LADA Diabetes as a Hybrid Disease – a Narrative Review

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ABSTRACT

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Latent autoimmune diabetes in adults (LADA) is a common hybrid disease because it combines features of both type 1 and type 2 diabetes [1]. It is a slow-onset autoimmune disease characterized by an initial relative insulin deficiency. Studies to date indicate a clear genetic overlap between LADA and type 1 diabetes. This is related to the variants in the human leukocyte antigen (HLA) region [2, 3], which encodes main histocompatibility antigens (MHC) [2, 3, 4]. Main histocompatibility antigens are responsible for immunoregulatory processes that are impaired in both type 1 diabetes and LADA, leading to immune system disturbances in individuals. Autoantibodies against pancreatic islets are produced, serving as key markers for distinguishing type 1 diabetes and LADA [5]. They are characterized by occurring at a lower level, as a result of which the destruction of the immune system progresses much more slowly. In the etiopathogenesis of this disease, environmental factors and lifestyle play a significant role, which are also associated with the pathogenesis of type 2 diabetes [6]. In most LADA cases, hyperglycemia does not reach levels as high as in type 1 diabetes, whith contributes to the misdiagnosis of it as type 2 diabetes. So far, an optimal treatment for LADA has not been established. Currently, the proposed treatment focuses on achieving good glycemic control and preventing or delaying the onset of complications. Some authors suggest that this effect can be achieved through the early use of insulin as the first-line pharmacotherapy. Emerging oral hypoglycemic agents used in other types of diabetes may also have a role in the treatment of this condition.

Hereby, we discuss the possible usage of Continuous Glucose Monitoring (CGM) in this entity for precise real-time control of blood glucose levels. Despite their many advantages, it is important to remember that these systems still require a certain level of user engagement.

Keywords: *LADA, type 1 diabetes, type 2 diabetes, autoimmune diseases*

STRESZCZENIE

Cukrzyca LADA jako choroba hybrydowa – przegląd literatury

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*Cukrzyca typu LADA (*latent autoimmune diabetes in adults*) to powszechna choroba o postaci hybrydowej, która łączy w sobie cechy zarówno cukrzycy typu 1, jak i 2 [1]. Jest to choroba autoimmunologiczna rozwijająca się powoli i charakteryzująca się początkowo względnym niedoborem insuliny. Dotychczasowe badania wskazują na genetyczne nakładanie się cukrzyc typu LADA i typu 1. Ma to związek z wariantami w regionie ludzkich antygenów leukocytarnych (*human leukocyte antigen*, HLA), które kodują główne antygeny zgodności tkankowej (*main histocompatibility antigens*, MHC) [2, 3, 4]. Antygeny te odpowiadają za procesy immunoregulujące, które zarówno w cukrzycy typu 1, jak i typu LADA są nieprawidłowe, w wyniku czego dochodzi do zaburzeń w obrębie układu odpornościowego. W przebiegu cukrzycy typu LADA wytwarzane są autoprzeciwciała przeciwko wyspom trzustkowym, które są kluczowymi markerami służącymi do rozpoznawania cukrzyc typu 1 oraz typu LADA [5]. Występują one w dość niskim mianie, w wyniku czego destrukcja układu odpornościowego postępuje stosunkowo wolno. Zaobserwowano również, że w etiopatogenezie cukrzycy typu LADA istotne znaczenie wykazują czynniki środowiskowe i styl życia, które również związane są z patogenezą cukrzycy typu 2 [6]. U większości osób z cukrzycą typu LADA hiperglikemia nie osiąga tak dużych wartości, jak w cukrzycy typu 1, co wpływa na błędne rozpoznanie jej jako cukrzycy typu 2. Dotychczas nie ustalono optymalnego leczenia cukrzycy typu LADA, a proponowane leczenie opiera się na próbach uzyskania dobrej kontroli glikemii oraz zapobieganiu lub opóźnianiu wystąpienia powikłań. Efekt ten według niektórych autorów może być uzyskany poprzez wczesne stosowanie insuliny jako pierwszej linii farmakoterapii. Swoje miejsce w leczeniu tej jednostki chorobowej mogą także znaleźć pojawiające się na rynku doustne preparaty hipoglikemizujące stosowane w innych typach cukrzycy.*

*W pracy została poruszona kwestia wykorzystania systemów ciągłego monitorowania glikemii (*continuous glucose monitoring, *CGM). Służą one do precyzyjnego kontrolowania poziomu glukozy we krwi w czasie rzeczywistym. Mimo ich wielu zalet należy jednak pamiętać, że systemy te nadal wymagają pewnego poziomu zaangażowania użytkownika.*

Słowa kluczowe: *LADA, cukrzyca typu 1, cukrzyca typu 2, choroby autoimmunologiczne*

Introduction

Latent autoimmune diabetes in adults (LADA) is the predominant manifestation of autoimmune diabetes, accounting for about 2–12% of all cases within this population [7].

