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LADA OR TYPE 2 DIABETES MELLITUS - A CHALLENGING DIAGNOSIS IN CLINICAL APPROACH

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Abstract: *Latent autoimmune diabetes in adults (LADA) is a frequently encountered condition in medical practice. It should be suspected in patients where the type of the diabetes mellitus is not certain. LADA consists of features from both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), being a condition which is often unnoticed. Considered as type 1.5 diabetes mellitus, the lack of insulin requirement at disease onset makes it initially to be included in T2DM in terms of therapeutic management. The improvement of the screening methods allows the detection of LADA at an early stage, therefore medical intervention should be effective in preserving beta-cell function and to delay the progression of the disease.*

INTRODUCTION

Diabetes mellitus (DM) is a complex disease, the current classification includes type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), secondary diabetes mellitus and gestational diabetes mellitus. Latent autoimmune diabetes in adults (LADA), is characterised by an autoimmune and genetic process similar to T1DM, which occurs in adulthood (>30 years). The similarity to T2DM is the lack of insulin requirements at the onset of the disease.(1,2)

LADA, referred to by some authors as diabetes mellitus type 1.5, has clinical and biological features of both T1DM and T2DM, being a borderline diagnosis. LADA is included by American Diabetes Association in T1DM, classified as autoimmune diabetes with a slower progression to insulinopenia, not being a particular type of DM.(3) Because of the similarity to T2DM at onset, the therapeutic management, according to current guidelines, is the same. World Health Organisation does not recognise LADA as a stand-alone diagnosis, referred to as slowly evolving, immune-related diabetes, currently included in the T1DM classification.(4) The term used for LADA in Japan is slowly progressive insulin-dependent type 1 diabetes mellitus (SPIDDM).(5)

Epidemiology of LADA

The incidence of LADA in diabetic patients varies between 2-12%, taking into account ethnicity and screening criteria such as measuring glutamic acid decarboxylase autoantibody (GADA) or islet cell autoantibodies (ICA) used in different countries. Recent studies show that 3% to 12% of patients initially diagnosed with T2DM have autoantibodies, thus resulting in the shifting paradigm of LADA diagnosis.(6,7)

Pathophysiology and genetics of LADA

The LADA pathophysiology is not fully clarified, the patients have the T1DM genotype and the intermediate phenotype of both T1DM and T2DM.(8) Regarding the process of pancreatic beta-cell self-destruction in LADA, partial or slowly progressive alteration of the pancreatic reserve (approximately two-thirds) is observed, compared to total destruction in T1DM.(9)

C-peptide levels reflect the insulin secretion and the pancreatic reserve at the time of DM diagnosis.

Genetic susceptibility is a topic still under investigation. LADA is associated with genes that encode human leukocyte antigen (HLA), cytotoxic T lymphocyte antigen 4 (CTLA4), tyrosine-protein phosphatase non-receptor type 22 (PTPN22) and insulin.(10,11,12)

The highest risk for LADA represents the association with the DRB1 0301 and DRB1 0401 genes. Also, DRB1 0401 and DQB1 0302 genotypes were associated with younger age at diagnosis and DRB1 1501 and DQB1 0602 with older age at diagnosis of LADA.(13,14) The autoimmune process involved in the development of the disease is evidenced by assay of autoantibody levels. The most important parameters in confirming the diagnosis are GADA and autoantibodies to the tyrosine phosphatases (IA-2A), but also insulin autoantibodies (IAA), zinc transporter 8 (ZnT8), and tetraspanin 7. GADA is the most specific marker in LADA screening, accounting for 94-99% of cases.(15,16)

Detection of glutamic acid decarboxylase 65 antibodies (anti-GAD65) by electrochemiluminescence assay facilitates the subclassification of LADA into two types: one without antibodies more similar to T2DM and one with positive antibodies more similar to T1DM.(17)

A high level of GADA is associated with a higher insulin requirement.(1) IA-2A, on the other hand, are present in this category of patients, with a lower sensitivity and specificity of 40-97%.(18)

