

Latent autoimmune diabetes

in adults (LADA)

✉ David Leslie and Cristina Valeri

Diabetes is classified into two major types: Type 1 (insulin-dependent) diabetes, and Type 2 diabetes. However, it is apparent that there are some forms of the condition which do not fit comfortably into these categories. Indeed, there is one form of diabetes which appears to straddle the two major types. While it appears to affect adults with Type 2 diabetes, it shows many of the genetic, immune, and metabolic features of Type 1 diabetes, and carries a high risk of progression to insulin dependency. This form of the condition is known as 'latent autoimmune diabetes in adults' (LADA). It is found in about 10% of initially non-insulin-requiring people with diabetes, and is therefore probably more prevalent than Type 1 diabetes. A major European Union initiative (ACTIONLADA) plans to learn more about LADA.



The development of diabetes is projected to reach pandemic proportions over the next 10-20 years. International Diabetes Federation (IDF) data indicate that by the year 2025, the number of people affected will reach 333 million – 90% of these people will have Type 2 diabetes. In most Western societies,

the overall prevalence has reached 4-6%, and is as high as 10-12% among 60-70-year-old people. The annual health costs caused by diabetes and its complications account for around 6-12% of all health-care expenditure.

Type 2 diabetes plays a major role in contributing to mortality and

morbidity in most countries.

Furthermore, 25-50% of people with non-insulin-requiring diabetes at diagnosis subsequently progress to insulin treatment. In some cases, this progression results from inadequate therapy. However, in most people this is due to the progression of the disease process itself, with continuing and eventually severe loss of insulin-secretory capacity.

Self-antibodies

In one sub-group however, circulating antibodies to the person's own insulin-producing islet cells can be detected, the same self-antibodies as are found in Type 1 diabetes. Those people with initially non-insulin-requiring Type 2 diabetes plus diabetes-associated auto-(self)-antibodies are defined as having LADA, and are now known to be at high risk of progression to insulin dependency.^{1,2}

The prevalence of LADA has been estimated in a number of studies of both European and non-European populations. In Europe, LADA is defined as initially non-insulin requiring diabetes diagnosed in people aged 30-50 years with antibodies to GAD – **glutamic acid decarboxylase**. This accounts for about 10% of cases. In populations

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outside Europe the frequency varies from zero in Papua New Guinea to 16% in the Congo, and to 16% in a Chinese population. We know that while Type 1 diabetes is relatively uncommon, Type 2 diabetes is very common. Given that an appreciable proportion of non-insulin-requiring people with diabetes have GAD auto-antibodies, it follows that LADA is probably substantially more prevalent than classic Type 1 diabetes.¹

Autoimmune non-insulin-requiring diabetes represents a sizeable proportion of the adult population with the condition.

Genetics

People with LADA often have the tissue-typing (histocompatibility – HLA) genes and immune changes which are normally associated with Type 1 diabetes.³ Indeed, the HLA genes associated with LADA are also the same as those associated with Type 1 diabetes. The presence of GAD auto-antibodies, as noted above, partly defines LADA. But people with LADA can also have other diabetes-associated auto-antibodies, including islet cell auto-



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antibodies and so-called IA-2 auto-antibodies. Those with GAD and IA-2 auto-antibodies progress more rapidly to insulin dependency than those with GAD auto-antibodies alone.^{2,4}

Clinical features

These genetic and immune features of LADA are consistent with an immune-mediated disease process which resembles Type 1 diabetes. People with LADA show many of the other >>

Glutamic acid decarboxylase (GAD) is an enzyme which is found in all human cells. It catalyzes the degradation of glutamic acid, part of the cycle for the disposal of a waste (ammonia) in the body. The presence in the blood of self-antibodies to GAD is an early marker of the process that leads to the destruction of insulin-producing islet cells, and thus of Type 1 diabetes.

Sulfonylureas are one of several different classes of drug which are used in the treatment of Type 2 diabetes to lower the level of glucose in the blood.

clinical characteristics of Type 1 diabetes. For example, they tend not to be obese (unlike most people with Type 2 diabetes) and show a striking insulin secretory deficiency where this is measured.

About 80% of adults apparently with recently diagnosed Type 2 diabetes but with GAD auto-antibodies (ie LADA) progress to insulin requirement within 6 years. While the average interval between starting therapy with oral drugs to lower blood sugar (glucose) levels and progression to requiring insulin is approximately 4 years in people with LADA, it is as long as 8 years in people who do not have diabetes-associated auto-antibodies.⁴ At present, no treatment can stop this progression to insulin-requiring diabetes, but it is clearly of major public health importance since LADA is so prevalent.⁵

Since the disease course in LADA is distinct from classic Type 2 diabetes, management strategies may also have to differ.

Management of LADA

There is no established management strategy for people who are diagnosed with LADA.⁵ The potential value of identifying this group at high risk of progression to insulin dependence includes:

- ♦ the avoidance of using metformin

treatment – theoretical associated risks exist of metformin in people with diabetes who become insulin-dependent

- ♦ the early introduction of insulin therapy
- ♦ the application of intervention trials to arrest or reverse the destructive disease process.

For those people diagnosed with diabetes in whom the primary defect is the loss of insulin secretion, treatment should aim to restore islet insulin secretion. Therapy to prevent progression towards insulin dependency could include immunotherapy, insulin, or oral hypoglycaemic drugs.

The efficacy of **sulfonylureas** has not been formally tested, although they often appear to be effective at first in these relatively insulin-sensitive people. However, it is evident that sulfonylureas do not arrest progression to insulin dependency in people with LADA. Whether metformin is of benefit is unclear. The drug may be contraindicated in those with LADA as there is a theoretical risk of severe metabolic disturbance in people who progress to insulin dependency whilst taking metformin.

David Leslie and Cristina Valeri

David Leslie is Professor of Diabetes and Autoimmunity at Queen Mary College, University of London, UK, and Principle Investigator of the European Union Study ACTIONLADA.

Cristina Valeri is Research Fellow at Queen Mary College, University of London, UK.

References

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1998; 21 (suppl 1): S3-519.
2. Leslie RDG, Atkinson MA, Notkins AL. Autoantigens IA-2 and GAD in type 1 (insulin-dependent) diabetes. *Diabetologia* 1999; 42: 3-14.
3. Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A, Nissen M, et al. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. *Diabetes* 1999; 48: 150-7.
4. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, et al, for UK Prospective Diabetes Study (UKPDS) Group. UKPDS 25: autoantibodies to islet cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. *Lancet* 1997; 350: 1288-93.
5. Palmer J. Therapeutic importance of subset of type 2 diabetes? *Diabetes Care* 2000; 23: 574-575.