Review Article

Latent Autoimmune Diabetes in Adults: The Current Diagnostic Challenges and Treatment

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Latent autoimmune diabetes in adults (LADA) is a heterogeneous disease characterized by adult-onset diabetes, low circulating islet autoantibody levels, and broad clinical phenotype compared with classical type 1 diabetes mellitus (T1DM). Hence, patients may present with clinical features of both type 2 diabetes mellitus (T2DM) and T1DM. Highly variable beta-cell destruction, varying degrees of insulin resistance (IR), and heterogeneous islet autoantibody titer and pattern that indicate different pathophysiological pathways partially explain the heterogeneous phenotypes of LADA. Because patients with LADA do not need exogenous insulin at the diagnosis of diabetes and are diagnosed by testing for islet-cell autoantibodies, detection of LADA in a clinical setting is challenging. Therefore, the misdiagnosis rate among patients with T2DM is high. Although several medical workers advocate a clinically oriented approach for screening patients with LADA, no criteria for autoantibody testing in adult-onset diabetes have been accepted universally. Therefore, the current challenges in LADA diagnosis and therapeutic approaches are presented in this review.

Key words: latent autoimmune diabetes in adults, islet autoantibodies, residual beta-cell function, treatment

Introduction

Latent autoimmune diabetes in adults (LADA), a slowly progressive form of autoimmune diabetes (AD), has an older age of onset and does not require insulin therapy for some time after diagnosis.[1-3] The Immunology of Diabetes Society (IDS) has established the following three main criteria to diagnose LADA: (1) age at diagnosis of at least 30 years, (2) presence of circulating islet autoantibodies, and (3) no need for insulin for at least 6 months after diagnosis.[4] Nevertheless, the definition of LADA remains controversial and these diagnostic criteria remain debatable. For instance, age and treatment requirements seem arbitrary. Patients aged < 30 years may present with a slowly progressive form of AD, which is indistinguishable from LADA in older patients.[5] Therefore, the presence of islet autoantibodies is the only objective requirement. The significant heterogeneous phenotypes in LADA impede the establishment of a priori algorithm treatment. Nevertheless, complete characterization of patients

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with LADA in terms of its course, pathogenesis, epidemiological features, and therapeutic approach warrants a considerable amount of effort. This review presents the current challenges in LADA diagnosis and therapy.

Current challenges in LADA diagnosis

The challenges of how to define and diagnose LADA has resulted in numerous debates regarding whether LADA is a distinct but heterogeneous clinical entity or just a variant of type 1 diabetes mellitus (T1DM).[6-9] Whether the introduction of the term LADA has been an asset or an obstacle to our understanding of diabetes is a controversial topic.[7,9,10] LADA, a slowly progressive form of AD, was first described over 30 years ago.[1] Subsequently, the clinical, metabolic, genetic, and immunological features unique to LADA were identified.[4,10-14] However, the rationale for the strict criteria most often used to define LADA, including age at diagnosis of at least 30 years and noninsulin requirement for at least 6 months after diagnosis,4 have been questioned repeatedly.[6,7,15,16] Moreover, the heterogeneity in LADA is considerable, with some cases being similar to T1DM and others sharing several features with type 2 diabetes mellitus (T2DM).[14,17]

Several authors and clinicians have explored the evidence to define LADA as a separate disease and proposed that LADA and T1DM are at the opposing ends of the same continuum of AD. Cochrane Database of Systematic Reviews demonstrated that the lack of a clear definition as well as the availability of only few randomized controlled trials of excellent quality pose challenges regarding a conclusive treatment strategy for patients with LADA.[18] Thus far, substantial information has been unveiled regarding the clinical features, cellular immune responses,[19-21] metabolic traits,[22-24] and genetic background[14,17,25] in adult patients with AD. Therefore, the concept of LADA has become a suitable tool for studying and connecting various pathophysiological aspects of AD in adults.