Risk factors and diagnosis of LADA

Risk factors include obesity, sedentary lifestyle, smoking, low birth weight, consumption of processed red meat, sweetened beverages and coffee. Fish fat and moderate alcohol consumption may have a protective effect.(19-22) Also, family history of DM may determine LADA resemblance more to

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T1DM or T2DM.(23)

Clinical presentation in LADA is less specific than T1DM and T2DM. The onset of the disease can range from insidious, without pathognomonic signs and symptoms, to acute manifestation of diabetic ketoacidosis. This broad spectrum is directly related to the degree of beta-cell destruction; a noisier onset may be an indicator of marked pancreatic destruction.(3,24)

A diagnosis of LADA can be considered in patients with the disease onset over 30 years of age, the presence of diabetes-associated autoantibodies (GADA, ICA) and the absence of insulin requirement within the first 6 months of onset.(1) Detection of anti-pancreatic antibodies, GADA and ICA, are considered predictor factors of insulin dependence.(25)

LADA is a mixed entity, at the border between T1DM and T2DM, sharing clinical and metabolic criteria on both sides, as mentioned in several studies (table no. 1).(3,10)

Table no. 1. Clinical and metabolic features between T1DM, LADA and T2DM

Main features	T1DM	LADA	T2DM
Age onset	Childhood or adolescence (rarely at adulthood)	>30 years	Adulthood (rarely before)
Family history of diabetes	Variable	Variable	Often positive
HLA susceptibility	Increased	Increased	Mild increased
Body mass index (BMI)	Normal	Normal	Overweight or obesity
Clinical onset	Acute (frequently ketoacidosis)	Silent or subclinical	Silent or subclinical
Autoantibodies	Increased	Mild increased	Absent
C-peptide levels at onset	Decreased or non-detectable	Detectable	Normal or increased
Insulin resistance	Mild	Variable	Increased
Insulin treatment	At onset	>6 months after onset	Absent or years after onset
Long-term complications at diagnosis	Rare	Rare	Frequent
Cardiovascular risk	Increased	Increased	Increased
Lipid profile	Normal	Normal or hypertriglyceridemia	Dyslipidemia

Screening of patients with LADA can be facilitated by using a risk score with a sensitivity of 90% and specificity of 71%. This includes: age at onset below 50 years, symptomatic hyperglycemia, body mass index (BMI) below 25 kg/m2 and personal or family history of autoimmune disease. Two of these criteria are required for diagnosis.(26)

When faced with a newly diagnosed diabetic patient, the first issue is to establish the etiological diagnosis. The current algorithm is to assay for GADA and C-peptide level, which helps in clinical practice to exclude T2DM. However, if the suspicion of LADA remains, with negative GADA, other less specific autoantibodies may be recommended to be identified, such as ICA, IA-2A, ZnT8. The presence of autoantibodies and a normal or low C-peptide level divides therapeutic management into two possibilities. A C-peptide level below 0.3 nmol/L requires initiation of insulin therapy. When C-peptide values are between 0.3-0.7 nmol/L metformin can be initiated and the patient should be reassessed at 6 months.(1)

Between LADA and T2DM, metabolic dysfunctions such as dyslipidemia is more noticeable in the second one, as well as metabolic syndrome, higher BMI and increased insulin resistance.(27,28,29) Homeostatic model assessment for insulin resistance (HOMA-IR) is lower in LADA than T2DM and increases proportionally with BMI value.(1)

The differentiation between LADA and T2DM on long-term is an active screening based on the determination of diabetes-associated autoantibody levels. Although this appears to be a reliable method of differential diagnosis, it cannot be used in daily clinical practice due to high costs.

Therapeutic management of LADA

Due to the phenotypic similarity of LADA with T2DM, these two are often confused; for this reason, the initiation of oral glucose-lowering therapy comes as a normal step in clinical approach. The differentiation between the two, in the absence of active screening, is made only by time, through lack of achieving glycemic control and the need to initiate insulin therapy.

Active follow-up and reassessment of diabetes cases where LADA is suspected represents the cornerstone of rapid screening and preservation of long-term beta-cell function.

