Abstract
Latent autoimmune diabetes in adulthood (LADA) is a slowly progressive form of autoimmune diabetes mellitus characterized by mature age at diagnosis, the presence of pancreatic autoantibodies, and the lack of an insulin requirement at diagnosis. Patients with LADA present with more preserved pancreatic beta-cell function than those with classic type 1 diabetes mellitus (T1DM), but they usually experience a rapid and progressive loss of beta-cell function. Unlike in individuals with type 2 diabetes mellitus (T2DM), LADA tends to become rapidly unresponsive to intervention with oral medications and parenteral agents such as incretin mimetics. Individuals with LADA should be identified and treated intensively so that any remaining beta-cell function may be preserved and to lessen the risk for developing long-term complications.

Key Words
Autoimmune diabetes, GAD-65 autoantibodies, metabolic memory

Introduction
“Doctor, what do you think I have, type 1 or type 2 diabetes?” The answer to this important question is not as simple as one might think. Unfortunately, the medications used to treat the different types of diabetes are not mutually exclusive. In patients with type 1 diabetes mellitus (T1DM), hyperglycemia is not likely to be controlled by oral agents, and parenteral agents can cause those with type 2 diabetes mellitus (T2DM) to experience weight gain and symptoms of hypoglycemia. Central to the treatment of diabetes is understanding the system used to classify diabetes. The American Diabetes Association (ADA) no longer recommends that diabetes be classified based on the treatment of hyperglycemia, but rather by the underlying pathophysiology of the disease state (1). As of 1997, the old nomenclature classifications of non–insulin-dependent
diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM) were replaced with the classifications of impaired fasting glucose (IFG), impaired glucose tolerance, (IGT), T1DM, T2DM, and 56 additional specific types of diabetes (e.g., acute and chronic pancreatitis, cystic fibrosis, surgical resection of the pancreas, leprechaunism, and hemochromatosis) (1).

The medical treatment of diabetes is becoming increasingly focused on the specific forms of diabetes and on aspects of the diabetic state, such as insulin resistance, insulin deficiency, and increased hepatic glucose output. By correctly categorizing the etiology of the state of chronic hyperglycemia, therapies that may help to correct the underlying metabolic defects can be introduced.

In the case of T1DM, early diagnosis and treatment can prolong the body’s ability to produce insulin endogenously and lower the risk of microvascular complications (2). Similarly, early recognition of IGT or IFG, collectively referred to as prediabetes, may delay or avert the development of T2DM (3). The ADA and the American Association of Clinical Endocrinologists recommend targeting glycemic levels in patients with diabetes to as close to normal (<6%) as possible while maintaining patient safety (3a,3b). Successful treatment of diabetes can be enhanced by making certain that the underlying disease mechanisms are being addressed both from a pharmacologic and a behavioral perspective.

**Differentiating Autoimmune Diabetes from Diabetes Caused by Insulin Resistance**

T1DM is caused by an absolute deficiency in insulin production. Thought to arise from autoimmune destruction of pancreatic ß-cells in genetically susceptible individuals, T1DM constitutes 5-10% of diabetes cases in the United States. (3c) Although more commonly diagnosed in children, T1DM can occur in any age group. Because patients with T1DM eventually develop an absolute deficiency of insulin, exogenous insulin replacement is the mainstay of treatment. Progression to absolute deficiency is variable, tending to be more rapid in children and slower in adults (4).
T2DM is a heterogeneous group of conditions that constitute 90-95% of diabetes cases in the United States. (3c) Both insulin resistance and relative insulin deficiency are the hallmarks of T2DM. Insulin resistance precedes insulin deficiency in most patients. Programmed beta-cell death (apoptosis) occurs through a number of nonautoimmune mechanisms that lead to a reduction in both beta-cell mass and insulin-secreting capacity. Because insulin deficiency in T2DM is relative rather than absolute, diabetic ketoacidosis occurs less frequently in T2DM than in T1DM.

Treatment for T2DM varies considerably from that for T1DM (5). The majority of patients with T2DM are clinically obese. Exercise and weight loss can lead to improvements in the disease state and even clinical remission in some individuals. Pharmacotherapies directed toward improving insulin sensitivity and increasing ß-cell insulin production are useful in T2DM but not in T1DM. Unlike T1DM, there is a strong genetic predisposition to developing T2DM.

Latent autoimmune diabetes in adulthood (LADA) is a less recognized and underdiagnosed subtype of T1DM. Although LADA can occur in any age group, including children and adolescents (5), the clinical manifestations of the disorder begin insidiously, progress slowly, and are not normally detected until middle adulthood. The element common to both T1DM and LADA is the presence of autoantibodies against pancreatic islet cell antigens.

