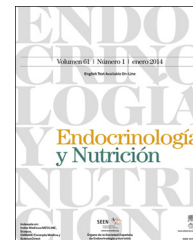




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EDITORIAL

Latent autoimmune diabetes in adults: are we paying sufficient attention?



Diabetes autoinmune latente del adulto: ¿estamos prestando suficiente atención?

Marta Hernández^a y Dídac Mauricio^{b,*}

^a Department of Endocrinology & Nutrition, University Hospital Arnau de Vilanova, Rovira Roure, 80, 25198 Lleida, Spain

^b Department of Endocrinology & Nutrition, University Hospital & Health Sciences Research Institute Germans Trias i Pujol, Carretera de Can Ruti, S/N, 08916 Badalona, Spain

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Heterogeneity has been recently highlighted as a relevant characteristic of diabetes mellitus¹. The current classification of diabetes mellitus includes two main types of the disease, i.e. type 1 and type 2 diabetes². The latter is by far the most prevalent one. Nevertheless, there is a significant proportion of subjects with autoimmune diabetes mellitus that are classified as type 2 diabetic patients. These patients are usually known to carry latent autoimmune diabetes in adults (LADA)³. As this subtype of diabetes is not accepted in the current classification of diabetes mellitus, subjects with LADA are classified as type 2 diabetes based on their clinical phenotypic characteristics. However, from the clinical point of view, it is really relevant to adequately characterize these diabetic patients¹.

The criteria traditionally accepted by clinicians for the diagnosis of LADA are based on previous consensus^{3,4}: presence of classical type 1 diabetes-associated circulating antibodies, age at diagnosis of at least 30 years, and treatment with non-insulin hypoglycaemic agents during the initial 6 months of the disease. However, the age and treatment requirements are clearly arbitrary in nature. For

example, subjects younger than 30 years of age may present with a slowly-progressive form of autoimmune diabetes that is not distinguishable from older patients with LADA⁴. Further, the decision on whether a patient is put on insulin is largely dependent on the treating clinician's judgment⁵. Therefore, only the presence of antibodies against islet antigens is an objective requirement. Although other antibodies may be also present in subjects with LADA, if any, antibodies to glutamic acid decarboxylase 65 (GAD) are the most frequently used in clinical practice to assess the presence or absence of islet autoimmunity in patients with type 2 diabetes^{3,4}.

The prevalence of LADA varies between 2-10% of patients with diabetes^{1,3,4}, and this frequency is partly dependent on different characteristics of the design of the research studies that have been published so far. Notwithstanding this subtype of diabetes is not accepted as a different entity in the current clinical classification of diabetes mellitus, the number of subjects affected by the disease is probably higher than the total number of patients with other diabetes types, e.g. type 1 diabetes. Thus, because of its prevalence LADA represents an important clinical issue that should be properly addressed. For the time being, it seems that there is a low awareness of this problem, especially among primary care physicians.

* Autor para correspondencia.

Correo electrónico: didacmauricio@gmail.com (D. Mauricio).

It is well-known that subjects with LADA have differential clinical, metabolic and genetic characteristics⁶⁻⁹. Fortunately, increasing scientific evidence is accumulating on different aspects of LADA; however, the number of studies are still insufficient, especially if we take into account that this condition was already recognized in the late 70s of the 20th Century. For instance, a PubMed search using the terms 'LADA' and 'diabetes' yielded only 359 references (accessed December 7th, 2014). Yet, a lot should be done to fully characterize this subset of patients in terms of the pathogenesis of LADA, its natural history, the therapeutical approach and its epidemiological features. Thus, it seems that the research interest on LADA is still insufficient.

Concerning their clinical profile, patients with LADA show differential features when compared with type 1 and type 2 diabetic patients^{6,8,9}. In relation to the frequency and the components of the metabolic syndrome, the characteristics of LADA are intermediate between type 1 and type 2 diabetes^{6,8,9}. Additionally, patients with LADA are younger, and have lower adiposity and c-peptide secretion than their antibody-negative type 2 diabetic counterparts^{8,9}. Thus, they usually have a more rapid progression to an insulin-deficient state that manifests frequently as proneness to ketosis and the earlier need of insulin treatment^{3,4}. Importantly, patients with LADA show poorer glycaemic control than type 2 diabetic patients despite the higher frequency of insulin treatment. Several pieces of evidence show that patients with high antibody titres have a low residual insulin secretory capacity and progress more rapidly to insulin dependence^{4,8,10}. All these features have obvious implications in the clinical setting as to the importance of an early identification of these subjects. This is a solid argument that speaks in favour of the clinical use of GAD antibody measurement in the routine diagnostic work-up of patients with newly-diagnosed diabetes.

There is insufficient data concerning the development of complications in patients with LADA. Recent data points to a similar risk of microvascular complications¹¹. The same study showed that the development of cardiovascular complications is not different from subjects with type 2 diabetes. This is noteworthy if we take into account that patients with LADA have a lower burden of associated cardiovascular risk factors. This indicates that in LADA subjects the cardiovascular risk treatment approach should be at least as intensive as in type 2 diabetic patients.

The time of insulin initiation in patients with LADA depends on the intensity of the autoimmune process, the natural history of the disease and especially on the bias of each treating physician^{3,9}. In the Action LADA study in Europe, we could demonstrate that the time to insulin initiation in these subjects is largely dependent on the local clinical judgment⁵. In those centres that included the use of GAD autoantibody assessment in the routine diagnostic work-up patients with LADA were treated much earlier with insulin⁵. The use of the GAD antibody determination is a widespread tool in many specialized centres, but this is not the case in the primary care setting where most subjects with LADA are seen at least during the initial stages of the disease process.

There is not enough evidence on which is the best approach to the treatment of hyperglycaemia in patients with LADA. Following the current treatment guidelines, the

vast majority of patients receive metformin as the initial hypoglycaemic agent of choice³. Pioglitazone, an agent that also targets insulin resistance, also proved to be useful in the treatment of LADA patients¹². As compared to sulphonylureas, intensive insulin treatment has been shown to better preserve residual insulin secretion in patients with LADA as add-on metformin or other oral non-sulphonylurea agents¹³. Current evidence points to the fact that insulin should preferably be introduced as a further step after metformin instead of a sulphonylurea drug¹⁴. Recently, sitagliptin was found to be effective in maintaining beta-cell function as add-on to insulin in a small trial¹⁵. However, much more evidence is needed concerning the adequate treatment approach in LADA. Thus, the available evidence points to the clinical utility of identifying these patients allowing for a better hypoglycaemic treatment choice.

In conclusion, the awareness on LADA as an important clinical and research issue among diabetologists and primary care physicians is low. We strongly believe that there is now sufficient evidence to recommend the routine clinical use of GAD autoantibodies in the diagnostic work-up of diabetes mellitus. The timely identification of LADA has clear implications in terms of treatment decisions and clinical follow-up of these patients. Also, much more research efforts should be devoted to the characterization of these patients. We believe that clinicians and researchers should pay much more attention to this condition.

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