Redondo proposed the hypothesis that clinical diabetes manifests when anti-islet autoimmunity in T1DM or non-autoimmune beta-cell dysfunction in T2DM decreases the insulin secretory capacity to below a threshold determined by insulin resistance (IR), which can vary from low in T1DM to high in T2DM.[26] In contrast to T1DM and T2DM development, three mechanisms underlie LADA development: anti-islet autoimmunity, non-autoimmune beta-cell dysfunction, and elevated IR.[26] This hypothesis is supported by the observation that at the onset of T1DM or LADA relative to T1DM, obese and overweight children have a greater beta-cell function than do leaner children.[27] However, the significance of autoantibody levels and their prognostic value associated with the disease process of LADA remain unclear.[15] Some studies have proposed clinically distinguishing LADA types based on the antibody titer: high or low titer.[28,29] This differentiation may lead to new sub–sub-categorizations, such as LADA type 1 (insulin-dependent) as opposed to LADA type 2 (non–insulin-dependent). Nevertheless, categorization based on residual beta-cell function (C-peptide), antibody titer (low or high), epitope specificity (C-terminal, middle, or N-terminal), genotype (T1DM or T2DM genes or their mixture), degree of overweight or obesity, positive T-cell immunoassay for antigen [glutamic acid decarboxylase antibody (GADA)], insulin autoantibody (IAA), islet-antigen-2A (IA-2A), or zinc transporter 8 (ZnT8A), in addition to the current categorization based on age, therapy, and positive autoantibody assay, will lead to more confusion.

Next, the controversial criteria of LADA are considered. The reported minimum cut-off age for LADA onset varies from 25 to 40 years,[1,13,14,30,31] but this is an arbitrary limit. We believe that a teenager or young adult (aged < 25 years) with T2DM phenotype, who re-

sponds well to oral hypoglycemic agents initially but has autoantibodies, could also be a LADA patient. Therefore, having no age limit would help us to understand better the underlying pathophysiology of the disease, which should be our main scientific focus. Ideally, longitudinal studies on patients with preclinical history of LADA must distinguish LADA from classic juvenile-onset T1DM on the basis of the metabolic and immunogenetic markers. LADA diagnosis has mainly relied on seropositivity for GADA. For instance, IAA, IA-2A, and ZnT8A have been reported in LADA infrequently.[7,32-38] Nevertheless, additional studies documenting the prevalence if IAA, IA-2A, IA-2β, and ZnT8A in LADA in different populations for an accurate profile of humoral immunity are warranted. GADA is not a sine qua non in adults with diabetes without insulin-dependence at diagnosis, and the presence of any islet autoantibody would currently categorize them as having LADA. A study revealed that the combined presence of GADA, IA-2, and IAA is associated with a more rapid clinical onset of hyperglycemia than if one type of antibody were present during the prediagnosis stage in children.[39] However, larger and long-term prospective studies are needed to confirm whether autoantibody status before a diagnosis could be predictive of the severity of clinical characteristics in LADA. However, a correlation was noted between multiple antibody positivity at LADA onset and increased risk of disease progression, which was highly predictive of further need for insulin requirement postdiagnosis.[40,41]

On the other hand, whether the autoimmune process of LADA begins in childhood with only inadequate insulin secretion followed by a series of precipitating events in adulthood remains unclear. Nevertheless, multiple islet antibodies or GADA alone at LADA diagnosis can predict future complete beta-cell failure. GADA was noted to persist in most patients after diagnosis (for up to 12 years)[42] and it might be relevant to antigen persistence in surviving beta cells, thereby sustaining prolonged immune response. Elevated GADA titers are predictive of the need for more intensive therapy early, but not later, in the disease course.41 Therefore, GADA levels are unreliable predictive markers of the decline in glycemic control and the requirement for insulin therapy. As indicated by Gale,[15] there are pitfalls in defining autoimmunity, suggesting that immune-mediated diabetes is widely prevalent in the adult-onset population, and this has numerous implications for our understanding of the condition and may have practical value.

However, to confirm this practical value, some additional questions need to be considered. The main obstacle is defining antibody positivity in antibody assays because "positivity" refers to a selected cutoff point; therefore, its definition is critical. It might depend on the assay methodology or even on the age or sex of the group wherein the assays were performed. The results from the Fourth International Workshop on the Standardization of Insulin Autoantibody Measurement suggested that radioimmunoassay (RIA) or similar assays that perform well should be used to measure IAA associated with insulin-dependent diabetes mellitus.[43] In addition, their presence could be assessed using the enzyme-linked immunosorbent assay (ELISA) in the routine laboratory practice. A reasonable concern would be how the available assays could positively and negatively distinguish diabetes-associated IAA from non–diabetes-associated IAA and from insulin antibody, but this is practicable through distinct idiotypes.[44] In the latest antibody assay workshops organized by the IDS and the US Centers for Disease Control and Prevention, various RIAs and some new ELISA kits revealed excellent concordance, as well as high levels of sensitivity and specificity.[45] However, on comparisons among adults,[46] the concordance between assays was not as strong as that in young children and adolescents,[45] indicating

that differences in epitope specificity or antibody levels arising from differences in affinity or capacity could significantly influence assay performance. Despite the limitations of the assays, autoantibody positivity probably implies an autoimmune process. The results of the UK Prospective Diabetes Study demonstrated that among patients aged > 55 years with or without antibodies at diagnosis, 44% of those with ICA, 34% of those with GADA, and 5% with neither antibody required insulin therapy within six years.[30] The cutoff value, expressed as a designated percentile of the control population, was selected because it offered the optimal balance of sensitivity and specificity for the intended purpose.

