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Diagnosing and Managing LADA: A Review of the Overlooked Diabetes Subtype

Authors:

1. **Maciej Wojszczyk**, University Clinical Hospital No. 1 of the Medical University of Lodz, ul. Kopcińskiego 22, 90-153 Łódź
   E-mail: maciej.wojszczyk@gmail.com
   ORCID: https://orcid.org/0009-0002-8668-8821
2. **Julia Kulbacka**, Central Teaching Hospital of the Medical University of Lodz, Pomorska 251, 92-213 Lodz, Poland
   e-mail: julia.kulbacka@o2.pl
   ORCID: https://orcid.org/0009-0005-1181-9104
3. **Karol Dziedzic,** Medical University of Lodz, Al T .Kosciuszki 4, 90-419 Lodz, Poland
   e-mail: karol.dziedzic@stud.umed.lodz.pl
   ORCID: https://orcid.org/0009-0007-8317-723X

4. **Filip Arczewski**, Medical University of Lodz, Al T .Kosciuszki 4, 90-419 Lodz, Poland
   e-mail: farczewski@interia.pl
   ORCID: https://orcid.org/0009-0008-5179-7255
5. **Michalina Wójcikiewicz**, Central Teaching Hospital of the Medical University of Lodz, Pomorska 251, 92-213 Lodz, Poland
   E-Mail: michalinawojcikiewicz@gmail.com
   ORCID:https://orcid.org/0009-0003-3671-1410
6. **Marta Chuncia-Ileczko**, Central Teaching Hospital of the Medical University of Lodz, Pomorska 251, 92-213 Lodz, Poland
   E-mail: marta.chuncia@gmail.com
   ORCID: https://orcid.org/0009-0000-0913-9752
7. **Julia Kacperczyk**, Medical University of Lodz, Al. T. Kosciuszki 4, 90–419 Lodz, Poland
   e-mail: jwkacperczyk@gmail.com
   ORCID: https://orcid.org/0009-0007-6354-301X
8. **Witold Czyż**, Central Teaching Hospital of the Medical University of Lodz, Pomorska 251, 92-213 Lodz, Poland
   e-mail: witoldczyz@googlemail.com
   ORCID: https://orcid.org/0009-0006-4442-9900
9. **Piotr Pasek**, Copernicus Memorial Hospital, ul. Pabianicka 62, 93-513 Łódź, Poland
   E-mail: pasek.piotrus@gmail.com
   ORCID: https://orcid.org/0009-0001-6218-9887
10. **Julia Ryniecka**, Medical University of Lodz, Al T .Kosciuszki 4, 90-419 Lodz, Poland
    E-mail: juliaryniecka@gmail.com
    ORCID: https://orcid.org/0009-0000-5937-9498

Affiliations:

1. University Clinical Hospital No. 1 of the Medical University of Lodz, ul. Kopcińskiego 22, 90-153 Łódź
2. Central Teaching Hospital of the Medical University of Lodz, Pomorska 251, 92-213 Lodz, Poland
3. Medical University of Lodz, Al T .Kosciuszki 4, 90-419 Lodz, Poland

4. Copernicus Memorial Hospital, ul. Pabianicka 62, 93-513 Łódź, Poland

Abstract

LADA (latent autoimmune diabetes in adults) is a dual form of diabetes, combining the autoimmune features typical of type 1 diabetes and the clinical and metabolic aspects of type 2 diabetes. Due to the slow development of symptoms and often late age of onset, LADA is frequently misdiagnosed as type 2 diabetes, which can lead to a delay in appropriate treatment. It is estimated that LADA affects between 4% and 12% of adults initially diagnosed with type 2 diabetes, making it a more common disease entity than previously thought. This paper examines current data on the epidemiology, pathogenesis, genetic factors and diagnostic criteria of LADA. Particular attention was given to the immunological and genetic aspects of the disease, which allow a more accurate differentiation of LADA from type 2 diabetes. The review also discusses the significance of early insulin therapy aimed at beta-cell preservation and the role of alternative treatments, such as DPP-4 inhibitors, which may influence disease progression. Diagnostic and therapeutic challenges stemming from the phenotypic similarities between LADA and type 2 diabetes are highlighted, along with potential benefits of early detection.

Aim of the study

The objective of this study is to provide a current and comprehensive review of issues related to latent autoimmune diabetes in adults (LADA), with a particular focus on its epidemiology, pathogenesis, genetic factors, and diagnostic criteria. The study aims to elucidate the clinical challenges associated with LADA and propose optimal therapeutic strategies tailored to its unique autoimmune characteristics.

