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Latent Autoimmune Diabetes in Adults

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Abstract

Latent Autoimmune Diabetes in Adults (LADA) is the term used to describe adults who have a slowly progressive form of diabetes mellitus (DM) of autoimmune etiology, but that may be treated initially without insulin. Although the American Diabetes Association (ADA) currently does not recognize this disease as a specific type, there is increasing information about it, as well as groups dedicated to its study. LADA shares some immunological and genetic aspects with DM type 1, it affects an age group that is typically affected by type 2 DM. Therefore, it could be considered a type of intermediate diabetes. This process can be detected by specific antibodies in the peripheral blood, months or even years before the clinical onset of the disease. Diagnosis is based on clinical and laboratory criteria: age of onset, initial response to oral hypoglycemic agents and the presence of specific antibodies for diabetes. Although the definitive treatment is insulin, glitazones may be useful in early stages of the disease. Currently, its management represents a challenge for the physician, including specialists, and it is a form of DM to keep in mind.

Keywords: diabetes mellitus type 1, diabetes mellitus type 2, adult latent autoimmune diabetes, autoimmunity, glutamic acid decarboxylase

1. Introduction

Diabetes mellitus (DM) is a complex and heterogeneous disease from a physiopathological point of view and often exceeds the somewhat rigid margins of the categories included in the current classification [1].

In 1986 Groop et al. reported a subgroup of diabetic patients who had cells specific for pancreatic beta cell (β) function, with characteristics different from the classic type 1 and type 2 DM [2]. Type 1 DM is caused by an autoimmune response that produces a progressive destruction of pancreatic (β). This process can be detected by specific antibodies in the peripheral blood, months or even years before the clinical onset of the disease [3].

The term Latent Autoimmune Diabetes in the Adult (LADA, Latent Autoimmune Diabetes of the Adult) by its abbreviations in English; it was coined by Tuomi et al. to describe patients with a slowly progressive form of autoimmune or type 1 DM who could be treated initially without insulin [4].

Both diseases, both DM type 1 and LADA; present specific antibodies: anti-decarboxylase of glutamic acid (anti-GAD), anti-beta cells (ICA), anti-tyrosine phosphatase (IA-2) and anti-insulin, the first of which is the most prevalent, followed by ICA [5, 6]; in more than 10% of adults with presumed DM type 2 (DM2) [7, 8], so LADA is the most prevalent form of autoimmune diabetes in adults and probably also the most prevalent form of autoimmune diabetes in general [9].

Clinically, these patients are difficult to distinguish from type 2 diabetic subjects who are positive for the markers that characterize patients with type 1 diabetes.

The presence or absence of islet autoantibodies is one of the most direct ways to distinguish between type 1 and type 2 diabetic patients [10].

And, although LADA is undoubtedly related to type 1 DM, its clinical presentation frequently features traits attributable to type 2 DM and is often misdiagnosed and treated for significant periods of time. This is helped by the fact that the current diagnostic criteria used to identify this variant of diabetes are imprecise and subject to controversy.

Although the American Diabetes Association (ADA) currently does not recognize this disease as a specific type, there is increasing information about it, as well as groups dedicated to its study.

2. Epidemiology

There is a big difference in the prevalence of type LADA DM among different population groups around the world. In North America it is estimated that 5–10% of new cases of DM in adult patients could correspond to this pathology [11].

In a UK Prospective Diabetes Study (UKPDS), about 10% of adults with suspected type 2 diabetes at the time of diagnosis had evidence of islet autoimmunity in the form of circulating ICA or GAD antibodies and most progressed to dependence on insulin in 6 years [12]. See **Table 1**.

In Central America there are still no studies that describe the prevalence of LADA type Diabetes. In countries like Honduras, its diagnosis is based on the clinic; this reduces the credibility of the diagnosis, especially when there is not enough equipment to corroborate the presence or absence of the antibodies described above.

Given that an appreciable proportion of people with diabetes who do not require insulin have a high proportion of antibodies against glutamic acid decarboxylase (GAD), it has been concluded that the LADA type Diabetes is probably much more prevalent than the DM type 1 but less frequent than DM type 2 [24]. This in turn explains the reason for the use of Anti-GAD, in comparison with other antibodies, to detect type LADA DM among subjects diagnosed as DM type 2 [13, 25].

