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REVIEW

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Prognosis and outcome of latent autoimmune diabetes in adults: T1DM or T2DM?

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Abstract

Latent Autoimmune Diabetes in Adults (LADA) is a type of diabetes mellitus often overlooked in clinical practice for its dual resemblance to Type 1 Diabetes Mellitus (T1DM) in pathogenesis and to Type 2 Diabetes Mellitus (T2DM) in clinical presentation. To better understand LADA's distinctiveness from T1DM and T2DM, we conducted a comprehensive review encompassing etiology, pathology, clinical features, treatment modalities, and prognostic outcomes. With this comparative lens, we propose that LADA defies simple classification as either T1DM or T2DM. The specific treatments for the disease are limited and should be based on the therapies of T1DM or T2DM that address specific clinical issues at different stages of the disease. It is crucial to identify LADA cases potentially misdiagnosed as T2DM, warranting prompt screening for poor blood sugar control, short-term blood sugar deterioration, and other conditions. If the prognosis for LADA is similar to T2DM, it can be managed as T2DM. However, if the prognosis fundamentally differs, early LADA screening is crucial to optimize patient outcomes and enhance research on tailored treatments. The pathogenesis of LADA is clear, so the prognosis may be the key to determining whether it can be classified as T2DM, which is also the direction of future research. On the one hand, this paper aims to provide suggestions for the clinical screening and treatment of LADA based on the latest progress and provide worthy directions for future research on LADA.

Keywords Latent Autoimmune Diabetes in Adults, Treatment, Prognosis and outcome, Complications, Management

Introduction

Latent Autoimmune Diabetes in Adults (LADA) is an autoimmune disease with some genetic, immunological, and clinical features shared with both Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). It is also known as type 1.5 diabetes or slow-onset diabetes in adults. Unlike typical T1DM, the destruction of β-cells in LADA occurs more slowly and has a longer latency. Epidemiological studies have shown that positive tests for islet-specific autoantibodies, mainly GADA, range from 2.6 to 14% in patients diagnosed with T2DM and differ geographically, particularly between 4% and 12% in European countries and 3.8% and 9% in Asian countries [1, 2]. It is important to note that there are methodological differences in these findings; on the other hand, it shows a large population of patients with LADA.

In 2019, the World Health Organization (WHO) considered LADA between T1DM and T2DM as mixed diabetes [3], and in 2020, the international panel also considered LADA as diabetes between T1DM and T2DM [4]. In 2021, Chinese experts believed that LADA should be classified as a slowly progressing autoimmune T1DM subtype according to etiology [5], and in 2022,

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the American Diabetes Association (ADA) proposed that LADA should be classified as a type of T1DM [6]. Controversies regarding these criteria remain, with the debate being dominated by the age of onset and time to initiation of insulin therapy, while consensus is being reached on factors like diabetes-related autoantibodies and the necessity of insulin at least 6 months post-initial diagnosis.

Considering these debates and evolving concepts, it is imperative to delve deeper into LADA, exploring not only from a diagnostic perspective but also delving into its underlying pathophysiology, clinical manifestations, and optimal management strategies. These controversies underscore the urgency of reaching a consensus to guide clinicians in accurately diagnosing and effectively managing LADA, considering the unique characteristics that distinguish it from both T1DM and T2DM.

Pathophysiology

LADA is a polygenic disease that involves genetic defects causing gradual β-cells destruction and insulin deficiency, combined with autoimmune features [7]. Genetically, LADA differs from T1DM and T2DM, with adult-onset LADA having a lighter genetic load, potentially explaining its gradual progression [8]. LADA shares similarities with T1DM in terms of autoantibody expression, both leading to autoimmune attacks on pancreatic β-cells. Compared to T2DM, LADA is more prone to triggering autoimmune reactions [9–11]. Currently, there are no autoantibodies specific to LADA, making it challenging to differentiate LADA from other types of diabetes based solely on immune markers. However, among the known autoantibodies, LADA can be detected early, similar to T1DM. This places LADA in the intermediate zone between the acute autoimmune response of T1DM and the slower progression of T2DM in the autoimmune diabetes spectrum [12]. Research on gut microbiota indicates associations with diabetes onset. Contrasting gut microbiota in LADA, T1DM, and T2DM may reveal distinct microbial patterns, offering a new perspective on understanding the diseases' pathogenic mechanisms [13].