Materials and methods

A literature review of the literature collected in the PubMed and Google Scholar database was conducted for information on LADA diabetes. The search included the keywords "LADA diabetes," "autoimmunity," "GADA antibodies," "diabetes genetics," "type 1 diabetes," "type 2 diabetes," "insulin therapy," "insulin resistance" and "risk factors for diabetes. The selection included recent scientific articles, systematic reviews and meta-analyses.

Summary

LADA diabetes represents a specific form of diabetes whose diagnosis and treatment encounter difficulties due to its hybrid nature. The disease combines elements of type 1

diabetes, such as the presence of autoimmune antibodies (e.g. GADA), with the late age of onset and the gradual clinical course characteristic of type 2 diabetes. LADA is more common than previously thought and its prevalence is geographically diverse. Diagnosis is mainly based on detection of specific antibodies and assessment of the patient's age and rate of progression of symptoms. Clinically, LADA can be divided into a non-insulin-dependent phase, in which the patient responds to lifestyle changes and oral medication, and an insulin-dependent phase, in which the introduction of insulin becomes necessary. Based on a review of the literature, early recognition of LADA and initiation of appropriate therapy are key to delaying beta-cell destruction and improving patient outcomes. Further research into the pathophysiological mechanisms and optimal treatments may contribute to better management of LADA diabetes.

Keywords: LADA diabetes, GADA antibodies, type 1 diabetes, type 2 diabetes, insulin resistance, insulin therapy.

Introduction

Diabetes is one of the escalating challenges of our time, along with obesity increasing its risk, it has been described as a disease of affluence. According to data from the International Diabetes Federation, as of 2021, as many as 537 million people aged 20 - 79 years have diabetes worldwide, with the highest proportion, over 90%, having type 2 [1][2]. Type 2 diabetes is primarily diagnosed in the adult population and is closely linked to an unhealthy lifestyle and obesity, the most significant risk factor [3]. Type 1 diabetes, of autoimmune origin, is influenced by various environmental and genetic factors and predominantly affects young people and young adults. In addition, there are also genetically determined types of diabetes so-called MODY, gestational diabetes, neonatal diabetes and secondary causes related to endocrinopathies, steroid use, etc.

Among these types is LADA, a form of diabetes combining features of both type 1 and type 2 diabetes. Its autoimmune component makes it similar to type 1 and its age of onset brings it closer to the type 2 patient population. Due to its unique features and relatively low prevalence of 3-12%, LADA is often misdiagnosed or diagnosed late [3]. Proper diagnosis requires a broader view of both clinical features and laboratory results, as the slow progression of symptoms makes an accurate diagnosis challenging. A correct diagnosis of the disease is crucial for the rapid implementation of insulin therapy, which is the cornerstone of LADA treatment.

Epidemiology

Recent epidemiological studies indicate that the prevalence of latent autoimmune diabetes in adults (LADA) in the population is not as rare as previously assumed [4]. Results from studies in Europe, Asia and North America show that between 4 and 12% of patients with type 2 diabetes have antibodies specific for type 1 diabetes, which is a diagnostic factor for LADA diabetes [5].

Regional differences in prevalence likely result from varying study methodologies, lifestyle factors, and diagnostic criteria. For example, research in Europe found pancreatic islet cell antibodies in 9.7% of individuals with type 2 diabetes [6]. In Italy, this percentage was 4.5% [7]. Similar research in China revealed these antibodies in 5.9% of patients with type 2 diabetes [8]. Understanding the epidemiology of LADA is essential for improving diagnostic practices and tailoring interventions to regional needs. For example, in areas with a higher prevalence of metabolic syndrome, screening for autoantibodies in patients diagnosed with type 2 diabetes could enhance early detection and prevent misdiagnosis.

Pathogenesis

As in type 1 diabetes, autoimmune processes underlie LADA, resulting in the production of antibodies targeting pancreatic beta cells. However, this process is much slower, leading to a more gradual onset of symptoms, which, combined with a later age of onset, brings the phenotypic characteristics of type 2 diabetes closer [11].

LADA is associated with specific antibodies, such as GADA, IA-2, insulin autoantibodies (IAA), and islet cell autoantibodies (ICA), which are essential for distinguishing it from type 2 diabetes [9]. The main antibody present in the largest number of patients is GADA, although its presence alone is not sufficient to make the diagnosis [10].