During its early decades, LADA typically manifests a latent phase, characterized by limited overt symptoms. Diagnosis typically takes place after patients reach the age of 35. Furthermore, LADA demonstrates clinical attributes reminiscent of type 2 diabetes; however, individuals afflicted by this variant also exhibit the presence of autoantibodies associated with type 1 diabetes. In contrast to type 1 diabetes, LADA evolves more gradually, primarily impacting adults rather than children and adolescents.

Due to the clinical resemblance to type 2 diabetes, it is often misdiagnosed and inadequately treated.

Etiology

Similar to type 1 diabetes, LADA has a genetic basis associated with human leukocyte antigen (HLA) genes, which encode major histocompatibility antigens (MHC) [8]. The major histocompatibility complex is responsible for immunoregulatory processes that are disrupted in both type 1 diabetes and LADA, leading to immune system disturbances in individuals affected by these types of diabetes. Studies indicate that carriers of *HLA-DRB1*04-DQB1*03:02* and *HLADRB1*03:01-DQB1*02:01* have the highest risk of developing this condition [2, 3, 6, 9, 10, 11, 12]. Similar to type 1 diabetes, LADA diabetes may result from the interaction between pancreatic islet β-cells with innate and acquired immune cells; however, the impact of immunity on disease onset and progression is not yet fully understood [13].

Environmental factors are also significant, including exposure to toxic substances and stress, overweight, lack of physical activity, alcohol consumption, and smoking, which can influence the development of LADA diabetes through immune system activation and other mechanisms [6].

Latent autoimmune diabetes in adults diabetes exhibits some similarities with type 2 diabetes, notably in terms of insulin resistance. In both conditions, there's reduced responsiveness of the body's cells to insulin, necessitating higher insulin levels to maintain normal blood glucose levels. Nonetheless, this insulin resistance is generally less pronounced in LADA when compared to type 2 diabetes, often linked to differences in BMI [14, 15, 16].

In contrast to individuals with type 2 diabetes, those with LADA tend to experience reduced insulin secretion and progress to insulin dependency more rapidly [14, 17]. However, the autoimmune process in LADA appears to be milder, and the decline in β-cell function is slower. This is evident in the consistently higher levels of C-peptide – an indicator of insulin secretion – seen in LADA patients. Consequently, many LADA patients do not require insulin therapy for some time after diagnosis [17].

While type 1 diabetes is typically characterized by the presence of various islet autoantibodies, LADA patients commonly test positive primarily for glutamic acid decarboxylase antibodies (GADA) [18, 19]. Thus, for research purposes, measuring GADA alone is often sufficient to differentiate LADA from type 2 diabetes. Additionally, GADA levels exhibit an inverse relationship with C-peptide levels, serving not only as an indicator of autoimmune activity but also providing insights into the extent of this activity [6, 14, 15, 16, 20].

As LADA is a relatively new area of research, investigations into its precise mechanisms and triggering factors are ongoing. Understanding the etiology of LADA diabetes is crucial for improving its diagnosis, treatment, and management.

LADA Diagnostic Criteria

The Immunology for Diabetes Society defined 3 diagnostic criteria for LADA:

1. age above 35 years,
2. presence of autoantibodies against pancreatic β-cell,
3. independence from insulin treatment for at least the first 6 months after initial diagnosis.

Criterion no. 2 involves assessing autoantibodies against:

- GADA,
- islet cell cytoplasmic antigens,
- insulin,
- protein tyrosine phosphatase.

Criterion no. 3 is contested as it is subjective and depends on the assessing doctor's judgment [21].

Due to the presence of autoantibodies against pancreatic β-cells, LADA exhibits immunological similarity to type 1 diabetes [22]. However, autoantibodies in LADA are present in lower titers, resulting in a much slower progression of immune system imbalance. Auto-reactive T cells of the immune system attack pancreatic β-cells. This autoimmune response leads to a reduction in the mass of these cells and a decrease in insulin production.

Research findings demonstrated that measuring GAD65 autoantibodies – GADA – lacks reliability as a diagnostic method, as both true and false positive results have been obtained. This indicates a distinctive phenotype within this form of diabetes. Detecting GADA antibodies is not conclusive evidence of

disease presence, as they can also be present in individuals without diabetes. It is worth noting that the mere presence of GADA is not associated with an increased risk of type 1 diabetes [23, 24].

Differential Diagnosis from Type 2 Diabetes

Type 2 diabetes is a metabolic disorder characterized by abnormal insulin secretion from pancreatic β-cells and inadequate response of insulin-sensitive tissues. This mechanism, known as insulin resistance, disrupts metabolic equilibrium and contributes to disease development.