Author	Country	Type of study	Universe	Prevalence %
Adeleye et al. [13]	Southwest of Nigeria	Based on the clinic	160	11.9
Ipadeola et al. [14]	Southwest of Nigeria	Based on the clinic	235	14.0
Agyei-Frempong et al. [15]	Ghana	Based on the clinic	120	11.7
Otieno et al. [16]	Kenya	Based on the clinic	124	5.7
Hwangbo et al. [17]	Korea	Based on the clinic	462	4.3
Tuomi et al. [18]	Finland	Based on population density	1122	9.3
Bosil et al. [19]	Italy	Based on population density	2076	2.8
Zinman et al. [20]	North America and Europe	Based on population density	4134	4.2
Arikan et al. [21]	Turkey	Based on the clinic	54	31.0
Brahmkshatriya et al. [22]	India	Based on the clinic	500	5.0
Lerman et al. [23]	Mexico	Based on the clinic	83	3.6

Table 1. Prevalence of positive glutamic acid decarboxylase antibodies (late autoimmune diabetes in adults) in subjects with type 2 diabetes among different population groups.

3. Genetics

Pathological studies have proposed that LADA and type 1 DM share physiopathological and genetic aspects; such as genes (HLA, INS VNTR and PTPN22) and with respect to DM type 2 (TCF7L2) [26], which suggest that it may represent a genetic admixture of the two types of diabetes, especially when non-insulin requiring.

It is known that LADA has a higher frequency of human histocompatibility antigens (HLA) characteristic of DM type 1: HLA-DR3 (28% of patients), DR4 (27%) and DR 3/4 (22%), in comparison with the general population [26, 27].

The dilemma persists in the fact whether this genetic mixture represents a totally different disease syndrome or is part of a continuum of an autoimmune process.

It is important to mention that in all the genome-wide association studies directed to the exome sequencing carried out until now or the sequencing of the whole genome exome, they have not yet been carried out in large cohorts of adult autoimmune patients.

As mentioned, both diseases have specific antibodies. Concomitantly, a decrease in the frequency and activation of “natural killer” cells in peripheral blood compared with healthy individuals has been demonstrated, which translates into a defect in the immune response [28].

4. Why are LADA and non-diabetic type 1?

Taking into account its subsequent and less aggressive presentation, different arguments have been formulated that explain the appearance of LADA. See **Table 2**.

4.1. When to think about LADA?

Some characteristics have been related, which in order of frequency associated with the disease in comparison with type 2 diabetics are: age of onset <50 years, symptoms of acute onset, BMI <25 kg/m² and personal or family history of autoimmune disease.

It is described that the presence of 2 or more of these criteria presents a 90% sensitivity and 71% specificity for the identification of LADA patients [25, 30].

In case of suspicion, specific antibodies should be requested to confirm the diagnosis.

-
- 1. Less marked exposure to environmental factors.
 - 2. Lower specific antibody titers.
 - 3. Intermittent crisis of autoimmune aggression.
 - 4. Greater capacity to regenerate beta cells and protection against the apoptotic process.
 - 5. Acquired immunotolerance.
-

The last three points would be the result of a better protection/risk gene balance compared to type 1 diabetics [3, 29].

Table 2. Postulates of Pozzilli and Di Mario [3], which differentiates LADA from DM type 1.

-
- 1. Appearance in adulthood, usually after 30 years
 - 2. Presence of specific auto antibodies, anti-GAD the most prevalent
 - 3. There is no need for insulin therapy at the onset of the disease, which should last at least 6 months
-

Table 3. LADA diagnostic criteria, proposed by Immunology of Diabetes Society (IDS).

Characteristics	DM type 1	LADA	DM type 2
Age of onset of the disease	Childhood or adulthood	Adulthood	Adulthood
Metabolic syndrome	Similar general population	Similar general population	80 and 90%
Ketoacidosis	Frequent	Infrequent	Absent
Autoimmunity	Present (ICA predominates)	Present (predominates anti GAD)	Absent
Insulin therapy	Since the diagnosis	Approximately 6 months without therapy requirement	Late

Source: Pollak et al. [31].

Table 4. Characteristics of DM type 1, LADA and DM type 2.

However, in order to clarify and have a more unified concept at the time of diagnosis, The Immunology of Diabetes Society (IDS) [4] has proposed 3 criteria for diagnosis, including: diagnosis of diabetes according to criteria established at a higher age at 30 years, independence of insulin for at least 6 months after diagnosis and positivity of antibodies against GADA (Tables 3 and 4).

5. Clinical presentation and relationship with chronic diseases

Andersen et al. mentions that patients with LADA have a higher body mass index (BMI) than type 1 diabetics, but less than type 2. The condition of normal weight is the most frequent nutritional status [32].

However, it is not a Sine Qua Non standard in its diagnosis.

