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UNDERSTANDING LATENT AUTOIMMUNE DIABETES IN ADULTS [LADA]: A COMPREHENSIVE REVIEW

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ABSTRACT:

Latent autoimmune diabetes in adults (LADA) encompasses a unique form of diabetes with characteristics bridging Type 1 and Type 2 diabetes. Latent Autoimmune Diabetes in Adults involves an autoimmune response targeting pancreatic beta cells, akin to Type 1 diabetes, yet its onset occurs in adulthood. This autoimmune process leads to a gradual decline in beta cell function, resembling the slower progression of type 2 diabetes. Often misdiagnosed initially as Type 2 diabetes, understanding Latent Autoimmune Diabetes in Adult's pathogenesis is essential for appropriate management, potentially requiring earlier insulin therapy than typical Type 2 cases. This review highlights the distinctive features and clinical implications of Latent Autoimmune Diabetes in Adults in the context of adult-onset autoimmune diabetes.

KEYWORDS: Latent Autoimmune Diabetes in Adults, Type 2 diabetes, Type 1 diabetes, cells

1. INTRODUCTION:

The hallmark of autoimmune diabetes is the existence of certain autoantibodies against the islet of pancreatic β-cells and the initial need for insulin therapy [1] A significant subset of individuals, the majority of whom began their illness in adulthood, have multiple traits in common with both T1D and T2D as they were originally defined more than 30 years ago [2] The condition, referred to as type 1.5 diabetes, includes the phenotypic, genetic, and pathophysiological characteristics of type 1 diabetes (T1DM) and type 2 diabetes (T2DM) [3] These individuals do not require insulin at the time of diagnosis and tend to have a slowly progressing type of autoimmune diabetes with serum T1D immune markers. Patients identified as having latent autoimmune diabetes in adults (LADA) account for 2–12% of all diabetes patients. The percentage of these patients varies substantially based on the type of autoantibody utilized for screening (antibody against glutamic acid decarboxylase [GADA] is the most common type), as well as ascertainment methods (primary care shows lower rates than secondary care). [2] The pathophysiology of LADA is influenced by various factors, ranging from genetics to clinical characteristics. These include markers of autoimmune diabetes, such as circulating autoantibodies, self-reactive T cells, evidence of lymphocytic infiltrates in β cells, non-obesity, associations with other autoimmune diseases, and increased insulin treatment, among others [4] Due to the latent and slowly progressive character of LADA, which increases the chances of misdiagnosis, the diagnostic criteria and differential diagnosis for this condition are still not entirely clear. Three important criteria have been set by the Immunology of Diabetes Society to diagnose LADA: the patient must be over thirty, have any autoantibodies against islet cells, and not require insulin for at least six months after diagnosis [5]. Over 6,000 adult-onset T2DM patients comprised the biggest cohort studied for LADA to date, which found a prevalence of 9.7% for adult-onset autoimmune diabetes. comparison to individuals with type 2 diabetes, individuals with LADA typically exhibit an earlier onset of diabetes, a lower body mass index (BMI), and a more marked reduction in insulin secretion, as indicated by decreased C-peptide levels and consequently higher insulin dosages.[6] Even though LADA is well acknowledged, there are no management guidelines available.[2] Since β-cell loss in LADA progresses more

quickly than in type 2 diabetes, medications that maintain β-cell function may be helpful in this condition. An incorrect diagnosis may delay the appropriate course of therapy, rendering patients at risk for side effects from ineffective medications, delaying the onset of normoglycemia, and eventually raising the possibility of long-term problems. [7]

2. EPIDEMIOLOGY:

An epidemiological study indicates that 3–11% of cases of adult-onset diabetes may be attributable to LADA. The frequency of LADA in individuals with T2DM residing in Western countries varies from 2.91% to 10%. The occurrence of it varies by region and ethnicity. Islet cell autoantibodies were found in nearly 10% of 6000 persons with adult-onset diabetes mellitus in the multicentric European 'Action LADA' investigation. Twelve percent of persons with a presumed diagnosis of type 2 diabetes had antibody positivity in the United Kingdom Prospective Diabetes Study (UKPDS). Based on a case-control and prospective analysis of two studies, obesity was linked to an elevated risk of LADA, according to the HUNT study from Norway and the ESTRID study. [8]

3. CAUSES:

Latent Autoimmune Diabetes in Adults (LADA) shares similarities with Type 1 Diabetes Mellitus (T1DM) in terms of autoimmune markers and immune response against islet cells. However, LADA progresses more slowly, leading to a gradual decline in beta-cell function compared to the rapid beta-cell destruction seen in classical Type 1 Diabetes.

