Chapter 39

Latent Autoimmune Diabetes in Adults

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ABSTRACT

Identification of latent autoimmune diabetes in adults (LADA) represents a major interest for many diabetologists, because its prevalence is relatively high and seems to be underestimated. Also, correct diagnosis of LADA patients allows an early and accurate therapeutic intervention. Latent autoimmune diabetes in adults is a disorder in which, despite the presence of islet antibodies at diagnosis of diabetes, the progression of autoimmune β-cell failure is slow. LADA patients are, therefore, not insulin requiring, at least during the first 6 months after diagnosis of diabetes. Among patients with phenotypic type 2 diabetes mellitus (T2DM), LADA occurs in 10% of individuals older than 35 years of age and in 25% below that age. Prospective studies of β-cell function show that LADA patients with multiple islet antibodies develop β-cell failure within 5 years, whereas those with only glutamic acid decarboxylase (GAD) antibodies (GADAs) or only islet cell antibodies (ICAs) mostly develop β-cell failure after 5 years. Even though it may take up to 12 years until β-cell failure occurs in some patients, impairments in the β-cell response to intravenous glucose and glucagon can be detected at diagnosis of diabetes. Consequently, LADA is not a latent disease; therefore, autoimmune diabetes in adults with slowly progressive β-cell failure might be a more adequate concept. In agreement with proved impaired β-cell function at diagnosis of diabetes, insulin is the treatment of choice. However, recent work has revealed genetic and immunological differences between LADA and type 1 diabetes mellitus (T1DM). The heterogeneity of LADA has also led to the proposal of criteria for its diagnosis by the Immunology of Diabetes Society. Although many workers have advocated a clinically oriented approach for screening of LADA, there are no universally accepted criteria for autoantibody testing in adult onset diabetes.

INTRODUCTION

Type 1 diabetes mellitus results from the destruction of the insulin-secreting islet cells by an immune-mediated process. This adverse immune response is induced and promoted by the interaction of genetic and environmental factors and is one of a group of autoimmune diseases that affect about 10% of the population in the developed world. Type 1 diabetes mellitus is used to be defined in terms of the absolute need for insulin therapy (insulin-dependent diabetes) or before that, the age at onset of the disease (juvenile onset diabetes). These defining features were then abandoned in favor of the term T1DM,1 when it became apparent that not everyone with autoimmune diabetes is either a juvenile or necessarily exhibits an absolute insulin requirement. Individuals diagnosed with autoimmune diabetes, i.e. diabetes associated with diabetes-associated autoantibodies, when they are adults may not initially require insulin treatment and have been classified as having LADA,2,3 latent because without testing for diabetes-associated autoantibodies it would not be possible to identify these patients as having autoimmune diabetes and adult because at that time it was suggested that this form of diabetes was not present in juveniles. This form of diabetes has also been called slowly progressing insulin-dependent diabetes4 or T1DM5 and officially, LADA is classified as T1DM by the World Health Organization. The frequency of LADA is underestimated.5 LADA is defined by three features including: (1) adult age at diagnosis, (2) the presence of diabetes-associated autoantibodies and (3) delay from diagnosis in the need for insulin therapy to manage hyperglycemia. Difficulties with the performance of islet cell and insulin autoantibody assays precluded them from being used routinely in defining LADA. Because insulinoma-associated antigen-2 (IA-2) autoantibodies are usually found with GAD autoantibodies but rarely in LADA, this condition is broadly defined by the presence of GAD autoantibodies. However, GAD autoantibodies are also found in T1DM, so it follows that using them in the definition of LADA lacks disease specificity.6