Environmental factors and lifestyle play a pivotal role in the pathogenesis of type 2 diabetes. These factors include aspects such as excess weight, poor dietary habits, lack of physical activity, excessive alcohol consumption, and smoking [25]. Genetic factors and a positive family history of diabetes also contribute to the onset of this diabetes type.

Latent autoimmune diabetes in adults, due to its clinical resemblance to type 2 diabetes, is frequently misdiagnosed and inappropriately managed. However, distinct characteristics in patients enable accurate diagnosis. In LADA insulin resistance is present, but individuals with this diabetes type might display mild manifestations of this phenomenon, maintain a normal body mass, and lack a positive family history of diabetes [26].

Treatment

Once the diagnosis is confirmed, recommendations encompass lifestyle adjustments: including adopting a calorically appropriate diet (particularly cautious carbohydrate consumption, emphasizing increased physical activity, and reducing alcohol consumption and discontinuing smoking, are of paramount importance. Notably, risk factor modification recommendations mirror those for type 1 and type 2 diabetes.

As of now, an optimal treatment for LADA diabetes has not been determined. The treatment strategy is based on 2 principles: achieving good glycemic control and preventing or delaying complications [27, 28]. There is not enough evidence confirming insulin's impact on disease progression; however, it is assumed that insulin is effective and safe in treating this type of diabetes, and early initiation of therapy is recommended [29]. This approach can prevent the self-destruction of pancreatic islets. In individuals with elevated BMI, metformin assists in blood glucose management, but it lacks a protective effect on β-cells, hence its efficacy in LADA diabetes therapy is not proven. The use of sulfonylurea derivatives is not recommended, as they reduce insulin levels in β-cells, as observed through decreased C-peptide levels and persistent antibodies [30]. Thus leading to β-cell destruction and consequently accelerating the need for insulin therapy [21].

In the context of treating LADA diabetes, there are studies suggesting the use of novel oral hypoglycemic agents including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor antagonists.

Dipeptidyl peptidase-4 inhibitors can be employed either in monotherapy or combined with insulin, thiazolidinediones, and GLP-1 receptor antagonists. These agents elevate GLP-1 levels, through diminishing glucagon secretion and enhancing insulin release post glucose load mediated by DPP-4 receptors activation in the gastrointestinal tract and brain.

Moreover, DPP-4 receptors are also present on the surface of T lymphocytes, participating in immune regulatory processes, thereby influencing the slowdown of immune system cell deterioration.

Dipeptidyl peptidase-4 inhibitors play a significant role in LADA diabetes treatment by achieving glycemic control and preserving β-cell function [21, 30, 31, 32, 33, 34]. Glucagon-like peptide-1 receptor antagonists lower glycated hemoglobin levels, infrequently causing hypoglycemia, they also reduce body weight and appetite, delay gastric emptying, and improve β-cell function [21, 35, 36].

Lin Yang et al. conducted an open-label randomized controlled clinical trial on 51 patients with LADA. These patients were randomly assigned to either the sitagliptin + insulin (SITA) group or the insulin-only (CONT) group for 24 months. In comparison to using insulin intervention by itself, the combination of sitagliptin and insulin treatment seemed to preserve β-cell function and enhance insulin sensitivity to a certain degree in individuals with LADA [37].

A personalized therapy with its primary objective of achieving optimal metabolic control which leads to the preservation of β-cell function is currently a topic of clinical interest.

Additionally, the incorporation of other hypoglycemic agents such as incretin-based therapy (GLP-1RA or DPP-4i), thiazolidinediones, and glucose-sodium cotransporter 2 inhibitors may offer additional benefits, such as weight loss and cardiovascular and renal protection [35].

Continuous Glucose Monitoring Systems

Continuous Glucose Monitoring (CGM) systems are innovative tools for individuals with diabetes, including those with LADA, allowing precise real-time monitoring of blood glucose levels. Continuous Glucose Monitoring employs a small sensor placed under the patient's skin, measuring glucose levels in interstitial

fluid and transmitting this information to a receiver or the user's smartphone. The receiver or mobile app presents real-time data, enabling individuals with LADA to track glucose level changes throughout the day.

Significant benefits of CGM systems in diabetes (including LADA) [38, 39, 40]:

1. **accurate monitoring**: CGM systems provide much more accurate and frequent glucose level measurements compared to traditional self-monitoring methods using a glucometer. This enables more effective glucose control and precise therapy adjustments [41];
2. **early detection of fluctuations**: people with LADA can experience glucose level changes that aren't always easy to identify. Continuous Glucose Monitoring allows for early detection of these changes and quick response, helping to avoid hypoglycemia and hyperglycemia;
3. **trends**: analyzing data collected by the CGM system allows individuals with LADA to track trends (increases/decreases) in glucose levels. This helps understand how the body reacts to various factors like meals, physical activity, and stress, facilitating lifestyle and treatment adjustments;
4. **hypoglycemia reduction**: continuous monitoring enhances the avoidance of dangerous glucose drops, especially at night. Continuous Glucose Monitoring systems often alert the user when glucose levels are too low or too high;
5. **decision support**: CGM systems provide data that can be used by healthcare professionals to evaluate therapy effectiveness and adjust insulin doses or other antidiabetic medications.