Genetics

Currently, studies on the LADA gene are based on T1DM, which shares some common genetic susceptibility genes with T1DM, including human leukocyte antigen (HLA) gene, insulin gene (INS), cytotoxic T lymphocyte-associated protein 4 gene (CTLA4), protein tyrosine phosphatase non-receptor type 22 gene (PTPN22), and SH2B adaptor protein 3 gene (SH2B3) [8, 14], Most studies of LADA susceptibility genes are limited to studies of HLA [15, 16]. M Hernández found that compared to T1DM, LADA has fewer high-risk HLA alleles but no significant difference in protective alleles [17]. In contrast to T2DM, LADA has more high-risk HLA alleles and fewer protective alleles. A study by Petrone revealed that the low frequency of susceptibility genotypes and the high frequency of protective haplotypes could account for the incidence of T1DM. However, this correlation does not hold true for LADA, likely due to the more diluted distribution of HLA-susceptible and protective haplotypes in LADA [18]. Moreover, LADA was found to have a similar distribution of risk alleles associated with patients diagnosed with T1DM after 30 years of age [16, 17]. Compared to LADA, the G/A genotype of PTPN22 rs2476601 is more common and the T / T genotype of INS SNP rs689 gene is less frequent in T1DM.

While the most studied T2DM susceptibility gene in LADA is transcription factor 7 analogue 2 (TCF7L2). And polymorphisms in these genes may increase the risk of patients developing LADA [19]. No significant differences were found in the PTPN22 and INS genes between LADA and T2DM [17]. TCF7L2 is the most studied T2DM susceptibility gene in LADA and promotes the development of LADA, and the TCF7L2 rs 7,903,146 polymorphism is a population-independent susceptibility locus for LADA in Europeans [20]. According to the Swedish Diabetes Incidence Study, variants in the TCF7L2 gene help distinguish autoimmune from non-autoimmune diabetes in young diabetic patients, but not in middle-aged patients [21]. In the NIRAD Study 5, it was demonstrated that the TCF7L2 gene polymorphisms rs12255372 and rs7903146 are specifically associated with adult-onset autoimmune diabetes presenting with low GADA titers [22].

Recently, it has been found that PFKFB3 and subtype-specific signatures in the HLA region may be LADA-specific site [23], but further studies are needed to determine their uniqueness in LADA. In comparison with the general population, an independent genome-wide signal was identified at the PFKFB3 gene locus, which persisted even after conditioning on nearby T1DM-associated signals [8]. Notably, most studies have been performed in a single ethnic population, and these genes are diverse and ethnically diverse. Further studies with larger numbers of patients are needed to clarify the genetic association supporting LADA.

Autoimmunity

LADA is a type of autoimmune-mediated diabetes from an etiological perspective. The immune characteristics of LADA include islet inflammation, islet autoantibodies, and reactive T cells to islet antigens [5]. Research on LADA autoantibodies is mainly based on T1DM, including GADA, IAA, IA-2 A, ZnT8A, and ICA [9]. Additionally, LADA have autoantibodies to transmembrane protein 7 (Tspan7) and carboxypeptidase H (CPH) [24, 25]. Among them, GADA is the most sensitive diagnostic

marker for LADA. In LADA, IA-2 A (256–760) autoantibodies may be associated with a higher frequency of autoimmune diabetes HLA-susceptible genotypes and an increased risk of developing thyroid autoimmunity. Claudio suggests testing for IA-2 A autoantibodies can help identify islet autoimmunity [26, 27]. LADA may have one or more positive insulin autoantibodies, but fewer individuals have multiple positive antibodies. Simultaneous detection of multiple antibodies can improve diagnostic sensitivity. Although these antibodies assist in diagnosing LADA, their lack of specificity limits their application in research. Increasing evidence suggests that acquired immunity and innate immunity play a key role in the etiology of LADA [10, 11]. Besides, research has found that gut microbiota and metabolites can participate in the physiological and pathological status of LADA through immune regulation [28].

Gut microbiota

Gut microbiota is closely related to human digestive and metabolic function and plays an important role in the pathogenesis and treatment of diabetes [29] and new studies have found that the function of intestinal flora is associated with immune effects [28]. A case-control study found that changes in gut microbiota in LADA were very similar to those in GADA-positive patients in T1DM, but not to those in T2DM [13, 30]. In addition, the abundance of CAG4 and CAG6, CAG6 and CAG12, and CAG4 alone was also significantly lower in the LADA group compared to T1DM and T2DM, suggesting a possible LADA-specific microbiota.