Another problem is how to define a cutoff value based on autoantibody titers because these antibodies are profusely distributed throughout healthy populations.[15] Hence, the clinical significance of a "positive" test for autoantibodies without a well-defined cutoff value is questionable. The ideal method would be comparing the prevalence of a marker in a test population with that in a background population from which the prevalence is drawn and then matching it with that in control cases of the same age and sex. The cutoff value for identifying those who progressed to insulin requirement could be selected retrospectively, after determining the distribution of the marker between the two populations. For instance, the threshold could be lowered to increase sensitivity to identify as many progressors as possible or it could be increased to prevent false positives and maximize specificity if an intervention is planned. This approach has an elastic nature of the self-imposed categories used, which is ideal; therefore, we contemplated why we are using these categories. Moreover, the present antibody assays are based on the measurement of radioactivity in RIAs or fluorescence in ELISAs, which is translated into units with continuous distribution. The causes of low assay signals of radioactivity or fluorescence could be attributed to background "noise," various reagents in the assays, nonspecific binding, or low targeted antibody levels.

Furthermore, false-positive autoantibody is another problem. The prevalence is estimated at 0.65% – 3.60% in subjects without diabetes who have positive autoantibody.[33,47] However, it is unknown whether autoantibody positivity reflects the weakness in the assays or represents an autoimmune process. Several studies have reported the development of diabetes during the long-term follow-up of the general population diagnosed with autoantibody positivity.[48-50] Nevertheless, these findings were made in a relatively small population, thereby warranting large, long-term prospective studies for further exploration. In addition, the dynamic changes in the humoral immune response during the progression to diabetes are a complicating problem. For example, prediabetic healthy adults with antibody positivity at baseline may become antibody-negative over time or vice versa. This dynamic change in autoantibodies after onset of the disease seems to be higher in children[51,52] than that in adults[53-55] and to be higher for ICA than that for others, such as GADA. A study observed that the GADA epitope specificities in the prediabetic period change dynamically. Specifically, the binding to a middle epitope and a C-terminal epitope increases during the follow-up period, causing a significant increase in the number of epitopes recognized.[55] However, interpretation of this autoantibody disappearance is a challenge. Is the autoimmune disease under remission, are the autoantibodies no more positive, or both in different subjects or at different times? These questions might mislead the clinical classification at least in some individuals. The clinical and metabolic characteristics of LADA have been studied extensively. The decreasing rate of islet beta-cell function is faster in LADA than that in T2DM but it is slower than that in T1DM.[4,15,42,56,57] Regarding insulin sensitivity, no apparent differences were noted

among LADA, T1DM, and T2DM, either in the prediabetic or diabetic stages.[1,23,58] However, features of metabolic syndrome are more common in patients with LADA than in those with T1DM[59,60] but still less common compared to those with T2DM.[28,33,61] In addition, patients with LADA appeared to have fewer macrovascular and microvascular complications than those in subjects with type 1 or type 2 diabetes.[60,62] Regrettably, an appropriate therapeutic choice is inconclusive if LADA is considered an entity. Nevertheless, an international, multicenter study would be of merit in comparing the relative residual beta-cell preservation effects and long-term disease outcomes of conventional oral therapy strategies involving early insulin treatment.

Another problematic criterion for LADA is insulin independence for at least six months after diagnosis[15,30,59] partly because of a lack of strict definition for insulin treatment.[4] Moreover, several factors may influence the period of insulin independence, including the natural course of the disease, the timing of diagnosis associated with natural course, and the physician's therapeutic bias on clinical judgment. These factors may differ from patient to patient. Moreover, the time elapsed until insulin treatment is dependent on clinical judgment but not on the disease process. Because clinical judgment is based on the presence of autoantibodies, defining LADA based on autoantibody positivity and the lack of initial need for insulin treatment is fraught with challenges because one often precludes the other.8 Notably, patients who are asymptomatic and diagnosed with diabetes based on elevated blood glucose levels are more likely to meet the criterion of the noninsulin dependence for a short time than those diagnosed with diabetes after being symptomatic. However, the current diagnostic criterion is biased, often excluding patients who are symptomatic, or the diagnosis of diabetes is delayed. Moreover, asymptomatic patients undiagnosed with diabetes for a period who eventually become symptomatic are likely to immediately start with insulin treatment; therefore, they potentially have classical T1DM. Nevertheless, how to categorize patients with autoantibodies who only receive insulin treatment initially for few weeks or months and are then treated subsequently with oral agents for years remains unclear. Hence, the issue of noninsulin dependence is more problematic and can be resolved only by conducting larger long-term prospective studies that have predefined criteria for starting insulin treatment and analyze the beta-cell function.