Despite the presence of antibodies typical of type 1 diabetes, insulin resistance in LADA is comparable to that in type 2 diabetes, as evidenced by the HOMA-IR index. Recent studies suggest that both obesity and a prediabetic state play key roles in the development of insulin resistance in LADA patients. These mechanisms leave LADA patients vulnerable not only to dysregulation of glucose metabolism, but also to other metabolic consequences of insulin resistance such as dyslipidemia and hypertension, characteristic of metabolic syndrome. [12]

Genetic factors

Genetic risk factors for LADA diabetes include characteristics of both, type 1 and type 2 diabetes. The primary risk is associated with the HLA region, particularly HLA-DR and HLA-DQ, which are also significant in T1DM [13].

In addition, T2DM-specific genes, such as the best studied TCF7L2, also play a role in the development of LADA. Its variant, rs7903146, is more frequently observed in patients with LADA than in patients with type 2, especially in those with low levels of GADA antibodies [14]. Such results highlight that patients with LADA diabetes may share genetic features of both major types. This reinforces the concept of LADA diabetes as, a combination of both traits and genetic backgrounds of both types [15].

The INS gene, a promoter of insulin production, plays a crucial role in immune tolerance by influencing the presentation of insulin as an autoantigen. Variants in this gene are strongly associated with type 1 diabetes and are also implicated in LADA, where they contribute to the gradual autoimmune destruction of beta cells. Studies suggest that these genetic variations highlight shared pathophysiological pathways between LADA and type 1 diabetes, emphasizing the autoimmune component underlying both conditions.

Similarly, the PTPN22 gene, which regulates T-cell activation and immune responses, is closely linked to autoimmune diseases, including type 1 diabetes and LADA. Variations in this gene lower the threshold for T-cell activation, leading to heightened autoimmune responses that target beta cells. In LADA, this results in a slower but progressive destruction of beta cells, aligning with its hybrid phenotype. Research on these genes underscores their role in bridging the autoimmune and metabolic features of LADA, suggesting overlapping mechanisms that contribute to the disease's development. [16,17].

Diagnostic criteria

The diagnosis of LADA diabetes is complex and there are still no clear, universally accepted criteria. The current diagnostic consensus proposed by the Immunology of Diabetes Society (IDS) includes:

- Onset age above 30 years,
- Presence of one or more pancreatic islet autoantibodies (e.g., GADA, ICA, IA-2A, ZnT8A, tetraspanin 7 autoantibodies)
- No requirement for insulin treatment within six months of diagnosis [18].

The detection of antibodies is a key element in the diagnosis, as their presence indicates an autoimmune background of the disease and allows the differentiation of LADA from type 2 diabetes. The most common antibody is GADA; however, its absence in the presence of other mentioned markers may also signify ongoing autoimmune processes [10]. Because of the features linking LADA with type 1 and type 2 diabetes, a correct diagnosis is difficult to make. In contrast to type 1 diabetes, patients with LADA do not present with severe hyperglycemia, ketoacidosis, or overt clinical symptoms at the disease onset. For this reason, unequivocal differentiation of LADA from type 2 diabetes without immunological testing is not possible [19].

Measuring C-peptide levels is a valuable diagnostic tool for assessing beta-cell reserve, as it reflects endogenous insulin production. In LADA, C-peptide levels are typically higher than in type 1 diabetes but lower than in type 2 diabetes, reflecting partial beta-cell function. This intermediate range helps differentiate LADA from other diabetes types, especially when combined with autoantibody tests. However, C-peptide levels vary with disease progression, being higher in early LADA and declining over time due to autoimmune beta-cell destruction. [20].

Clinical features

As previously mentioned, LADA symptoms progress slowly, resembling features of both diabetes types. The vast majority of patients with type 2 diabetes exhibit symptoms of the metabolic syndrome, such as obesity, dyslipidemia, and hypertension. Although LADA patients usually have a lower body mass index (BMI) than those with T2DM and are less likely to develop metabolic syndrome, many still show its traits.[21]

The progression of LADA symptoms can be divided into non-insulin-dependent and insulin-dependent phases [22]. During the non-insulin-dependent phase, the course of the disease resembles type 2 diabetes, without the symptom's characteristic only of LADA. At this stage,

it is possible to menage glycemic levels with oral hypoglycemic agents. In some patients, the disease can be controlled through diet, weight reduction, and increased physical activity [23]. As a consequence of the progression of the disease and the subsequent autoimmune damage to the pancreatic islets, a point is reached where insulin therapy becomes necessary.