In LADA, the decline of C-peptide, which indicates the body's ability to produce insulin, tends to be slower compared to the rapid decline observed in Type 1 Diabetes. Consequently, there's often a positive correlation between age at the diagnosis of autoimmune diabetes and fasting C-peptide levels, reflecting the slower progression of beta-cell impairment in LADA.

Glutamic acid decarboxylase autoantibodies (GADAs) tend to be the most commonly detected marker in both adult-onset Type 1 Diabetes Mellitus (T1DM) and Latent Autoimmune Diabetes in Adults (LADA). However, while GADAs are prevalent in both, other autoantibodies like insulin autoantibodies, protein tyrosine phosphatase IA-2 (IA-2A), and islet-specific zinc transporter isoform 8 (ZnT8) autoantibodies, which are commonly found in younger individuals with T1DM, are detected in only a small percentage of LADA patients.

4. PATHOGENESIS:

The pathophysiology of LADA is still unknown, but numerous investigations have demonstrated that cell-mediated immunity is the primary cause of LADA.[9] T cells and B cells, two types of adaptive immune cells, are crucial in the development of autoimmune diabetes. Many studies have documented phenotypic changes in T and B cells among individuals with LADA. LADA patients have autoantibodies, a sign of an autoimmune pathogenesis similar to type 1 diabetes. However the autoimmune response appears to be milder and the beta-cell failure progression is slower; this is supported by the fact that patients with LADA consistently show higher levels of C-peptide, an indicator of insulin secretion, and that they do not require insulin for a while after diagnosis. Patients with type 2 diabetes produce more insulin than those with LADA, and they also become insulin-dependent more quickly.[8] Patients with LADA release more insulin at diagnosis than those with T1DM, suggesting that the pathogenesis may involve mechanisms other than the autoimmune destruction of beta cells. It has been demonstrated that individuals with LADA develop insulin resistance as a result.[5]

4.1 ADAPTIVE IMMUNITY:

T cells and B cells, two types of adaptive immune cells, are crucial in the development of autoimmune diabetes. Many studies have documented phenotypic changes in T and B cells among individuals with LADA.[10]

4.1.1 T-CELLS

The primary effector cells of β cell autoimmunity are autoreactive T lymphocytes. Generally, different genetic and environmental stimuli cause damage to or death of pancreatic β cells, which release autoantigens. After coming into contact with islet autoantigens, pancreatic draining lymph nodes activate naïve T lymphocytes, which then infiltrate the islets.[11]

4.1.2 B-CELLS

The role of B cells in β cell death mediated by the immune system is also becoming more and more evident. B cells collect and present autoantigens to activate autoreactive CD4+ T cells and promote the survival and development of CD8+ T cells. They also produce islet autoantibodies to aid in the diagnosis of autoimmune diabetes.[12]

4.2 INNATE IMMUNITY

AGE	Age >30 years
CAUSE	Genetic or personal history of autoimmunity
OCCURRENCE	It develops slowly in adults and is not likely in children.
BMI	Low BMI compared to T2DM
ANTIBODIES	GAD and ICA are more dominant antibodies in LADA.
C-PEPTIDE	C-peptide levels are decreased at diagnosis.
COMPLICATIONS	No metabolic syndrome features such as obesity, high blood pressure, or cholesterol levels are more common in T2DM.
RISKS	Cardiovascular disease risks are similar to those of type 2 diabetes.
INSULIN	Non-insulin-requiring at the onset of diabetes.

The number of studies on the function of innate immune cells in LADA has gradually expanded in the past few years. The immune cells that play a major role in innate immune responses are neutrophils, NK cells, macrophages, basophils, and eosinophils. Before the onset of adaptive immunity, innate immunity is a crucial stage. Macrophages are innate immune system cells that are present in nearly all tissues. In addition to supporting homeostasis and repair of the internal environment, they serve as the primary immune response regulator. Neutrophils perform a variety of antibacterial functions, such as degranulation, phagocytosis, and the creation of neutrophil extracellular traps (NETs). Neutrophils are implicated in the onset and progression of LADA, according to an increasing body of evidence. According to our clinical research, LADA patients have neutrophil counts that are higher than those of T1D patients and lower than those of T2D patients. Innate immune cells, known as "NK cells," can directly kill pathogenic microorganisms through cytotoxicity. They can also control antigen presentation, T-cell activation, and the secretion of several cytokines.[13]