EPIDEMIOLOGY OF LADA

The epidemiology of LADA like T1DM is influenced by geography, genetic susceptibility, environmental factors, gender and age at diagnosis. In Northern Europe and North America about 5–10% of newly diagnosed non-insulin requiring diabetes patients have LADA, according to the mode of ascertainment, the sourced population, the age of the patient (frequency is higher in younger age groups) and the definition of the disease.7,8 The percentage of non-insulin requiring diabetic patients with LADA will depend on the initial metabolic state, i.e. in A Diabetes Outcome Progression Trial (ADOPT) study non-insulin requiring diabetes patients were selected because they were not receiving tablets or insulin to lower their blood glucose and the proportion of them with GAD autoantibodies was low (4.7% in north America) and the mean age at diagnosis was 56 years.7 LADA patients tend to have poor metabolic control at diagnosis, so selecting non-insulin requiring diabetes patients with mildly altered metabolism will limit the numbers of LADA cases ascertained. Furthermore, since progression to insulin treatment is more rapid in LADA patients than those without GAD autoantibodies, it follows that the longer the period of ascertainment from diagnosis, the less likely they are to be LADA.

LADA AND GENETIC FACTORS

Type 1 diabetes is genetically determined as shown by family, twin and genetic studies and the disease is more frequent in siblings of diabetic patients [e.g. in the United Kingdom (UK) 6% by the age of 30 years] than in the general population (0.4% by the age of 30 years),9 with the concordance rate being higher in identical than non-identical twins.10
The most important genes implicated in the genetic susceptibility to T1DM are those of the histocompatibility human leukocyte antigens (HLA) region of chromosome 6. HLA alleles associated with diabetes susceptibility, include HLA DR3, DQB1*0201 and DR4, DQB1*0302, while others are associated with disease protection, e.g. HLA DR2, DQB1*0602, DRB1*0403. Type 1 diabetic children show an increased prevalence of the heterozygous alleles HLA DR3, DQB1*0201 and DR4, DQB1*0302, the proportion of heterozygotes declining with age at diagnosis. Children with the diabetes-protective HLA DR2, DQB1*0602 are unlikely to develop diabetes while in adult-onset diabetes the same alleles carry less protection. If LADA is a form of autoimmune diabetes similar to T1DM then we would expect that it too showed a similar HLA association. Whilst the genetics of T1DM is well characterized, there is only one substantial report about LADA. LADA was associated with increased frequencies of HLA DR3 (28%), DR4 (27%) and DR3/4 (22%) and as with T1DM, these risk allele frequencies declined with age at diagnosis. As with adult-onset T1DM, HLA DR2 appears to play little role in disease protection. So the evidence is that the genetic susceptibility, as mediated by HLA risk alleles, is no different between adult-onset T1DM and LADA, a conclusion supported for HLA and MICAS.1 respectively by two further studies, albeit using small numbers of patients.

**LADA AND IMMUNE CHANGE**

Latent autoimmune diabetes in adults and T1DM are associated with the presence of serum autoantibodies, which include autoantibodies to GAD, IA-2 and ICAs but not insulin which are predominantly found only in children with T1DM. Further, these autoantibodies are similar in that they tend to be isotype restricted [immunoglobulin (Ig) G1 predominantly] and polyclonal. The presence of IA-2 autoantibodies in both LADA and T1DM is associated with HLA DR4 and the frequency declines with the age of onset of diabetes in both forms of autoimmune diabetes. In the prediabetic period, IA-2 autoantibodies are associated with a more rapid progression to diagnosis and insulin dependency whilst in LADA the same autoantibodies are associated with a more rapid progression to insulin therapy. Cellular immune changes are not so clearly defined in autoimmune diabetes, though we believe that they are the principal pathogenetic mediator.

