intervention to reduce the risk of cardiovascular disease in patients with obese T2D. In fact, LADA is prevalent in patients with phenotypic T2D, and over one-third of LADA patients were overweight and obese.[9] Some studies reported that the clinical features of LADA and T2D are largely overlapped. Therefore, some patients with phenotypic T2D undertaking bariatric surgery may actually be attributed to LADA, which raises concern. Manning *et al*[29] reported one LADA patient who underwent bariatric surgery failed to achieved diabetes remission. Similarly, a recently published observation of ten patients with obese LADA found that, after bariatric surgery, these patients showed no improvement in glycemic control during a 62-month follow-up. Moreover, they were at increased risk of post-surgery ketoacidosis.[30] These data highlight the importance of the screening to diagnose LADA early, as the metabolic surgery may not improve glycemic control in patients with LADA.

Recently, the international consensus statement was published to standardize the management of LADA. The consensus proposed a modified algorithm for LADA based on the ADA/EASD algorithm for T2D,[5] which is driven by the level of C-peptide. Notably, subjects with LADA show high heterogeneity in clinical features and pathogenesis, so personalized therapy may be warranted. The therapy effectiveness may be varied according to patients with high and low GADA titer or other influencing factors, making the optimal therapeutic strategy for LADA challenging.

Conclusion and Perspective

To date, many studies have been made to unveil the essence of LADA. It was described as phenotypes with characteristics in-between those of T1D and T2D. LADA encompasses different degrees of β cell autoimmunity and insulin resistance and is highly heterogeneous in clinical phenotypes, autoimmunity, and genetics. However, the etiology, phenotype, and pathogenesis of LADA have only partly been elucidated. The nomenclature, definition, classification, and diagnostic criteria of LADA remain controversial. These have sometimes provoked considerable discussion and intense debate. The treatment of LADA patients is far less elucidated than is the case for T1D and T2D. A personalized medicine approach is requested to achieve optimal metabolic control and preserve β-cell function. Although our understanding of LADA is steadily increasing, there is still a long and tortuous road to fully understand the disease. A worldwide collaborative study including large-sample LADA cohort studies and clinical drug intervention trials will contribute

to reveal the essence of LADA and precise treatment methods in the future.

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Conflicts of interest

None.

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