5. CLINICAL FEATURES:

When autoimmune diabetes is first diagnosed, its clinical manifestations can range widely, from hyperglycemia managed with diet alone or hypoglycemic medications to diabetic ketoacidosis. Within this framework, individuals classified as having LADA who do not initially require insulin span a broad range of phenotypes, from prevalent insulin deficiency to prevalent insulin resistance, and share intermediate clinical and metabolic characteristics between T1DM and T2DM. Patients with LADA typically exhibit fewer metabolic syndrome indicators, such as improved blood pressure and cholesterol profiles, a lower body mass index, and a smaller waist-to-hip ratio, when compared to T2DM patients. Accordingly, the A Diabetes Outcome Progression Trial (ADOPT) discovered that among newly diagnosed T2DM patients, those who tested positive for GADA had lower triglyceride and higher high-density lipoprotein cholesterol levels, along with a decreased incidence of metabolic syndrome . The majority of research, however, revealed that LADA appears to have a higher prevalence of metabolic syndrome characteristics than does typical T1DM. (15).

6. DIAGNOSIS:

The Immunology of the Diabetes Society has identified three criteria that are commonly used to diagnose LADA.

(a) the age at which the condition first manifested as an adult (>30 years);

(b) the existence of any islet cell autoantibodies;

(c) the ability to function without insulin for at least six months after diagnosis [SSS15]

7. COMPLICATIONS:

SMALL FIBER NEUROPATHY:

Small-fiber neuropathy (SFN), which is linked to a higher HbA1C and inadequate glycemic management, has been shown to occur earlier and more frequently in LADA compared to T2DM. Compared to T2DM patients who are age and duration matched, those with LADA are more likely to develop severe SFN. Large nerve fiber impairment, however, is not distinct from type 2 diabetes. It is advised that tests for SFN detection be performed while evaluating a patient with LADA. Tiny nerve fibers transmit feelings of pain and warmth, modulate perspiration, and control vascular tone, which in turn manages blood flow. The warm sensation threshold (WST), cold sensation threshold (CST), intraepidermal nerve fiber density (IENFD), and ocular confocal microscopy are tests used to diagnose SFN. The accuracy of nerve conduction studies (NCS) in identifying SFN is low and not recommended[16].

SPHINGOLIPIDS IN INSULIN RESISTANCE COMPLICATIONS IN DIABETES:

Different sphingolipids have been connected in recent decades to the pathophysiology of numerous genetic and metabolic illnesses, and it is becoming clear how sphingolipids mediate disease processes. Several sphingolipids are implicated in the regulation of cell growth and migration, inflammation, angiogenesis, apoptosis, and senescence, according to extensive in vitro and in vivo studies on the metabolism and activities of several sphingolipids. Deficits in the enzymes involved in the sphingolipid metabolism pathway might lead to an intracellular buildup of sphingolipids. For instance, it was discovered that patients with Fabry disease had higher amounts of globotriaosylsphingosine (LysoGb3) in their plasma, urine, and cellular lysosomes. This test can be used to confirm the diagnosis in people with atypical Fabry disease and to ascertain the need for treatment. This demonstrates how sphingolipid levels in serum or other body fluids can be measured to forecast how a disease will proceed and to help select the best course of therapy. As a matter of fact, sphingolipids have been suggested as potential biomarkers for a number of conditions, including multiple sclerosis, rheumatoid arthritis, diabetes, asthma, chronic obstructive pulmonary disease (COPD), coronary artery disease, and Alzheimer's disease. Lupus erythematosus (SLE), type 1 diabetes, and autoimmune diseases like these have also been linked to sphingolipids. A thorough analysis of the literature has also been done on the role of sphingolipids as metabolic illness biomarkers and the significance of abnormal levels of various sphingolipid species in blood, urine, and cerebrospinal fluid as disease biomarkers. Linking the occurrence or development of disease to the blood sphingolipid level can may offer a dependable means of assisting with the diagnosis and subsequent care, hence improving results in specific disease conditions. In this work, we evaluated published data on sphingolipid alterations in obesity and insulin resistance, type 1 and type 2 diabetes, and the relationship between sphingolipids and the development of macro- and micro-vascular problems associated with diabetes, both from our own research and from their groups [17].