The gut microbiota produces short chain fatty acids (SCFAs) by digesting carbohydrates, proteins, and peptides that cannot be digested and absorbed by the small intestine in food [31]. SCFAs are known to exert anti-inflammatory effects by modulating T cells and inhibiting histone deacetylase activity, enhancing intestinal barrier function [32, 33]. In non-obese T1DM mouse models, key features of the disease were found to be inversely correlated with concentrations of the microbial metabolites acetate and butyric acid in blood and feces [34], which were able to reduce insulitis damage and delay the progression of diabetes in non-diabetic mice [35]. The same results were in case-control studies and LADA, not only were there severe defects in SCFA-producing organisms such as Fecalis, Roseburia, and Blautia [30], but also specific metabolites, such as branched-chain amino acids and aromatic amino acids produced by intestinal bacteria, were found in feces and blood, unlike T1DM and T2DM.

Clinical manifestations and diagnosis

As a framework for future research and regulatory decision-making, the ADA divides the progression of T1DM into three stages [6], whereas Chinese experts summarize the evolution of LADA into four stages [5]. They share similar views regarding the clinical non-insulin-dependent and insulin-dependent periods, with the main difference lying in the preclinical phase before the clinical characteristics appear. Compared to T2DM, the genetic susceptibility and autoimmune mechanisms of T1DM and LADA are better understood, while the specific pathways and mechanisms underlying β-cell dysfunction in T2DM remain incompletely elucidated (Table 1).

LADA has a significant genetic background, with susceptibility genes for both T1DM and T2DM contributing to its onset [39]. In genetically predisposed individuals, environmental factors trigger autoimmune responses, including insulitis and islet autoantibodies [40]. Studies have shown that the risk factors of LADA are similar to those of T2DM and closely related to diabetes-related factors, such as obesity, hypertension, and metabolic syndrome [41, 42]. Under the influence of these risk factors, various immune regulatory processes come into play, affecting β-cell autoimmunity and leading to the production of multiple autoantibodies, suggesting that the immune system is attacking islet cells. Before the onset of clinical symptoms, islet cell function was impaired to some extent, but the threshold for clinical diagnosis of diabetes had not been reached. Blood glucose levels showed normal or mildly elevated, but no significant hyperglycemia symptoms emerged.

Clinically, LADA is divided into non-insulin-dependent and insulin-dependent stages. The early clinical phase is primarily the non-insulin-dependent stage, where oral hypoglycemic drugs are effective, and insulin treatment is not required for at least six months, which helps differentiate it from classic T1DM and ketone-prone T2DM. During this period, LADA's clinical presentation tends to resemble T2DM: thirst, polyuria, and weight loss, making initial diagnosis challenging. As islet function in LADA continues to deteriorate, lifestyle interventions

Table 1 Staging of T1DM and LADA

	Disease	State 1	State 2	State 3	State 4
Characteristics	LADA [5, 36–38]	Autoimmunity Normoglycemia Presymptomatic	Autoimmunity Normoglycemia Presymptomatic	Autoimmunity Dysglycemia Presymptomatic	Autoimmunity Overt hyperglycemia Symptomatic
	T1DM [6]	Autoimmunity Normoglycemia Presymptomatic	Autoimmunity Dysglycemia Presymptomatic	Autoimmunity Overt hyperglycemia Symptomatic	

and conventional hypoglycemic drug therapies become ineffective, necessitating intensive insulin therapy. The progression to insulin dependence in LADA varies greatly, depending on factors such as age of onset, antibody titers, and the presence of multiple islet antibodies. Blood glucose and HbA1c levels in LADA fall between those of T1DM and T2DM, with greater blood glucose variability than T2DM [43].

LADA has its characteristics at all stages, however, individual differences and clinician confirmation are required at some stage of the disease. As Sinead Brophy contends that clinical symptoms and GADA testing, rather than time to insulin, should be used to identify people with LADA [44]. Several cross-sectional studies have shown that GADA titers are associated with phenotypic heterogeneity of clinical characteristics in LADA [45, 46]. Analysis of GADA titers reveals a bimodal distribution: high GADA titers (>32 arbitrary units) and low GADA titers (≤32 arbitrary units), which correspond to distinct clinical, immunological, and genetic features [47, 48] (Table 2) and (Fig. 1).