Treatment

Even though various recommendations are available for the treatment of subjects with T1DM and T2DM, no specific guidelines for the treatment of patients with LADA have been published thus far. Therefore, patients with LADA currently receive treatment similar to that for those with T2DM, resulting in rapid progression to an insulin-dependent state,[63] especially those who present with clinical and biochemical features more identical to T1DM than to T2DM.[3,64]

Lifestyle modifications

The therapeutic diet strategy in patients with LADA is akin to that of classical T1DM. Obese patients with LADA benefit from calorie restriction and increased levels of physical activity.[65] Results from the Nord-Trøndelag's study suggested that increased age, excess weight, and physical inactivity are strong risk factors for LADA.[66] These findings suggest a crucial role of IR in LADA pathogenesis and have significant public health implications because they suggest that LADA is considerably influenced by environmental factors and hence preventable.

Insulin sensitizers

To date, no large, long-term prospective studies have evaluated the efficacy of metfor-

min in LADA treatment.[67] Patients with LADA could benefit from therapy with a thiazolidinedione (TZD) because they could increase the ability of beta cells to detect and respond to fluctuations in glucose levels within the physiological range, improve insulin sensitivity, preserve pancreatic islet structure and insulin secretory function, protect beta cells from oxidative stress and apoptosis, increase beta-cell mass, as well as exert anti-inflammatory and anti-atherogenic properties.[68,69]

One randomized controlled trial comparing insulin alone versus rosiglitazone plus insulin in patients with LADA suggested that rosiglitazone plus insulin may preserve islet beta-cell function in patients with LADA.[70] However, this study did not clarify the effects of TZD monotherapy. Similarly, another study revealed that rosiglitazone combined with insulin preserved beta-cell function in patients with LADA after three years.[71] The authors speculated that rosiglitazone might promote the regulatory potential of $CD4^{+}CD25^{+}$T cells, which have protective effects against AD.[72] Pioglitazone prevents or delays the progression of insulin deficiency in patients with LADA.[73] However, another study revealed that pioglitazone might accelerate the disease course of LADA.[74] Therefore, to clarify whether pioglitazone could affect the progression of LADA, additional prospective and interventional studies are needed to explore this aspect further.

Sulfonylureas

It is reasonable to speculate that sulfonylurea (SU) would accelerate the progressive deterioration in beta cells and shorten the starting time of insulin therapy in LADA, and several studies have confirmed this hypothesis.[65,75-79] Thus, these data suggest that SU should not be used as the first-line therapy in patients with LADA.

Dipeptidyl peptidase-4 inhibitors

Patients with LADA were reported to express higher dipeptidyl peptidase-4 (DPP-4) activity compared with patients having T1DM or T2DM.[80] DPP-4 inhibitors might represent an appropriate therapeutic approach that offers metabolic control and improvement in the natural history of the disease in patients with LADA. Linagliptin may have attenuated the rate of decline in C-peptide levels in patients with LADA over a two-year disease trajectory.[79] Sitagliptin may maintain beta-cell function in patients with recent-onset LADA after 12 months of follow-up.[81] A post hoc analysis revealed that saxagliptin can effectively lower blood glucose levels and is generally well tolerated in patients with GADA positivity.[82] Therefore, saxagliptin appears to improve beta-cell function in these patients; however, a longer treatment duration may be needed to confirm this finding.[82] A recent study conducted in Japan observed that treating LADA with sitagliptin rather than insulin may be more effective in preserving the beta-cell function for at least four years, possibly through the immunemodulatory effects of DPP-4 inhibitors.[83] Altogether, these data suggested that DPP-4 inhibitors have critical therapeutic implications in LADA. Further investigation involving a larger cohort is warranted to assess the clinical outcomes and thoroughly explore the mechanism of beta-cell preservation in these patients.

