Time to insulin initiation can not be used in defining Latent Autoimmune Diabetes in Adults [LADA].


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Running title: Time to insulin in the definition of LADA

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ABSTRACT

Objective: Latent Autoimmune Diabetes in Adults [LADA] 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.

Methods: Patients were recruited in 9 European centres and clinicians reported on criteria for initiating insulin. All patients were tested for glutamic acid decarboxylase autoantibodies (GADA) in a central laboratory. We examined time to insulin treatment for GADA positive patients in 6 participating centres.

Results: There was inter-centre variation in the criteria used to initiate insulin. Median time to insulin was 16.15 months (IQR: 6.7 – 25.5) in centres with GADA testing compared to 45.6 months (IQR: 29.5-61.8) in centres without routine GADA testing (p<0.002).

Conclusion: Time to insulin should not be used to define patients with LADA as it is dependent on local clinical judgment and the use of laboratory tests for GADA.
Latent Autoimmune Diabetes in Adults [LADA] is a term applied to patients with apparent type 2 diabetes but who have pancreatic islet cell auto-antibodies. 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]. Whilst 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.

**RESULTS**

The criteria for initiating insulin varied between centres. All used HbA1c and weight loss, 8 out of 9 considered ketones, 7/9 considered complications, 6/9 considered patient preference and/or other treatments and 5/9 used age and/or C-peptide. All the centres except two in the UK used GADA testing.

In centres where GADA testing was performed the median time to insulin treatment for those testing GADA+ in the central laboratory was earlier compared to centres with no GAD testing [Figure 1]. For GAD testing centres; Odense (n=32), Barcelona (n=67), Vienna (n=35) and Lyon (n=68)) the median time was 4.8 (interquartile range: IQR: 0-12.8), 9.4 (IQR: 1.1-17.8), 31 (IQR: 3.5-59) and 29.4 (IQR: 17.6-41) months respectively compared to non-GADA testing areas (Belfast (n=66) and London (n=50)) where median time (months) to insulin treatment was 38.1 (IQR: 20.5-55.6) and 47 (IQR: 29.5-64.8) months (p<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 auto-antibodies. The wide-spread clinical use of GADA testing on the continent but not in...
the UK means that the presence of a diabetes-associated autoantibody is no longer latent in many European centres. The level of GADA antibody titre influences progression to insulin therapy. In UKPDS 71 [14], the risk of requiring insulin in patients with GADA levels of 20 units – 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 GAD antibody titres. 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; in our hands a cut off of 70 WHO units was employed. 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 it is distinct from ketosis prone diabetes (KPD), 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 auto-antibodies, without ketoacidosis at diagnosis, and irrespective of time independent of insulin treatment.

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REFERENCES


Time to insulin for LADA patients (as identified by the central laboratory) in centres with GAD testing compared to those without GAD testing (p=0.002, hazard ratio 0.587 (95% CI: 0.4-0.8))

Figure 1: Time to insulin in Centres with GAD testing compared to non-GAD testing