5.1. Metabolic characteristics

Patients with adult onset autoimmune diabetes generally have a better metabolic profile than those with type 2 diabetes, with lower levels of triglycerides, higher HDL cholesterol and lower BMI, waist/hip ratio, and blood pressure [18, 33–37].

5.1.1. Body mass index and LADA

A clinical point of view that persists is that patients with LADA are usually thin at the time of diagnosis [5] similar to children with diabetes type 1. However, documentation of BMI in LADA populations of European extraction does not support this point of view. Most of the larger LADA cohort studies report an average BMI in categories of overweight or obesity ($\text{BMI} > 25.0 \text{ kg/m}^2$) [20, 38–40] and most report a BMI similar to the diabetes type 2 cohorts [20, 38, 40]. Therefore, a normal BMI ($<25.0 \text{ kg/m}^2$) should not be a diagnostic criterion for LADA.

5.1.2. Metabolic syndrome and LADA

The increase in the prevalence of metabolic syndrome (MetS) worldwide is alarming, even more so if we take into account that it is considered a risk factor for the development of diabetes, or a pre-diabetic state. The impact of MetS has been demonstrated by the increase in subclinical atherosclerotic disease in patients with the syndrome, even without the diagnosis of diabetes [41]. In countries such as the United States and Mexico, the prevalence of MetS is around 25% of its adult population [42].

Through a cross-sectional population-based study conducted by Wong-McClure et al. they claim that the general prevalence of MetS in Central America is high, being higher in Honduras (21.1%, CI: 16.4–25.9) than in the other countries of the isthmus [43].

Given the presented and due to the absence of data in primary care in Honduras [44], a descriptive study is carried out; in which the prevalence of MetS was determined using the criteria of the third report of the Group of Experts in Adult Treatment (Adult Treatment Panel III) of the National Program of Education on Cholesterol or by its acronym in English «National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) [45] being 65.8%.

Multiple studies on MetS and its relationship with DM type LADA estimate that at least 30% of patients diagnosed with type LADA have metabolic disorders [36].

Given the age of onset and the frequency of this syndrome in the adult population, the coexistence of both pathologies is not infrequent. It is estimated that approximately 42% of patients may present with metabolic syndrome, a figure lower than in type 2 DM, in which the association reaches 84% [36].

It is probable that some patients present insulin resistance (IR) although the importance of this phenomenon in the onset of the disease is not clear. It has been shown that adiponectin levels are similar to individuals without DM, suggesting that IR is not part of the etiopathogenesis of the disease [46].

In turn, the presence of dyslipidemia and hypertension is higher than in type 1 diabetics [47], but less frequent than in type 2 diabetics, which could result in an intermediate cardiovascular risk between both types.

5.1.3. DM type 2 and LADA

Multiple studies have found that patients with LADA require treatment with insulin more frequently and earlier after diagnosis than those with type 2 diabetes who are negative for antibodies. GADA positivity in adult patients with diabetes who do not require insulin is associated with decreased fasting C-peptide and a decrease in peptide-C response to oral glucose [12, 18, 48, 49].

It is mentioned that, the magnitude of this insulin response is inversely related to the GADA titer [18]. Curiously, insulin secretion was similar in patients recently diagnosed with LADA and DM type 2, as mentioned in two large studies conducted by Zinman et al. and Lundgren et al. [20, 50]

A metabolic study of insulin secretion and insulin sensitivity, conducted by Juhl et al. in 2014; confirmed the lack of weight difference in the groups with LADA and DM type 2 [51].

However, despite these early characteristics, over time, the increased propensity to reduce the function of b cells in LADA becomes evident [12, 18, 48].

Among GADA-positive patients, these altered metabolic parameters tend to be significantly better in those with high GADA titer compared to low GADA titer, but without a clear distinction between groups [18, 33–35].

These wide differences in metabolic parameters translate into negative GADA patients with more signs of metabolic syndrome than positive GADA patients, regardless of whether the latter have LADA or adults with diabetes onset Type 1 [34, 35, 51].

The formal examination of insulin resistance indicates that patients with LADA are more insensitive to insulin than healthy controls, but their insensitivity to insulin is comparable to or lower than that of patients with DM type 2 and is dependent on BMI [20, 40, 50, 52].

6. Clinical features

At the time of diagnosis, the clinical phenotype of patients with apparent autoimmune diabetes can be remarkably broad, ranging from diabetic ketoacidosis to the characteristics of diabetes that can be controlled only with diet.

