Diabetologia (2023) 66:955–957
https://doi.org/10.1007/s00125-022-05858-4

LETTER

Determination of autoantibodies in type 2 diabetes: one simple way to improve classification

Johnny Ludvigsson[1]

Received: 12 October 2022 / Accepted: 28 November 2022 / Published online: 11 January 2023

Abstract

This letter aims to increase interest in better classification of type 2 diabetes. This can be done in a simple and cheap way via determination of autoantibodies. Autoantibody analysis can be used to detect the 7–12% of people with diabetes that is phenotypic of type 2 diabetes but is, in fact, latent autoimmune diabetes in adults (LADA), which may be regarded as a variant of type 1 diabetes. This may help to explain why some individuals with type 2 diabetes do not go into remission after reducing their weight, while others do, and why remission sometimes ends earlier than expected. Improved classification of diabetes may play an important role in determining adequate therapy.

Keywords GAD autoantibodies · LADA · Remission · Type 1 diabetes · Type 2 diabetes

Abbreviation

LADA Latent autoimmune diabetes in adults

To the Editor: At the EASD congress in September 2022 there was an interesting and important session called 'Remission of type 2 diabetes – fact or fiction?' [1]. Amy E. Rothberg from the University of Michigan, MI, USA, gave an overview of diabetes remission, including definition, diagnosis and monitoring, and then Michael Lean, from the University of Glasgow, UK, presented convincing data showing that a large proportion of individuals with type 2 diabetes can go into remission, mainly by reducing weight, as shown by the Diabetes Remission Clinical Trial (DiRECT) [2]. However, weight reduction is not enough to induce remission in all individuals with diabetes, and it has been questioned as to what factors predict remission [3]. This was the topic covered by Blandine Laferrère, from the Columbia University Irving Medical Center, NY, USA, who discussed why remission of type 2 diabetes may not last, and a number of possible and plausible reasons were presented. However, autoimmunity was not mentioned. When this was queried, both Michael Lean and Blandine Laferrère responded that GAD autoantibodies were not determined in the studied populations, and latent autoimmune diabetes in adults (LADA) does not seem to be discussed in the studies of predictors of remission [3].

Type 2 diabetes is a serious disease with worse prognosis and shorter survival than many malignant diseases. In many types of diseases, such as in oncology, it is self-evident to classify the disease as well as possible in order to be able to offer the best treatment, but in diabetes there is an incomprehensible lack of interest in correct classification. For a very long time, interest in classifying insulin-dependent diabetes was minimal, which provides one explanation for the slow progress of disease-modulating therapies [4]. In paediatric diabetes there has finally been a growing awareness of MODY and interest in classifying this disease has gradually increased [5, 6]. In line with this there has been an increasing awareness that interventions aimed at preservation of residual beta cell function might have a better chance of succeeding in paediatric diabetes if the different patient groups are considered [7]. For example, anti-CD3 treatment has been shown to be more effective in individuals with type 1 diabetes who are <18 years of age [8], while GAD-autoantigen treatment seems to be most efficacious in individuals with a specific HLA type (*HLA-DR3-DQ2*) [9, 10].

In contrast, most physicians treating type 2 diabetes, and even researchers, seem to be willing to spend thousands of US dollars per year on treatment, but not 10–20 US dollars on the

✉ Johnny Ludvigsson
Johnny.Ludvigsson@liu.se

[1] Division of Pediatrics, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

determination of autoantibodies to get a more correct diagnosis. Already in 1977 it was shown that 11% of individuals with phenotypic type 2 diabetes had autoantibodies (islet cell autoantibodies [ICA]) [11], but this information passed almost unnoticed. Later, it was shown that 7–12% of individuals with phenotypic type 2 diabetes actually had autoimmune signs and were defined as having LADA [12, 13]. LADA is a disease that has many similarities with type 1 diabetes, sometimes even being regarded as type 1 diabetes, with a more rapid decline of beta cell function than type 2 diabetes, leading to insulin dependency. In line with this, the UK Prospective Diabetes Study (UKPDS) showed that while only 14% of individuals with type 2 diabetes without autoantibodies needed insulin after 6 years of follow up, 84% of those with autoantibodies needed insulin therapy [12] and it has been shown that high GADA titres increase the risk of insulin requirement [14]. Similar to those with type 1 diabetes, many individuals with LADA have autoantibodies several years before diagnosis [15, 16] and they also have similar HLA types to those with type 1 diabetes [17].

It should be noted that in recent years there has been an increasing interest in diabetes classification in the scientific community, with several studies and reviews being conducted on this topic [18–20]. Moreover, nowadays LADA is included as a variant of type 1 diabetes in the ADA classification of diabetes [21]. Progress has been made both in better classifying the disease based on residual C-peptide levels [22] and in determining autoantibodies in a more precise way [23, 24], and the importance of HLA types has been studied more carefully [25]. However, even though it has become clearer that type 2 diabetes is not one single entity [26], and in spite of the recommendations given by the ADA, EASD and JDRF [21, 22], the determination of autoantibodies in individuals with type 2 diabetes has still not become generally accepted. It should be of clinical value to know whether an individual with phenotypic type 2 diabetes has LADA [27], and LADA may help to explain why some individuals with type 2 diabetes do not go into remission with lifestyle changes or why remission does not last. There are some studies on the aetiology and pathogenesis of LADA [27–29] but, surprisingly, few intervention trials have been conducted to find out how LADA should be treated [30], and only recently have efforts been made to dampen the immune process in individuals with LADA [31].

In conclusion, a better diagnosis of diabetes is needed both in type 1 diabetes [32] and type 2 diabetes to ensure optimal management and treatment of these conditions.

Authors' relationships and activities The author declares that there are no relationships or activities that might bias, or be perceived to bias, his work.

Contribution statement The author was the sole contributor to this paper.

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