Prognosis and outcome

Research indicates that LADA overlaps with both T1DM and T2DM regarding pathological and clinical features, positioning it between the two conditions. Consequently, throughout the disease course of LADA, there are distinct differences from both T1DM and T2DM. Complications may arise more quickly than in T2DM but more slowly than in T1DM. Starting with microvascular complications, early studies suggest a lower risk in the initial post-diagnosis years compared to T2DM, but the risk gradually aligns with or even exceeds that of T2DM in the long term [49, 50]. Notably, glycemic variability in LADA is strongly correlated with diabetic retinopathy, indicating a distinct pattern from T2DM [51]. Moving on to macrovascular complications, despite typically presenting with a lower cardiovascular risk profile, including younger age and healthier lipid and blood pressure parameters [52], conflicting data warrants further exploration of its underlying pathophysiological mechanisms [53, 54]. Regarding neuropathy, the risk in LADA appears complex, showing fewer symptoms before onset but manifesting more severe small fiber neuropathy at a comparable time [55, 56], which suggests unique mechanisms compared to T1DM and T2DM [57].

Moreover, LADA may contribute to the development of other autoimmune diseases [58, 59]. Studies have found that LADA have a higher prevalence of Associated Autoimmune Diseases (AADs) compared to T1DM, especially autoimmune thyroid and gastrointestinal diseases, with GADA-positive patients showing even higher AADs prevalence [60–62]. It is assumed that the pancreas, brain, thyroid, and stomach share the GAD-65 enzyme. The T-cell response induced by GADA in the pancreas may lead to the destruction of similar antigens in other neuroendocrine tissues [63]. Furthermore, LADA with high GADA levels tend to require insulin therapy earlier compared to those with lower GADA levels [64].

Understanding the unique characteristics of LADA is crucial for developing targeted and efficient management strategies in diabetes treatment. Despite potential differences in initial complication risks, the long-term trajectory of LADA often matches or surpasses that of T2DM. This emphasizes the necessity of implementing comprehensive monitoring and intervention strategies precisely tailored to address the intricate nuances of LADA-related complications.

Management and treatment strategies

LADA's management and treatment strategies primarily focus on preserving β-cell function and achieving optimal blood glucose control through multifaceted approaches [65]. Due to the unique nature of LADA, treatment strategies need to combine methods used for both T1DM and T2DM, including insulin and hypoglycemic drug therapy, as well as immunotherapy [28, 66].

Insulin and hypoglycemic drug therapy play a key role in LADA management, aiming to delay pancreatic function loss and mitigate inflammation, thus positively influencing the disease course [67, 68]. Given LADA's gradual insulin-dependent progression characteristic, insulin is

Table 2 The characteristics of LADA typical T1DM typical T2DM

LADA	Typical T1DM	Typical T2DM
• Age>30 years • Family/personal history of autoimmunity • Non–insulin required at the onset of diabetes • C-peptide levels decrease more slowly than in T1DM • Positivity for GADA as the most sensitive marker; other autoantibodies less frequent (ICA, IA-2 A, ZnT8A, and Tspan7 autoantibodies) • Reduced frequency of metabolic syndrome compared with T2DM—lower HOMA, lower BMI, lower blood pressure, and normal HDL compared with T2DM • No disease-specific difference in cardiovascular outcomes between these patients and those with T2DM	• Age<30 years • Nonobese body type • Diabetes symptoms were evident • Usually starts with ketosis or ketoacidosis • Significant decrease in fasting or postprandial serum C-peptide concentrations • Islet autoimmune markers, such as GADA, ICA, IA- 2 A, and ZnT8A appear	• Adulthood • overweight or obesity • Diabetes symptoms were evident • some degree of insulin resistance