The heterogeneous nature of LADA results from various factors, including differences in onset age, BMI, genetic and immunological factors, lifestyle, and environmental influences. The disease's progression and the duration of its autoimmune stages vary for each patient.

Interestingly, studies indicate that overweight/obesity itself is a risk factor for LADA [24]. However, obese patients show a lower incidence of insulin dependence and, in addition, have better preserved B-cell function. The reason why beta-cell destruction progresses more slowly in obese patients remains unclear [25][26].

LADA symptoms include typical diabetes manifestations such as increased thirst, frequent urination, fatigue, and weight loss. However, due to delayed insulin therapy, these symptoms may be milder than in type 1 diabetes, further complicating the diagnosis [27].

Treatment

Due to the autoimmune etiology of the disease, the need to take insulin after a certain period is unavoidable. The main therapeutic goal is to preserve pancreatic β-cell function for as long as possible. The cornerstone of treatment is based on methods that ensure proper glycemic control, which helps to maintain beta-cell function, delay their destruction, and prevent diabetes-related complications. [23].

Considering the unique characteristics of the disease, LADA treatment employs methods used for both T1DM and T2DM, including insulin and hypoglycemic agents [28].

Studies show that early implementation of insulin therapy preserves β-cell secretory function for longer and reduces the severity of β-cell inflammation [29]. The protective effect of insulin is probably due to a reduction in antigen expression and a reduction in the destructive autoimmune effect by inhibiting β-cell activity through exogenous insulin supply [30].

Sulfonylureas are not recommended for LADA treatment. Clinical studies have demonstrated that this drug accelerates the progression of the disease, increases beta-cell destruction and causes a more rapid decline in C-peptide levels. Consequently, this leads to an earlier need for insulin therapy. [31,32].

Dipeptidylpeptidase IV (DPP-4) inhibitors are a promising therapy for LADA patients. Besides their beneficial effects on glycemic regulation, they have also been shown to improve

β-cell function. DPP-4 receptors have been identified on the surface of T lymphocytes, and studies suggest they are involved in immune regulation, which may play a significant role in slowing the destruction of pancreatic islet b cells [33]. This makes them an attractive therapeutic choice, especially in the early stages of LADA, when beta-cell activity is still present. However, further research is needed to fully understand their long-term effects and to establish their role in comprehensive LADA management.

Metformin is the most commonly used hypoglycemic drug in type 2 diabetes for this reason also, most patients with LADA diabetes take it in the early stages of the disease. Metformin improves insulin sensitivity, reduces body weight, lowers LDL levels and the risk of atherosclerosis progression [34]. However, there is a lack of conclusive evidence to support or discourage its use in LADA. Ongoing clinical trials aim to provide more detailed information on its effect in this patient group.[18]

Conclusions

Latent autoimmune diabetes in adults (LADA) represents a diagnostic and therapeutic challenge due to its hybrid nature, combining features of type 1 and type 2 diabetes. Late onset, the absence of distinct symptoms, and the slow clinical course make it difficult to differentiate LADA from type 2 diabetes, often delaying appropriate treatment. A key element in the diagnosis is the detection of anti-islet antibodies, confirming the autoimmune basis of the disease. Measuring of C-peptide levels may assist in evaluating beta-cell function and serve as a valuable diagnostic tool.

Treatment of LADA requires an individualized approach. Early implementation of insulin therapy plays a critical role in protecting β-cells from further damage. Supporting therapy with drugs that improve insulin sensitivity or support metabolic function may be beneficial in certain cases.

Further research on the pathophysiological mechanisms of LADA is essential to better understand the complexity of this disease. Developing more precise diagnostic criteria and effective therapeutic strategies is key to improving patients' quality of life and reducing the risk of complications.

Disclosure

Author's contribution

Conceptualization: Maciej Wojszczyk and Julia Ryniecka; Methodology: Karol Dziedzic; Software: Filip Arczewski; Check: Michalina Wójcikiewicz and Marta Chuncia-Ileczko;

Formal analysis: Julia Kacperczyk and Witold Czyż; Investigation: Piotr Pasek and Julia Kulbacka; Resources: Julia Kulbacka; Data curation: Witold Czyż; Writing - rough preparation: Maciej Wojszczyk and Julia Ryniecka; Writing - review and editing: Julia Kacperczyk and Marta Chuncia-Ileczko; Visualization: Piotr Pasek; Supervision: Witold Czyż; Project administration: Filip Arczewski and Karol Dziedzic; Receiving funding - no specific funding. 10 All authors have read and agreed with the published version of the manuscript.

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