Time to Insulin Initiation Cannot Be Used in Defining Latent Autoimmune Diabetes in Adults

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OBJECTIVE — Latent autoimmune diabetes in adults is type 1 diabetes presenting as non–insulin dependent diabetes. One feature of the selection criteria is time independent of insulin treatment. We examine the validity of this criterion.

RESEARCH DESIGN AND METHODS — Patients were recruited in nine European centers, and clinicians reported on criteria for initiating insulin. All patients were tested for GAD antibodies (GADAs) in a central laboratory. We examined time to insulin treatment for GADA-positive patients in six participating centers.

RESULTS — There was intercenter variation in the criteria used to initiate insulin. Median time to insulin was 16.15 months (interqartile range 6.7–25.5) in centers with GADA testing compared with 45.6 months (29.5–61.8) in centers without routine GADA testing ($P < 0.002$).

CONCLUSION — Time to insulin should not be used to define patients with LADA because it is dependent on local clinical judgment and the use of laboratory tests for GADA.

Diabetes Care **31:439–441, 2008**

Latent autoimmune diabetes in adults (LADA) is a term applied to patients with apparent type 2 diabetes but who have pancreatic islet cell autoantibodies. LADA patients have features of type 1 diabetes, including genetic risk markers and reduced rates of the metabolic syndrome (1–3). However, the selection criteria used in LADA research varies greatly (4–13). While time from diagnosis to insulin treatment is not included in some definitions, others require freedom from insulin treatment for a variable period ranging from 3 to 12 months. In this study, we examine the validity of using time to insulin treatment as part of a definition of LADA.

RESEARCH DESIGN AND METHODS

— Nine centers recruited patients (aged 30–69 with primary diabetes, diagnosed within the past 5 years). GAD antibody (GADA) tests were performed in St. Bartholomew's Hospital and in the London Hospital using a Diabetes Antibody Standardization Programme (DASP) validated assay (in the 2005 DASP antibody workshop, the assay had a sensitivity 72% and specificity 95%). Values >70 World Health Organization units were regarded as positive. All patients were assayed in duplicate and included an in-house positive and negative control subject.

Clinicians in all nine centers completed a questionnaire reporting the criteria for initiating insulin in their center. One questionnaire per center reported the consensus opinion of the clinicians in that center. Center size varied between two and seven clinicians. The medical notes of the GAD-positive patients (522 of 5,812) were analyzed to examine time to insulin. Three centers were excluded from the analysis because these data were not in a format that could be analyzed. Cox regression/Kaplan-Meier analysis were used to examine survival in terms of time to insulin in GAD-positive patients in centers performing routine GADA testing compared with those not testing for GADA.

RESULTS

— The criteria for initiating insulin varied between centers. All used A1C and weight loss, eight of nine considered ketones, seven of nine considered complications, six of nine considered patient preference and/or other treatments, and five of nine used age and/or C-peptide. All the centers except two in the U.K. used GADA testing.

In centers where GADA testing was performed, the median time to insulin treatment for those testing GADA positive in the central laboratory was earlier compared with that for centers with no GAD testing (Fig. 1). For GAD testing centers (Odense, $n = 32$; Barcelona, $n = 67$; Vienna, $n = 35$; and Lyon, $n = 68$), the median time was 4.8 (interquartile range 0–12.8), 9.4 (1.1–17.8), 31 (3.5–59), and 29.4 (17.6–41) months, respectively, compared with that of non–GADA testing areas (Belfast, $n = 66$; London, $n = 50$) where median time (months) to insulin treatment was 38.1 (20.5–55.6) and 47 (29.5–64.8) months ($P <$

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Received for publication 9 July 2007 and accepted in revised form 10 December 2007.

Published ahead of print at http://care.diabetesjournals.org on 14 December 2007. DOI: 10.2337/dc07-1308.

*A full list of the members of the Action LADA Group can be found in an online appendix at http://dx.doi.org/10.2337/dc07-1308.

Abbreviations: GADA, GAD antibody; LADA, latent autoimmune diabetes.