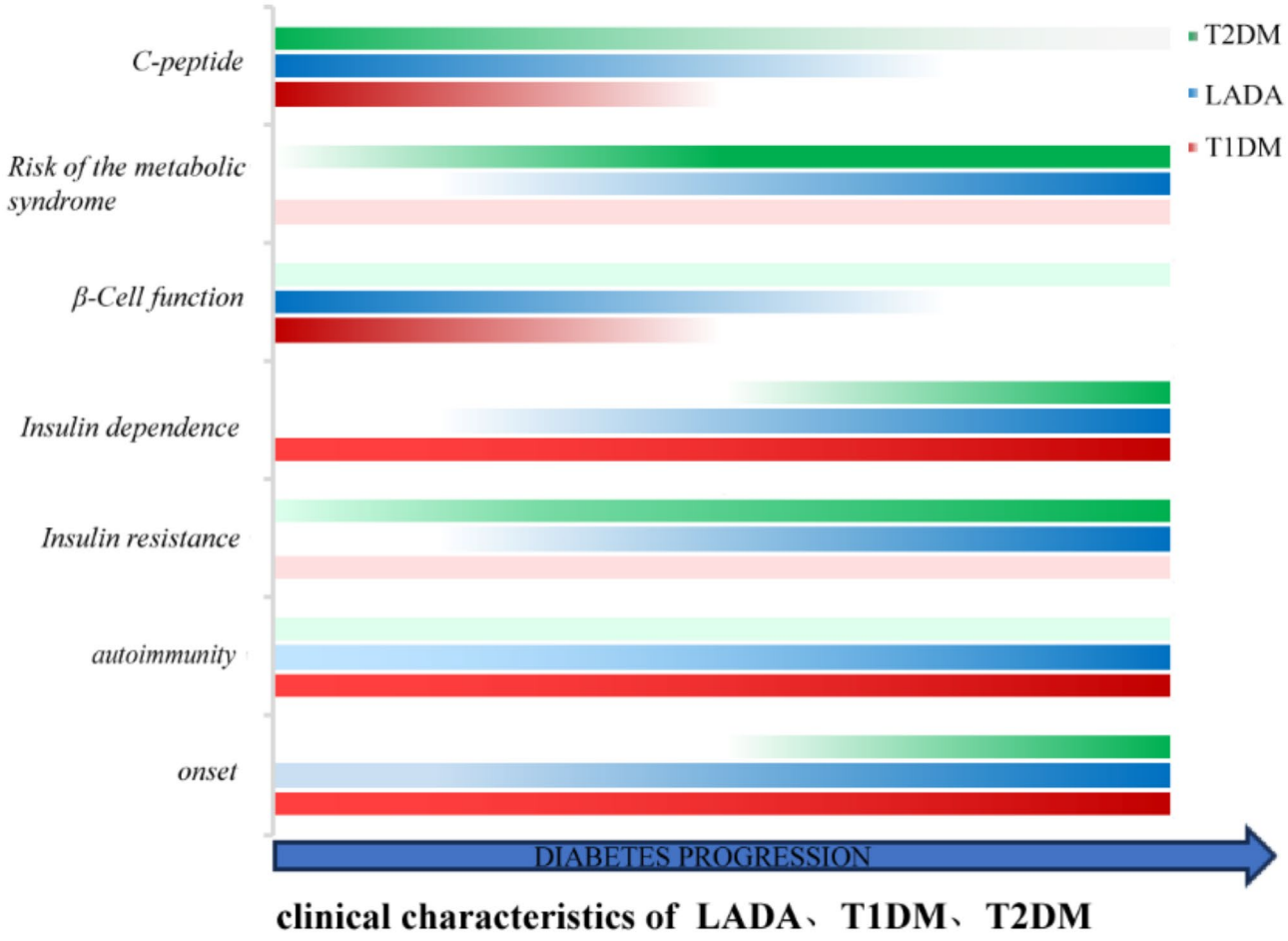

Fig. 1 Change in profile between LADA, type 2 diabetes mellitus (T2DM), and type 1 diabetes mellitus (T1DM) (darker color indicates a more prominent profile.)

deemed necessary even during the clinical insulin-independent state [69]. Research indicates that insulin therapy effectively preserves residual β-cell function [70, 71] and reduces the severity of insulitis [72]. When using insulin, it is important to monitor C-peptide levels. For patients with C-peptide levels > 0.7 nmol/L, treatment can be managed similarly to that for T2DM. For those in the "gray area" (≥0.3 and ≤0.7 nmol/L), therapy should begin with metformin and other non-insulin agents based on blood glucose levels and the patient's risk for cardiovascular and renal complications. C-peptide levels should be reassessed every six months to monitor the development of insulin deficiency. With C-peptide levels < 0.3 nmol/L should be treated following the management protocols for T1DM. DPP-4 inhibitors, such as saxagliptin and sitagliptin, have been shown to preserve β-cell function and better glycemic control in patients with lower C-peptide levels [73, 74]. Compared to SGLT-2 inhibitors and sulfonylureas, DPP-4 inhibitors have a more pronounced effect on reducing HbA1c levels. GLP-1 receptor agonists, such as dulaglutide, have also proven effective in lowering HbA1c in LADA patients [75].