**LADA AND METABOLIC CHANGES**

Latent autoimmune diabetes in adults may be associated with decreased insulin sensitivity, but the prediabetic individuals may also show reduced insulin sensitivity and in those who are most insulin resistant, the rate of progression to frank diabetes is most rapid. One manifestation of insulin resistance is the metabolic syndrome characterized by associated abdominal obesity, hypertension, dyslipidemia and altered glucose tolerance. Patients with LADA have a reduced frequency of metabolic syndrome compared to other GAD autoantibody negative cases of non-insulin requiring diabetes. However, the frequency of the metabolic syndrome remains appreciable in LADA patients being detected in 77% of cases in one study and in 42% of cases in another, ascertainment biases dictating the differences in the syndrome frequency. Thus, in metabolic terms the distinction between T2DM and LADA is not always clinically apparent and since therapy is currently directed toward improving the metabolic status of the patients, the management of both conditions need not differ. There is no established management strategy for people diagnosed with LADA and for this reason, the European Union has funded a major initiative to study the characteristics of LADA and report on how to treat it. A recent report of UK Prospective Diabetes Study (UKPDS) failed to identify a clear difference in outcome in LADA patients treated conventionally with sulphonylureas or diet. A study in China raised the possibility that metformin could be beneficial in the metabolic control of hyperglycemia in T2DM, it remains probable that the combination of metformin with insulin could be beneficial in LADA. Indeed, there is at least one study in which adolescents with T1DM also benefited from the addition of metformin to their insulin regime. The optimal insulin regime for LADA patients whether initially or once insulin dependence has ensued remains unclear. Given the broad loss of insulin secretory capacity it might be argued that the early introduction of long-acting insulin could be beneficial. Alternatively the loss of rapid insulin release in LADA suggests that replacement with fast-acting insulin would be of value.

An alternative strategy could involve modulation of the disease process in an effort to limit the progression to insulin dependence. Given the immune features of LADA it remains possible that immunomodulation might prove valuable. A preliminary study of LADA patients with GAD autoantibodies found that a tolerance induction plan using alum formulated whole GAD had a significant effect on the C-peptide response consistent with modulation of the aggressive process by the regime. Such pioneering studies offer a novel approach to maintain islet cell function and open a new area in diabetes management.
interventions for this group. Studies on sulfonylureas have suggested that stimulation of insulin release might be associated with increased autoantigen expression, which could be deleterious in LADA because it might accentuate the ongoing autoimmune process. These results suggest that therapy with sulfonylureas in LADA would actually expedite the progression toward β-cells depletion and the necessity of insulin initiation, and several studies have confirmed this hypothesis.30

Two randomized controlled trials conducted in Japan compared sulfonylureas (glibenclamide) with insulin treatment in LADA patients. The first study included ICA-positive subjects and reported that two of five patients treated with sulfonylureas required insulin treatment within 24 months due to failure of treatment with secondary oral hypoglycemic agents. At the end of study (30 months), the sulfonylureas group had a worsening of metabolic control and showed a progressive deterioration of β-cell function [during the study period, serum stimulated C-peptide immunoreactivity (CPR) (after an oral glucose tolerance test) decreased with almost 40% from baseline]. The second study (the Tokyo study, which included GADA-positive subjects) reported that the group receiving sulfonylurea therapy progressed in greater proportion to the insulin-dependent stage during 57 months of follow-up. Several studies conducted in LADA patients have shown that insulin treatment is associated with better outcome in terms of metabolic control, insulin secretion, and autoimmune responses against pancreatic β-cells. In two studies, patients receiving insulin monotherapy had improved markers of autoimmunity (six of eight patients in one and four of five patients in the other became ICA negative).31 Glycemic control was significantly improved with insulin monotherapy (after exclusion of sulfonylureas) in the 12-month Cuban study, as evaluated by fasting blood glucose (FBG). The rationale for early insulin intervention though would be improving glycemc control while protecting β-cell function. The exact mechanisms for the apparent beneficial effects of insulin treatment reported in several studies are not yet fully understood, but it is thought that administration of exogenous insulin would allow β-cell rest, at least in parts by downregulating the β-cell metabolism and/or by releasing them from the hyperglycemic stress. The consequence is a decrease in the severity of insulitis and in the number of infiltrative antigen-presenting cells in and around the pancreatic islets. A number of experiments suggested that active β-cells, producing high amounts of insulin, are more susceptible to immune-mediated killing and are also associated with higher antigen expression. Thus, a reduction of β-cell function and of inflammatory processes in the islets would lead to decreased antigen expression on β-cells and subsequent reduction of T-cell responses. Other possible explanations would be that exposure to exogenous insulin would actually promote T-cell helper type 2 (Th2) immunity in humans, as indicated by an increase in IgG1 and IgG4-IA (antibodies to insulin) (although no secondary spreading to other autoantigens) and induce an activation of insulin-specific regulatory T-cells (Tregs).32 Also, as insulin is a major autoantigen in diabetes (mainly in type 1A), it is thought that immunization with exogenous insulin would determine immune modulation possibly by tolerance induction or “bystander” suppression of autoreactive T-cells through the local release of regulatory cytokines.33