An individualized approach of the patients is necessary, with the choice of the optimal pharmacologic regimen being an important challenge to achieve target glycemic values and good metabolic control.

C-peptide values below 0.3 nmol/L require initiation of prandial, basal or combination of both insulin therapies.(1)

C-peptide values between 0.3-0.7 nmol/L may allow the use of metformin with reassessment at 6 months. Metformin is preferable in obese patients with insulin resistance in whom diet does not achieve target glycemic values.(1,26)

It is recommended to be avoided the sulfonylureas in non-insulin therapy. These glucose-lowering drugs may promote insulin depletion simultaneously with C-peptide depletion, with exacerbation of autoimmunity and a much faster progression to insulin therapy.(30) Nowadays, the modern pharmacological techniques target the most efficient procedures in order to obtain the best clinical results. However, there are modified released (MR) formula for some antidiabetic drugs, like gliclazide MR, which have as aim the preservation of the pancreatic beta-cells and this could be a future focus in the management of LADA.(31-34)

The thiazolidinediones (TZD) increase insulin sensitivity, preserve beta-cell function and maintain long-term C-peptide concentration.

Dipeptidyl peptidase 4 inhibitors (DPP-4i) also lead to protection of beta-cell function, by blocking the destruction of glucagon-like peptide-1 (GLP-1). Recent studies have demonstrated additional benefits in preserving pancreatic function by combining saxagliptin with 2000 IU/day of vitamin D3.(35,36) Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i) can also be used in LADA therapy. It should be noted that the treatment with SGLT2i requires caution because of the diabetic ketoacidosis risk especially in patients with BMI below 27 kg/m2.(1,37,38)

As regards GLP-1 RA, dulaglutide has shown effectiveness on reducing the glycosylated hemoglobin (HbA1C) levels in one-year follow-up, thus improving metabolic control.(39)

In choosing the optimal treatment, the parameter that guides therapeutic management is the HbA1C value. Taking in consideration the HbA1C value, cardiovascular and renal risk of LADA patients it is recommended the addition of the above-mentioned drug classes to the therapy regimen. The aim of this association is to achieve and maintain HbA1C level within

target values.

Immunomodulatory therapy with autoantigen administration or lymphocyte receptor blockade can also be mentioned as another therapeutic approach, but safety studies are currently limited.(40)

Future perspectives in LADA management

The diagnosis of LADA is a professional challenge for specialist physicians, as consequence of the patient features considered at borderline between T1DM and T2DM.

Comparing LADA with T2DM in terms of disease progression and prognosis, LADA has a lower mortality and risk for any future cardiovascular events such as acute myocardial infarction, heart failure, stroke.(41) Nevertheless, because of the time period elapsed between the onset of the disease and the diagnosis of LADA, studies show a higher severity of diabetic neuropathy progression in patients with LADA compared to T2DM.(42,43)

Proper LADA screening and diagnosis along with lifestyle changes can bring major benefits to a patient's quality of life.(44,45,46)

The development of a therapeutic management guideline is necessary for a complete medical approach.

CONCLUSIONS

LADA is an autoimmune disease that falls within the spectrum of adult-onset diabetes mellitus. The diagnosis of this condition is overlooked in clinical practice due to laborious and costly investigations. LADA, despite the presence of autoantibodies, which are not routinely performed, is misdiagnosed as T2DM, because of the similar phenotype.

In most cases, the diagnosis of LADA involves the clinical judgment of the specialist physician and in borderline cases, must presume LADA and investigate further accordingly. Regarding therapeutic management, progression to insulin therapy is slower, therefore antidiabetic drugs that preserve beta-cell function are preferred.

Active screening of C-peptide levels and autoantibodies with the involvement of the specialist physician helps in detecting LADA at an early stage. Thus, achieving the two main goals in management, such as preserving beta-cell function and improving metabolic control, can improve quality of life and reduce long-term complications. Further studies are necessary to develop a therapeutic approach that leads to early detection of LADA in those patients where the type of DM diagnosis is uncertain.

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