The classification of these patients also covers a range that may seem arbitrary; for example, in the European Action LADA study, patients with GADA who started taking insulin in the first month of diagnosis were designed as classic type 1 diabetes, those who started with insulin in 6 months were not published and those who started with insulin 6 months or later were designed LADA. Compared with patients with type 2 diabetes, patients with adult onset autoimmune diabetes, even when they do not require insulin (LADA), have a lower age at the time of diabetes, lower BMI and waist/hip ratio, but a higher Pronounced loss of C-peptide and an increased likelihood of treatment with insulin [18, 35, 48].

Phenotypically, patients with high GADA titres tend to have these same characteristics, but they are more marked and more similar to classic type 1 diabetes, with younger patients at the time of diagnosis being thinner with a high risk of progression to treatment with insulin.

Patients with a low GADA titer are phenotypically more similar to those with DM type 2 diabetes. These differences are also observed in the metabolic syndrome, which is more frequent in type 2 diabetes than type 1 and LADA diabetes, and more prevalent in low-grade patients than patients with GADA high titer [18, 33, 35, 48].

Because the high GADA titer tends to be associated with multiple diabetes-associated auto-antibodies (DAA), it is not surprising that the NIRAD study found that among patients with adult diabetes, more DAA were detected plus these patients needed insulin treatment and had an earlier age [53].

However, there is sufficient overlap for these clinical parameters between patient groups to make it impossible to accurately distinguish autoimmune diabetes from adult type 2 diabetes in clinical characteristics only when considering individual patients [4, 54].

7. Complications

The frequency of ketoacidosis has not been documented in LADA, but it is assumed to be very low. Chronic vascular complications associated with type 1 diabetes and type 2 diabetes are also present in LADA [55].

7.1. Chronic complications

Few studies have addressed this issue. Cabrera-Rode et al. describe a lower incidence of retinopathy, nephropathy and peripheral vascular disease, in comparison with type 2 diabetics, although without significant differences given the small number of patients. Recently, a study in Korea,

with more than 300 patients (5.3% classified as LADA, 70% in insulin therapy), reveals that the risk of developing microvascular complications is similar to diabetic patients type 1 and 2 [55, 56].

7.2. Diabetes microvascular and macrovascular complications

It has been observed that the prevalence of microvascular complications in LADA is broadly similar to that observed in patients with type 2 diabetes, however in a small study conducted by Myhill et al., reported a lower risk of nephropathy [51, 55–57].

It is important to mention that patients with LADA generally have a more favorable cardiovascular risk profile than those with type 2 diabetes. However, to date, different studies have found no evidence of a lower risk of macrovascular disease in patients with DM type LADA [51, 55, 57].

The independent associations of hypertension, hyperlipidemia, obesity and hyperglycemia with macrovascular disease in diabetic patients are well established. Interestingly, hypertension, hyperlipidemia and obesity were less frequent in LADA than in type 2 diabetes [55], but the rates of macrovascular complications were similar. Possible explanations include differences in pathogenesis or treatment.

Given the autoimmune pathology, patients with LADA may have greater systemic inflammation, involved in vascular pathology [58].

It is a fact that patients with LADA can be treated suboptimally because they often start treatment with insulin later than clinically indicated, due to unrecognized insulin deficiency, detection of specific antibodies and a reluctance to change oral therapies to injections.

They are also likely to have a shorter duration of treatment with metformin, an oral agent associated with a lower rate of ischemic heart disease in the UKPDS [59].

Although these studies were small, there is no evidence to support a less aggressive treatment policy for cardiovascular risk factors in patients with LADA.

8. Therapeutic update for DM type LADA

Currently there is no established intervention for patients with LADA-type DM, despite the fact that they represent a considerable number of patients with diabetes. Considering that these patients present hyperglycemia, there is no doubt that they require specific therapy to control blood glucose levels.

Therefore, there is no doubt that the best therapeutic option in patients with LADA (while trials are expected to prevent the depletion of B cells) is to achieve good metabolic control and prevent chronic complications.

As a cornerstone in the treatment it is important to keep in mind that glycemic control is a strong risk factor for the development of cardiovascular disease in patients with LADA at a

higher level than in patients with type 2 diabetes and could be related to the lower prevalence of the metabolic syndrome in the first ones [60].

Different studies show that insulin therapy is the ideal treatment to achieve a better metabolic control in subjects with type LADA DM.

This procedure is useful to reduce the destruction of β -cells when there is a break in their activity, which determines a decrease in the expression of pancreatic antigens in β -cells [3, 61–68].

The application of an early insulin treatment in subjects with LADA who present a discrete insulin secretion is beneficial, and influences the preservation of pancreatic β -cell function. The early and correct identification of the LADA is necessary to define the adequate therapeutic behavior and improve the prognosis of these individuals.