Because at least some patients with LADA have features of metabolic syndrome and a certain degree of insulin resistance, they might benefit from therapy with an insulin-sensitizing drug that improves the peripheral action of insulin and thus indirectly protects β-cells from continuous hyperstimulation of its release. The specific role of metformin in LADA is not known, since there are no studies evaluating it in this specific group of patients. In addition, a potential risk associated with its use is occurrence of lactic acidosis in patients that progress toward insulin dependency. There are a few studies evaluating glucagon-like peptide (GLP)-1 (and exendin-4) in subjects with T1DM and they showed reduction of fasting hyperglycemia and glycemic excursions after a meal, accompanied by inhibition of abnormal rises of blood levels of glucagon. Additionally, in islet transplant recipients, exendin-4 has stimulated insulin secretion and demonstrated an ability to reduce exogenous insulin requirements. Current clinical trials test the hypothesis that its use at the time of islet transplantation might be of help in preserving islet mass. Although not evaluated yet in LADA, these agents have a potential therapeutic value in such a setting.34

Since LADA is an autoimmune disease caused by failure to maintain tolerance to autoantigens, targeting them through administration of autoantigen in a tolerogenic regimen should provide an effective means of controlling the autoimmune process by inducing tolerance through deviation of the T-cell helper type 1 (Th1) phenotype of the antigen-reactive cells toward a Th2 phenotype. The beneficial effect of an immune intervention in LADA in protecting residual β-cell function may be hampered by several factors such as age at diagnosis, metabolic control and extension of β-cell destruction. The latter is influenced by HLA genotypes. Whether different HLA genotypes associated with LADA may affect the outcome in terms of β-cell function is still unknown, but recent data seem to indicate that patients possessing a moderate- or low-risk HLA genotype, as is the case in LADA, have a higher residual β-cell function. It may speculate that LADA patients with such genotypes might benefit more in terms of β-cell protection after immune intervention. The antigens that have been used so far as tolerogens in LADA have included the following: insulin, GAD, heat shock protein (HSP) and their constituent peptides.34

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Diagnostic features of type 2 diabetes (T2D), latent autoimmune diabetes in adults (LADA) and type 1 diabetes (T1D)</th>
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</thead>
<tbody>
<tr>
<td>Features</td>
<td>Type 2 diabetes mellitus (T2DM)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Present</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>Absent</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td>Present</td>
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<tr>
<td>Microvascular complications</td>
<td>Present</td>
</tr>
<tr>
<td>Islet cell autoantibodies</td>
<td>Negative</td>
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<tr>
<td>Treatment with insulin</td>
<td>Required at diagnosis</td>
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childhood T1DM, it will be interesting to determine whether these treatments are similarly effective in LADA.

CONCLUSION

In conclusion, it can be revealed that the LADA should be approached as a clinical entity different from T1DM and T2DM although it shows overlapping features of both types. Also, a standardized nomenclature of LADA should be propagated in view of its heterogeneous manifestation. This is especially important with regard to the subtypes of LADA based on GADA levels. Early instigation of insulin therapy is a must in LADA T1DM (high GADA levels) to delay the rapid islet cell failure. For those individuals with low GADA levels, classified as LADA T2DM, the phenotype is very similar to T2DM and the treatment strategy appears to be ambiguous. Should insulin be started in combination with oral hypoglycemics to delay the progression of β-cell destruction and also tackle the insulin resistance? Also, with the recent developments in immunomodulatory therapies (antiCD3 monoclonal antibodies) in T1DM with potential differences in antigenicity and genetic background in LADA, one cannot simply assume that these therapies would be equally effective in LADA as in T1DM.

REFERENCES