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Latent Autoimmune Diabetes in Adults

The disease we know as diabetes mellitus actually includes a set of distinct diseases, which are more difficult to differentiate than their classification suggests. Furthermore, many types of diabetes are heterogeneous and variable in themselves. Although this fact is especially prominent in type 2 diabetes mellitus (T2DM), it can also be seen in type 1 diabetes mellitus (T1DM). Under the term T2DM, some subtypes of diabetes are classified that end up being reconsidered, after a longer or shorter period of evolution, as another type of diabetes. One of them, less known but equally important, is latent autoimmune diabetes in adults (LADA). This form of diabetes can share characteristics with both T1DM and T2DM at different times and circumstances, which often complicates its diagnosis and appropriate treatment (1–3). However, classically, it is well known that people with LADA at the time of diagnosis are often classified as T2DM due to the characteristics that confuse it with the latter type of diabetes. This is especially due to the fact that they are adults, sometimes even elderly, who do not require insulin treatment for months or even years after diagnosis.

LADA is a type of autoimmune-based diabetes that appears in adults, generally older than 30 years, and develops and progresses more slowly than T1DM (3). What distinguishes LADA from T2DM are some of its clinical characteristics (3), but it is precisely its autoimmune origin that originally distinguishes it from T2DM. This means that the person's immune system, as in T1DM, mistakenly attacks the beta cells of the pancreas, which are responsible for producing insulin (3). As these cells are destroyed, insulin production gradually decreases, eventually leading to a need to administer insulin externally.

The World Health Organization (WHO), in the revision of its classification of diabetes published in 2019, recognized LADA as a differentiated type of diabetes under the term "slowly progressive immune-mediated diabetes in adults," highlighting its hybrid nature with characteristics of both T1DM and T2DM (4). However, the American Diabetes Association (ADA) does not consider it a separate category, but includes it within T1DM once the characteristic antibodies of this type of diabetes are identified (5). However, the ADA itself recognizes in its current recommendations that there is a debate about whether this form of diabetes should be called LADA or simply T1DM. The clinical importance in the detection of LADA is to be aware that this slow autoimmune destruction of β cells can occur in adults and entails a longer duration of residual insulin secretory capacity than in people with T1DM in its classic form (6). For the ADA classification, all forms of diabetes mediated by autoimmune destruction of β cells, regardless of the age of onset, are included under the term T1DM (5).

The use of the term LADA is common and acceptable in clinical practice, and has an important practical impact, as it increases awareness about a population of adults in whom there is progressive destruction of pancreatic β cells. LADA patients have lower insulin secretion than T2DM patients (6). This means that, unlike people with T2DM, the need to use insulin to control blood glucose occurs much sooner than would generally be expected. Furthermore, this loss of insulin secretion leads to poorer blood glucose control, and a greater risk of hyperglycemic decompensation in the form of diabetic ketoacidosis, the latter being very typical of T1DM.

Although LADA, like T1DM, has an important genetic component, the genes that lead to greater susceptibility are also present in a large part of the population. Certain genes have been identified, such as those of the HLA system, that increase the risk of developing this condition (7). In addition, as in T1DM and T2DM, there are certainly environmental factors that play an important role in its appearance (1). Another relevant aspect is that people with a family history of T1DM or autoimmune diseases, such as celiac disease or autoimmune thyroiditis, have a higher risk of developing LADA (1).

IDENTIFICATION OF PEOPLE WITH LADA

In some cases, people with this type of diabetes see their diabetes categorized as T2DM for quite some time, not being identified as LADA until even years later in the course of their diabetes. The diagnosis of LADA, according to its own definition, is confirmed by a blood test that detects the presence of specific antibodies, such as anti-GAD (glutamate decarboxylase) antibodies, which are the most common in this type of diabetes (they are also the most common in classic T1DM) (1,3). There are other autoantibodies more characteristic of T1DM that may also be present in LADA, although less frequently than the above-mentioned. In addition, measuring C-peptide in a blood test, as an indicator of the amount of insulin that the person's pancreas is producing, can also help in the diagnosis (1). Although the cost of determining these tests is relatively low, there is a debate among professionals about whether the presence of anti-GAD antibodies should be determined in all people with a new diagnosis of diabetes mellitus, regardless of the clinical characteristics or suspicion of the type of diabetes. Currently, clinical guidelines do not recommend its widespread use. However, its determination could significantly contribute to avoiding delays in the identification of LADA cases, thus allowing more appropriate management from the beginning.