In patients initially diagnosed as type 2 diabetic, a number of therapeutic options are possible that coincide with present available treatments of hyperglycemia.

It is at this moment where conjecturing or establishing a therapeutic goal is a challenge; because alternatives have been sought for the management of our patients, among which are mentioned.

8.1. Sulfonylureas

Beside diet, sulfonylureas are largely used in patients with type 2 diabetes. Sulfonylureas stimulate insulin secretion by promoting closure of the ATP-dependent potassium channels on pancreatic β -cells.

They are effective as blood glucose reducers, however, there is experimental evidence that they can increase the immune response, so they are considered imprudent, as they could accelerate the progression towards insulin dependence [3, 22].

In 1996, Kobayashi and 114 others observed that the administration of small doses of insulin was an effective treatment in individuals with recently diagnosed LADA, which is expressed by a high rate of negative conversion of the AHF and an increase in the levels of C-peptide. In serum, on the other hand, when a sulfonylurea (glibenclamide) is used alone in these diabetics, the persistence of the ICA is maintained and there is a progressive decrease in the levels of C-peptide in the serum.

8.2. Biguanides

Treatment with metformin has no direct action on the β cell, and it could be indicated in patients with LADA with clinical characteristics of metabolic syndrome or with obesity. This treatment allowed a good control of HbA1c and caused a drastic decrease in insulinemia [69]. In these cases, a combination therapy of metformin with insulin could also be considered.

Nevertheless, one potential problem associated with the use of metformin is the development of lactic acidosis in a patient at high risk of becoming insulin-dependent.

8.3. Glitazones

Theoretically they could have their value in the treatment, not only to improve the sensitivity of the insulin but also to exert an anti-inflammatory effect that would favor the preservation of the β cell mass [2, 70].

There is interesting evidence that glitazones increase insulin synthesis and the insulin content of islet cells as well as improve the secretory response of islets [71].

Zhou and others have demonstrated the efficacy of treatment with rosiglitazone in combination with insulin, which helps preserve the function of the cell compared to insulin alone in LADA [2, 70, 71].

Sitagliptin is a potent DPP-4 inhibitor which results in the delay of degradation of incretin hormones (glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP)), thereby improving beta-cell function and resulting in better glycemic control in patients with T2D.

Recent studies demonstrate that the use of sitagliptin in individuals with T1D improved overall the glycemic control and reduced insulin requirements without altering the amount of endogenous insulin production [72].

A prospective study of 1-year duration demonstrated maintenance of beta-cell function through the administration of sitagliptin in patients with recent-onset LADA [73]. A similar study proved that c-peptide secretion and glycemic control was improved by the use of another DPP-4 inhibitor, saxagliptin, versus placebo in LADA patients [74, 75]. All these accumulating evidences support the hypothesis that this may be a class effect; however, further studies are required.

8.4. Potential strategies for preventing b-cell destruction in LADA

A clinical trial showed that insulin therapy was the best treatment in this type of diabetic, and that the use of glibenclamide produced a persistence of the ICA (the ICA persisted in 100% of the subjects with LADA treated with glibenclamide + insulin), and that its exclusion decreased the presence of these antibodies (the ICA disappeared in 75% of the individuals with LADA treated only with insulin) [76, 77].

The use of glibenclamide or another sulphonylurea is not recommended in the treatment of these patients or their combination with insulin [65, 66], since it could contribute to the persistence of the autoimmune process and the probable progressive destruction of pancreatic cells.

Finally, a meta-analysis on pharmacological treatment [71], with a total of 8 publications (735 patients), concludes that:

- There are no benefits in the metabolic control when associating hypoglycemics with insulin therapy.
- Better metabolic control with insulin compared to sulfonylureas.
- Insulin dependence earlier in patients treated with sulfonylureas.
- Preservation of initial C peptide with early insulin therapy or rosiglitazone, which would position these therapies as the choice.

9. Conclusions

9.1. Summary: knowledge and uncertainty

Patients with DM type LADA are more likely to have lower C-peptide, associated with fewer signs of metabolic syndrome; higher levels of HbA1c, faster progress to insulin therapy. It is not yet clear how DM type LADA is associated with the loss of insulin secretion capacity.

9.2. Summary: knowledge and uncertainty

There are no clear clinical features that distinguish autoimmune diabetes from type 2 diabetes. However, there is a tendency for adult patients with GADA, even when they do not require insulin, being younger at the time of diagnosis and thinner with a greater tendency to progress to treatment with insulin. Within a cohort of positive GADA adult patients, the GADA titre and the number of LADA patients impact the clinical and biochemical differences of type 2 diabetes. The clinical phenotype should drive the management strategy.

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