Immunotherapy aims to address abnormal immune responses and slow down autoimmune destruction of the pancreas [76]. Direct injection of autoantigens and GAD-alum administration have been explored as potential immunotherapeutic approaches [77, 78]. The DIAGNODE-2 trial found that GAD-alum improves glycemic control in recently diagnosed T1DM carrying HLA DR3-DQ2 [79]. Additionally, injecting GAD-alum into GADA-positive LADA has shown promising results in regulating immune responses and maintaining β-cell function in these patients [80].

Additionally, emerging research suggests that vitamin D supplementation may play a role in immune regulation and protecting β-cell function in LADA. However, further studies are needed to elucidate its exact mechanisms [81, 82]. Studies have indicated that combining vitamin D with antidiabetic drugs can protect β-cell function through immune regulation [83–85]. Traditional Chinese medicine (TCM) also offers unique advantages in

regulating immune-related diseases, and it has been confirmed that Tripterygium wilfordii Hook F, Berberine, and Pangolin exhibit immune-regulating effects [86, 87]. However, more research is required to fully understand the therapeutic pathways of TCM in the treatment of metabolic and immune-related diseases like LADA.

In summary, optimizing the management of LADA hinges on tailoring treatment strategies to individual needs, encompassing insulin and hypoglycemic drug therapy, along with immunotherapy. Guiding these strategies based on disease characteristics and biomarkers such as serum C-peptide levels is crucial for achieving favorable outcomes in LADA management [88]. Additionally, recognizing the complex interplay between metabolic and immune factors is essential for developing treatment plans that promote long-term metabolic stability and prevent complications in LADA.

Conclusions

LADA genetically overlaps with T1DM and T2DM and is influenced by immune factors, which may lead to islet cell damage and different degrees of insulin resistance, showing intermediate characteristics between T1DM and T2DM. Genomic association studies have confirmed that the genetic characteristics of LADA are mostly similar to those of typical T1DM and more characteristic of T1DM.

Although similar to the clinical presentation of T2DM at initial diagnosis, differences between them become progressively apparent as diabetes progresses. Therefore, the detection of islet cell autoantibodies is necessary, although not specific, combining Electrochemiluminescence assay [89] and C-peptide level helps to identify T2DM and predict the progression of insulin dependence in LADA and improve the therapeutic effect of LADA [90, 91]. At the same time, LADA is associated with a high risk of other autoimmune diseases, and the detection of thyroid-associated antibodies may be considered when detecting islet autoantibodies.

The treatment of LADA is another difficult problem, due to the specificity of LADA, without specific treatment strategies, it is necessary to develop a personalized treatment plan in combination with the clinical characteristics and biochemical parameters of each patient, to control blood glucose, aim to protect β-cell function and reduce the occurrence of diabetic complications. In therapeutic efficacy, exogenous insulin does not completely replace endogenous insulin. Studies have shown that early treatment with insulin delays the rate of β-cell damage in patients with LADA is beneficial for residual β-cell function, and reduces the severity of insulitis [70, 71]. In the long run, early insulin intervention in patients with LADA can help to improve their quality of life. The occurrence of diabetic complications is closely related to blood glucose control, and for patients with LADA, more attention should be paid to their blood glucose control. Multiple groups of clinical studies have shown that DPP-4 inhibitors are beneficial in maintaining β-cell function and can be used as adjuvant therapy in LADA therapy [73, 74]. Further exploration of treatment strategies for LADA is required.

Author contributions

Zhipeng Zhou conceptualized and wrote this manuscript. Mingyue Xu, Pingjie Xiong, and Deqing Zheng contributed to the critical revision of the report. Jing Yuan involved in chart production. Shenghua Piao assisted with the edited version. All authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

NA-for this type of manuscript ethical approval is not required.

Informed consent

NA- this is a review paper.

Competing interests

The authors declare no competing interests.

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