Within the group of CGM, there are 2 subtypes of devices:

1. personally owned devices intended for regular or continuous usage, comprising real-time CGM (rtCGM),
2. intermittently scanned CGM (isCGM),

and professional CGM devices utilized in clinical settings for specific periods. The available sensors can be either disposable (rtCGM and isCGM) or implantable (rtCGM).

For individuals with LADA diabetes utilizing CGM, the frequency of sensor use plays a pivotal role in predicting A1C reduction across all age groups. Additionally, improved outcomes are associated with the frequency of scanning using isCGM devices.

Specific devices, like FreeStyle Libre 2 (isCGM), Dexcom G6, and FreeStyle Libre 3 (rtCGM), have attained Integrated CGM (iCGM) designation, meeting a higher standard set by the FDA to facilitate integration with other digitally connected devices [42, 43].

It is important to remember that despite all the advantages, CGM systems do not replace traditional glucose monitoring methods and still require a certain level of user involvement. Collaboration with the medical team and proper understanding and interpretation of CGM data are crucial to achieving optimal control of LADA diabetes.

Continuous Glucose Monitoring Systems Targets

The International Society for Pediatric and Adolescent Diabetes supports the established standards for the duration spent in each glycemic band [44]. These include the time spent:

- >70% between 3.9 and 10 mmol/L (70–180 mg/dL),
- <4% <3.9 mmol/L (70 mg/dL),
- <1% <3.0 mmol/L (54 mg/dL),
- <25% >10 mmol/L (180 mg/dL),
- <5% >13.9 mmol/L (250 mg/dL).

Ensuring CGM accuracy is crucial, particularly in the hypoglycemic range. According to the consensus statement, the recommended maximum allowable time spent below 3.9 mmol/L (70 mg/dL) is 4%. It is noteworthy that individuals without diabetes may spend around 3.2% of their time in this range, but rarely below 3.0 mmol/L (54 mg/dL), contingent on the accuracy of the sensor utilized. Hence, the primary focus is on minimizing the duration spent in the very low range below 3.0 mmol/L (54 mg/dL). Thankfully, successive generations of CGM have demonstrated improved accuracy, leading to the approval of several CGM and intermittently scanned CGM (isCGM) systems for non-adjunctive use. It is recommended to confirm hypoglycemia using Self-Monitoring of Blood Glucose (SMBG). Additionally, SMBG confirmation is advised when there is a disparity between symptoms of hyperglycemia or hypoglycemia and a seemingly normal sensor glucose value [44].

Treatment of LADA can also involve the use of an insulin pump, and currently, the most effective approach is combining pump therapy with CGM. This integrated method allows for more precise insulin delivery, better glucose management, and enhanced overall control of the condition. Furthermore, the combination of insulin pumps and CGM not only improves glycemic control but also empowers individuals with LADA to make informed decisions about their daily activities, dietary choices, and insulin dosages. The real-time data provided by CGM allows for a proactive and individualized approach to managing blood sugar levels, minimizing the risk of both high and low blood glucose episodes.

Summary

Latent autoimmune diabetes in adults, similar to type 1 diabetes, is an autoimmune disease where

pancreatic β-cells are destroyed by autoantibodies targeting the islet cells. As of now, the impact of insulin on disease progression has not been established, but it is assumed to be effective and safe in therapy, significantly surpassing the efficacy of oral antidiabetic medications which come with various side effects. The most significant of these side effects is the lack of protective action and influence on β-cell destruction. However, DPP-4 inhibitors play a key role in the treatment of LADA diabetes. They effectively regulate blood sugar levels and help maintain β-cell function. Considering the observed impact of lifestyle on LADA, its progression can be slowed down by adopting an appropriate diet and paying special attention to carbohydrate intake and calorie consumption. In achieving optimal diabetes control, CGM systems can be also helpful. Avoiding a sedentary lifestyle and excessive alcohol consumption is also recommended. Striving to increase physical activity and reduce body weight in overweight or obese individuals is crucial. It's also advised to avoid stressors and quit smoking [6, 45].

Conclusions

Due to its hybrid nature, LADA remains a challenging disease to diagnose. Establishing the diagnosis requires a thorough analysis and observation of clinical symptoms by the physician, as these symptoms are often nonspecific and closely resemble those seen in type 2 diabetes. An early and accurate diagnosis enables the implementation of appropriate treatment, which can mitigate potential harmful consequences.

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