Glucagon-like peptide-1 receptor agonists

More recently, a study investigated treatment with the glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), exenatide or liraglutide, in patients with LADA for six months, revealing a nonsignificant reduction in the adjusted mean level of glycated hemoglobin (HbA1c), lower than the reduction observed in antibody-negative patients.[84] Moreover, the glycemic response to GLP-1RA therapy was considerably weaker in those who were GADA or IA2 antibody positive or had severe insulin deficiency.[84] Another study

reported a favorable effect of the GLP-1 RA dulaglutide on glycemic control in LADA.[85] Nevertheless, additional studies with a larger cohort and longer treatment duration assessing whether these therapies are effective for suppressing progression to insulin dependence and lowering diabetic complications in patients with LADA are warranted.

Insulin therapy

Insulin therapy rather than SU treatment has been preferred to reverse or preserve beta-cell function among patients with LADA.[78] Subgroup analysis demonstrated that insulin intervention was highly effective in patients with LADA having high GADA titers and preserved beta-cell function at baseline.[78] In Japan, two similar studies suggested better preservation of beta-cell function with insulin than that with SU in patients with phenotypic T2DM having ICA and GADA positivity.[86,87] A three-year follow-up study demonstrated that early insulin treatment in LADA was safe and well tolerated and it provided better metabolic control.[88] Several studies have revealed that progression to an insulin-dependent state in LADA differs based on clinical and biochemical features.[3,30,64]

However, the optimal insulin regimen in patients with LADA remains unclear. Given that rapid loss of insulin release occurs early in LADA, replacement with multiple doses of insulin might be beneficial. However, from a practical viewpoint, it might be challenging to initiate various insulin injection therapies in patients with LADA, particularly if their blood glucose levels are moderately elevated. In such patients, a long-acting insulin injection might be a good alternative.[67,78] Recently, in a Swedish–Norwegian randomized clinical trial, patients with LADA on metformin were randomized to add-on treatment with either insulin or sitagliptin, revealing that early insulin treatment may be advantageous in LADA but does not protect against an autoimmune assault on beta cells.[89] An ongoing trial in China is investigating the protective efficacy of saxagliptin and vitamin D3 in patients with LADA previously treated with insulin.90 Data from 104 weeks of intervention are presently being analyzed. Overall, to date, studies regarding early insulin therapy in LADA and its benefits in preserving beta-cell function have several discrepancies. Hence, larger-scale studies are warranted to clarify these uncertainties.

Immune modulation

Most immune intervention trials on AD have either failed to achieve success in preserving beta-cell function or demonstrated only a transient effect.[91-94] Several clinical trials of GAD65 have been performed, and others are ongoing.[95] Clinical and immunological data can be expected in the near future, but currently there is still insufficient evidence to support its efficacy. Much has been learned over the past decades with the significant increase in clinical trials regarding AD, but much more remains to be elucidated.

Conclusion

Adult-onset AD is a heterogeneous disease encompassing a broad spectrum of clinical and metabolic features, ranging from classical T1DM with onset from childhood to inconspicuous LADA in adulthood. Much information has been unveiled regarding the clinical features, cellular immune responses, metabolic traits, and genetic background of adult patients with AD. Therefore, an updated international expert consensus on the definition and diagnosis of LADA is warranted. To date, the most effective therapy for LADA has not been identified because of the wide range of variation in its biochemical and clinical presentations. Therefore, the mainstay of therapeutic management of LADA is to preserve beta-cell function and prolong insulin independence as much as possible by offering excellent metabolic control and improving the natural history of the dis-

ease. Although no strong evidence supporting or discouraging the use of metformin in LADA has been reported, SUs are positively discouraged. TZD might potentially be of interest in LADA, but this needs to be confirmed through more prospective and interventional studies. DPP-4 inhibitors may be effective for LADA, while GLP-1RAs have no potential beneficial effects on either HbA1c reduction or glycemic response in LADA. Immunomodulatory agents might be of benefit, but clinical studies are yet to demonstrate their therapeutic benefits in LADA. Therefore, insulin seems to be the cornerstone of management. Based on C-peptide levels, insulin should be initiated as early as needed, and as early as possible. Nevertheless, recent clinical treatment studies regarding LADA have not provided a solid basis for an official treatment strategy for patients with LADA. Therefore, further high-quality studies evaluating various aspects of this form of autoimmune disease and defining the best therapeutic approach are warranted to possibly help in preventing insulin dependence in younger individuals who are susceptible to T1DM.

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