8. MANAGEMENT:

INSULIN THERAPY:

Individuals who have just received a diagnosis of LADA exhibit elevated C-peptide levels, which indicate a degree of β-cell function preservation, and develop absolute insulin reliance more slowly.

Several preclinical investigations have shown that exogenous insulin therapy would support β-cell function, reducing hyperglycaemic stress and insulitis severity, despite the fact that the pathophysiological basis of the protective effect of insulin therapy is not well understood [18].

INSULIN-SENSITIZERS:

Thiazolidinediones and Metformin. Before being classified as having LADA, most people with T2D are first treated with metformin based on a clinical diagnosis. The panel came to the conclusion that, notwithstanding the paucity of data supporting metformin use, there is also no evidence to oppose it. Metformin can lower weight, LDL cholesterol

levels, and the risk of atherosclerosis development. It can also enhance insulin sensitivity in T1D patients but there is no evidence that it can improve long-term glycemic control . Further information regarding the exact function of metformin will be available through the outcomes /of upcoming clinical trials that examine how monotherapy or adjunct metformin affects β-cell function, metabolic control, and tolerance in LADA patients.

Thiazolidinediones (TZD) and insulin together maintained β-cell activity in LADA in a limited trial (n = 23 patients), although further research is required.

54 Chinese participants participated in a four-arm, randomized experiment wherein patients with LADA were randomly assigned to receive either rosiglitazone (n = 15) or sulfonylurea (SU) medication if their fasting C-peptide was >0.3 nmol/L and their GADA was less than 175 units/ml. C-peptide levels post-oral glucose and delta C-peptide were higher with rosiglitazone compared with the SU group after 18 months and up to 36 months ($P < 0.05$ for all comparisons), despite the fact that fasting C-peptide did not differ between the two groups.

Evaluation of Data Quality:

• Restrictions Moderate coherence

• Moderate Relevance

- Sufficient but not outstanding

• All in all: poor

The panel came to the conclusion that the effectiveness of both drugs is unclear because there is little data to support the use of TZD and little evidence to support the use of metformin. The usage of these medications for TZD may be restricted due to the possibility of weight gain, macular edema, and unusual bone fractures.[19]

DIPEPTIDYL -PEPTIDASE- 4 INHIBITORS:

Dipeptidyl-peptidase-4 inhibitors, or DPP-4is, have shown promise in protecting β-cell function in patients with lipodystrophic acidemia. After using sitagliptin for a full year, a randomized controlled experiment noted alterations in T-cell phenotype, downregulation of messenger RNA expression, and enhanced glycemic management in LADA patients. Similarly, recent research has found that in patients with LADA, saxagliptin improves islet β-cell activity. Furthermore, current research has demonstrated that islet β cells benefit from the combination of saxagliptin and vitamin D. DPP-4is may, mechanistically, affect how individuals with LADA regulate their glucose metabolism. Additionally, via activating DPP-4 receptors, DPP-4is raise glucagon-like peptide-1 levels and decrease glucagon levels, which increases insulin production following glucose loading. Moreover, research has indicated that DPP-4 receptors, which are also present on the surface of T cells, are linked to immune modulation and may play a crucial part in preventing and postponing β-cell immune destruction in LADA [20].

SULFONYLUREAS:

Insulin treatment and glibenclamide were evaluated in two randomized controlled studies for people with SPIDDM. Using a stimulated C-peptide assay, a pilot study evaluating 4,089 non-insulin-dependent SPIDDM patients with a disease duration of at least five years revealed that subjects treated with glibenclamide impaired β-cell function more quickly than those treated with insulin at the 30-month follow-up. The development rate to an insulin-dependent state was lower in the insulin group than in the sulfonylurea group in this multicenter, randomized, non-blinded clinical trial, while C-peptide values during the oral glucose tolerance test were better preserved in patients receiving insulin treatment. The notion that sulfonylureas could activate β-cells and possibly increase their antigen expression is supported by these studies aggravating the autoimmune disorder. Thus, it is advised that people with LADA/SPIDDM refrain from using sulfonylureas.[14]

9. CONCLUSION:

In conclusion, latent autoimmune diabetes in adults (LADA) is a slowly progressive form of autoimmune diabetes that can be difficult to diagnose. It is important to be aware of the risk factors and symptoms of LADA so that it can be identified and treated early. Early diagnosis and treatment can help to prevent complications of diabetes, such as heart disease, stroke, kidney disease, and nerve damage.

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