In the presence of clinical characteristics that suggest LADA (1), all expert recommendations and scientific societies agree that anti-GAD antibodies, and in many cases also C-peptide, should be determined. Among these characteristics that should make us suspect LADA, it is important to highlight the following: 1) age < 50 years at diagnosis of T2DM; 2) presence in the course of diabetes of onset of typical symptoms of hyperglycemia without a concomitant triggering factor; 3) normal weight (BMI < 25 kg/m2); 4) poor glycemic control in people who have been prescribed hypoglycemic drugs of conventional use in T2D; 5) presence of other autoimmune diseases in the same person (thyroiditis, celiac disease, etc.).

IS LADA COMMON?

There are some studies worldwide that have tried in recent decades to characterize the prevalence of LADA (1,8). Not all studies are sufficiently extensive or representative of the reference populations; in addition, the prevalence is very variable in different countries. Most studies have been conducted by investigating the presence of antibodies in T2DM populations. As we said, the prevalence is variable, with the mean rate in a recent review being 8.9%, with variation between just over 2% and up to 19% of people with T2DM (8). In Europe, the prevalence is between 3 and 12%. If we take as an average the prevalence of 8.9% of T2DM patients, this means that LADA is an entity with a prevalence at least as high as classic T1DM. Therefore, its clinical relevance and the need for proper diagnosis and management should not be underestimated.

IMPORTANCE OF IDENTIFYING PEOPLE WITH LADA

There are different facts that justify the need to identify people with LADA, and also the importance of doing so early (1,3,7). Taking into account what has been said so far about this type of dia-

betes, the accelerated loss of the ability to produce insulin, present in a large part of people with LADA, makes it necessary to adjust the management of hyperglycemia to this reality, which often implies treatment with insulin. We must consider that there are people with LADA who can control blood glucose in the initial phases of their diabetes with classic drugs used in the treatment of T2DM, although they may subsequently present a more marked deterioration of blood glucose than would be expected. However, there are patients who do not respond at all or do so clearly insufficiently to these classic therapeutic measures even from the earliest stages of their diabetes. The fact of not knowing that we are dealing with a case of LADA can lead to a delay in the appropriate intensification of treatment and in the introduction of insulin treatment in the management of hyperglycemia in these patients. If blood glucose control is inadequate, it can lead to a greater risk of acute decompensation and long-term chronic complications of diabetes. There is also evidence from long-term studies that poorer diabetes control for considerable periods of time can lead to a greater risk of microvascular complications (1,7).

An important consideration in relation to the fact that blood glucose control is inadequate is that the person with LADA may have the perception that poor control may be attributed to the fact that self-management of diabetes is not correct on their part, which can lead to a worse perceived quality of life and worse satisfaction with the treatment of people with LADA; this facet is not sufficiently studied, although in a study by our group it was found that people with LADA have a worse perception of their quality of life and worse satisfaction with treatment than people with other types of diabetes (9).

The lack of specific recommendations for the diagnosis and management of people with LADA led an international group of expert researchers on the subject to issue recommendations on LADA (10). That document included the available evidence on the need for its early identification and the best way to do it, and also the evidence on the best therapeutic management of this type of diabetes. D

CONCLUSIONS

Latent autoimmune diabetes in adults is an often underdiagnosed and lesser-known disease by both people with diabetes and health professionals in general. However, it requires specific attention, and appropriate and individualized therapeutic management. Although an early diagnosis of LADA and personalized management can not only facilitate better glycemic control, it can also significantly contribute to a better quality of life for people with LADA and prevent diabetes-associated complications.

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