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LETTER

Determination of autoantibodies in type 2 diabetes: one simple way to improve classification. Reply by Lean et al to Ludvigsson J [letter]

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Abbreviation
LADA Latent autoimmune diabetes in adults

To the Editor: Thank you for this opportunity to comment on the very constructive letter from J. Ludvigsson [1] on the *Diabetologia* Symposium 'Remission of type 2 diabetes – fact or fiction?' held at the EASD congress in September 2022 [2]. Ludvigsson [1] suggested that it might be useful to measure autoantibodies in people who are diagnosed on purely clinical grounds with type 2 diabetes, in order to identify the small number who actually have latent autoimmune diabetes in adults (LADA) but who do not yet show the clinical features of type 1 diabetes. This testing might avoid disappointment when these individuals lose weight and fail to achieve remission of their diabetes, and allow more appropriate treatment at an earlier stage.

Among the studies that have published prevalence data for diabetes-related antibodies in the supposed population with type 2 diabetes, uncertainty remains over exactly which tests at what titre are the most reliable to detect LADA in which population. Cross-sectional data on clinical populations might initially have inflated numbers, as these individuals do less well with diet and oral medications and are more likely to continue to attend clinics, but over a longer duration LADA will usually be reclassified as type 1 diabetes. Autoantibodies are associated with poorer glycaemic control, but prevalence rates vary. Among the more recent studies, 3–11% of Iranian patients with type 2 diabetes had one of three diabetes-related antibodies (GAD65, ZnT8A, IAA), which were associated with poorer diabetes control (but not necessarily LADA, or a failure to respond to weight loss) [3]. In Korean patients with type 2 diabetes, positive tests were present in 2–5%, but only three out of 39 of these patients progressed to needing insulin within 3 years [4]. The predictive power of autoantibodies may thus be rather weak. The US GRADE study found islet cell autoantibodies in 13.5% of 400 participants with type 2 diabetes of a mean duration of 4 years, but also T cell autoreactivity against islet proteins in over 40% [5]. There is much we do not understand about immunity and diabetes. To evaluate the potential of autoantibody tests for predicting an individual's future re-diagnosis as type 1 diabetes, analysis by receiver operating characteristics (ROC) is needed of autoantibodies at different titres at the time of diagnosis; however, to date, this does not appear to have been carried out.

As we begin to understand the disabling and life-shortening consequences of type 2 diabetes, especially in younger people, achieving a durable remission is rapidly becoming the primary management goal, at least in the eyes of patients and their families. It is very exciting that this has become a realistic prospect for many people, through weight loss without the need for surgery or drugs. We are just at the beginning of this new phase of global diabetes care and a great deal more research and development is needed, especially into ways to maintain weight loss, and specifically the loss of ectopic hepatic and pancreatic fat, which appears to drive the disease process.

Even a low prevalence of undiagnosed LADA within the enormous numbers with type 2 diabetes is a problem. The DiRECT trial, which opened this chapter of treatment through weight management as a priority, was conducted entirely in primary care, so mechanistic investigations were limited to the subset who underwent MRI and insulin kinetic studies. Although autoantibody testing was not conducted, we do not feel that this is a serious criticism of the trial. The mean duration of diabetes was 3.0 years at baseline. By this time, many or most cases of LADA would have been reclassified as type 1

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diabetes and therefore such patients would have been less likely to be recruited into the trial. Of the 149 participants randomised to the weight management intervention arm of DiRECT, most (>80%, comparable with the results of bariatric surgery) were in remission at both 1 and 2 years if they had lost >15 kg [6]. Most who failed to achieve remission did not lose enough weight, which for some may be >15 kg. We identified and interviewed six participants who had lost >10 kg at 12 months but whose HbA_{1c} level did not improve by at least 10 mmol/mol (1.13%). This is the subgroup that might include individuals with LADA, but none were positive for anti-GAD antibodies. What we did find, on more detailed interviews with these participants, was that some had concealed rather longer durations of diabetes than the maximum of 6 years required for recruitment: two had a past history of recurrent severe abdominal pains requiring hospitalisation, one was previously diagnosed with pancreatitis, one gave a history of previous alcoholism and one revealed a history of severe childhood malnutrition in Bosnia, during the war with Serbia. These insights cannot necessarily be translated more widely, but they do suggest that other factors may conspire to damage the pancreas and produce diabetes, which would be labelled as type 2 diabetes. The small numbers included in randomised trials such as DiRECT, which randomised 302 participants, are insufficient to quantify these categories; large observational studies are a better study design.

Given the capacity of substantial weight loss to eclipse the benefits of any drug treatment for type 2 diabetes, and the relationship between cardiovascular complications and duration of diabetes, we have argued for introducing meaningful weight loss, in an attempt to achieve remission, at the earliest possible stage after diagnosis. It is very possible that this will identify greater numbers who have LADA, who cannot achieve lasting remission. A diagnosis of LADA could already be advanced by observing an unexpected lack of blood glucose and HbA_{1c} improvement with weight loss.

We agree with Ludvigsson [1] that a more clinically relevant classification of diabetes is needed, and suggest that this should include the large category of overweight, or 'over-fat'-induced diabetes, that is, diabetes that is reversible into a non-diabetic state by substantial weight loss (perhaps, specifically, loss of ectopic fat in vital organs, although no current measurement method for liver or pancreatic fat is reliable enough for use in individuals). An inexpensive autoantibody test with high sensitivity and specificity for LADA would allow us to advise overweight patients with diabetes who test positive that their benefits from weight loss are less likely to include remission, and also allow the earlier introduction of insulin or potentially, in the future, immunomodulatory therapy. Applying the technologies developed during the COVID-19 pandemic might decrease the cost and difficulty of autoantibody testing. For the time being, we do need to be aware of other causes of pancreatic injury and make clear that remission is likely but not guaranteed when recommending major weight loss. It should also be remembered that sustained intentional weight loss will bring many other health benefits.

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