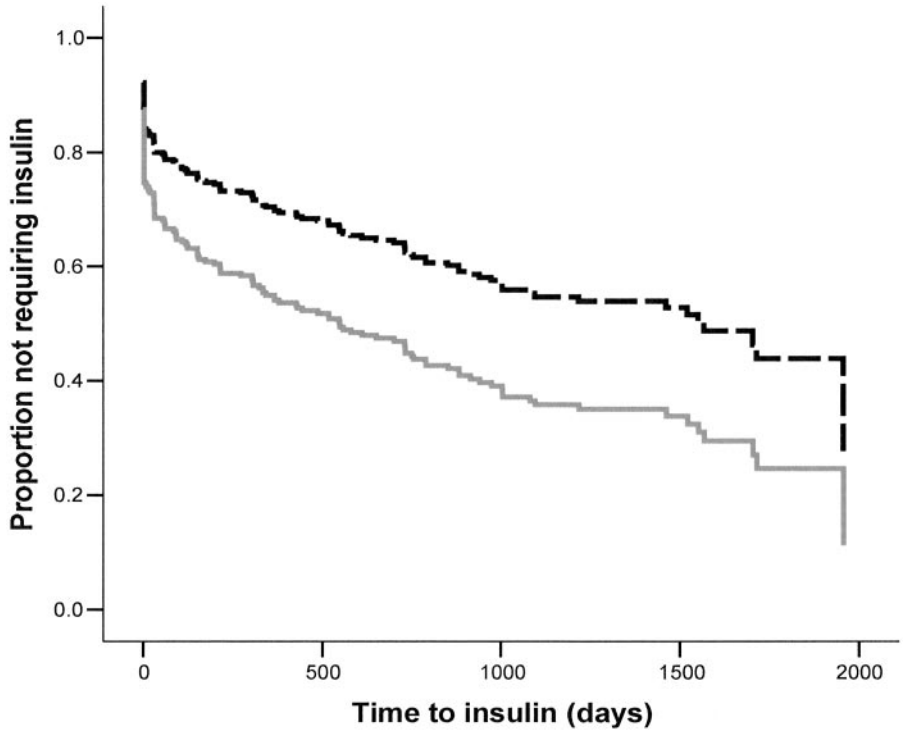

Figure 1—*Time to insulin for LADA patients (as identified by the central laboratory) in centers with GAD testing (solid line;* n *= 218) compared with that in centers without GAD testing (dotted line,* n *= 116) (hazard ratio 0.587 [95% CI 0.4–0.8],* P *= 0.02.*

0.0001). Therefore, if a definition of LADA stated that a person should be independent of insulin for 6 months (1,7,11), estimates of prevalence would be low in Denmark, Austria, France, and Spain but high in Belfast and London.

CONCLUSIONS — Time to insulin treatment is dependent on local clinical judgement and not on the disease process. Since that judgement is based on the presence of GADA, it follows that to define LADA on GADA positivity and the lack of initial need for insulin treatment is fraught with difficulties since the one often precludes the other.

The term latent, when applied to LADA, refers to the latency of autoimmunity, which is only revealed by testing for autoantibodies. The widespread clinical use of GADA testing on the continent but not in the U.K. means that the presence of a diabetes-associated autoantibody is no longer latent in many European centers. The level of GADA titer influences progression to insulin therapy. In the UK Prospective Diabetes Study 71 (14), the risk of requiring insulin in patients with GADA levels of 20–37.4 units was 20%, but GADA levels of 37.5–101 units give a 50–75% risk. These findings are supported by Buzzetti et al. (15), who found a bimodal distribution of GADA titers. It is important to note that there is large variation between laboratories with respect to GADA levels defining an abnormality, and caution should be exercised in using defined units; for our study, a cutoff of 70 World Health Organization units was used. Therefore, to accurately identify patients with LADA, perhaps a minimum level of GAD units should be selected within a definition (16).

Another feature of LADA not considered here is the presence of ketonuria. Ketonuria is a feature of classical type 1 diabetes but can also occur in type 2 diabetes. Some patients, from certain ethnic groups, can present with ketoacidosis but subsequently come off insulin treatment, and some may have GADA. In LADA patients, neither ketonuria nor ketoacidosis is present at diagnosis, and in this way LADA is distinct from ketosis prone diabetes, though the distinction may in some cases be more apparent than real (17). To separate LADA from classical type 1 diabetes, we may need to use some defined level of ketonuria or ketonaemia at diagnosis.

A further criteria used in the diagnosis of LADA is age. However, patients with GADA can present with non–insulin requiring diabetes in childhood (17,18). In our opinion, criteria to define LADA could include the presence of diabetes-associated autoantibodies, without ketoacidosis at diagnosis and irrespective of time independent of insulin treatment.

Acknowledgments— The projected was funded by the 5th Framework Programme of EU and DeveloGen. D. Mauricio was supported by a grant from Instituto Carlos III, Spain (Project FIS 061104)

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