Patients with LADA typically test positive for only a single autoantibody (Table) (6a), whereas individuals with T1DM often have ≥2 autoantibodies detectable at the time of diagnosis. (8) In addition, the autoantibody profiles appear to differ between LADA and T1DM. Compared with T1DM, patients with LADA are positive more frequently for autoantibodies to the 85-kDa isoform of glutamic acid decarboxylase (GAD-65 antibody) and/or islet cell antibodies (ICA) but not for antibodies against the tyrosine phosphataselike protein (islet cell antigen 2 [IA-2] antibody) or insulin autoantibodies (IAA) (Table).
Prevalence of LADA

Approximately 10% to 30% of adults with T2DM test positive for autoantibodies, depending on the age and ethnicity of the study group (7). In the United Kingdom Prospective Diabetes Study (UKPDS 25), (8) GAD-65 antibodies were positive in 10% of the cohort of >5000 patients with T2DM, whereas ICA were positive in 6% of the patients. The prevalence of these antibodies was also found to be higher in younger patients. GAD-65 was positive in 34% and ICA in 21% of patients aged 25 to 34 years.

A recently published Italian study evaluated 881 consecutively recruited T2DM patients with a mean disease duration of 8 years for the presence of autoimmune markers (8b). Of the patients evaluated, 7.1% had ≥1 autoantibody, the most prevalent of which was GAD-65 (6.6%). Two or more autoantibodies were found in only 2% of patients. IA-2 and IAA were found most often in association with patients also positive for GAD-65. Autoantibody positivity was associated most often with female gender (1.5 x higher frequency than men) and higher glycosylated hemoglobin (A1c) levels, as well as lower body mass index (BMI) and waist/hip ratios.

Pathogenesis of LADA

Patients with LADA have an autoimmune process similar to that found with T1DM. (10) Why, then, do patients with LADA experience a slower progression of beta-cell destruction and tend to become insulin dependent at a later stage than patients with T1DM?

The hyperglycemia associated with T1DM is thought to be the end-stage result of an interaction between susceptibility genes and an abnormal immune response toward pancreatic beta-cells following exposure to an environmental stimulus. Patients who possess HLA-DR4-DQ8 antigens are at high risk for developing an aggressive and rapid autoimmune-driven course of beta-cell destruction leading to T1DM (9). Other alleles, such as HLA-DQB1*0602 and HLA-DQA1*0102 when present, appear to protect an individual from developing diabetes. Patients with LADA have these protective genetic components, yet they still develop a slowly progressive form of T1DM, which suggests
that, although these alleles are somewhat protective, an individual who receives multiple environmental “hits” may, over time, develop an inflammatory response within their beta-cells. Eventually, the beta-cells become so inflamed by these repetitive environmental insults that they begin to succumb to autoimmune destruction (10, 11).

Thus, the underlying immune-mediated destruction of beta-cells in patients with LADA leads to insulin dependency more rapidly than in T2DM, but the more attenuated genetic and immune factors associated with LADA lead to an older age at onset and a slower progression to insulin dependency than in T1DM. (11)

**Screening and Testing for LADA**

Despite the frequency of LADA, there are no universal recommendations regarding testing for islet autoantibodies in adult-onset diabetes. A recently published study identified a subset of patients with T2DM who had characteristics placing them at a higher statistical risk of having LADA (12). In this prospective validation study, patients having ≥2 of the 5 distinguishing clinical features of LADA (ie, a LADA risk score ≥2 at diagnosis) had a 90% sensitivity and a 71% specificity for detecting LADA via autoantibody testing. Furthermore, a LADA risk score of ≤1 was a highly reliable method for excluding LADA (negative predictive value of 99%). In addition, because most patients with LADA are overweight or obese, if only those patients with a BMI <25 kg/m² were screened for the presence of GAD autoantibodies, >70% of patients with this autoimmune disorder would not be diagnosed. Although the positive predictive value of this screening assessment may be considered low (only 21%), the negative predictive value is extremely high (99%). Therefore, most patients with T2DM can be identified and screened efficiently for LADA using this noninvasive and free clinical assessment tool.

**Treatment of Patients with LADA**

Because patients with LADA lose the ability to produce endogenous insulin within the first few years after diagnosis, exogenous insulin should be initiated expeditiously (13). As beta-cell function begins to decline and oral agents loose their ability to maintain targeted fasting and postabsorptive glycemic levels, patients are at higher risk for
experiencing oxidative stress (14). Oxidative stress plays a major role in the pathogenesis of long-term diabetic complications (15).

The Diabetes Control and Complications Trial (DCCT/Epidemiology of Diabetes Intervention and Complications (EDIC) study demonstrated the benefits that can be achieved with early intensification of diabetes management (17–21). EDIC followed patients who had been enrolled in and completed the DCCT as they returned to the care of their community-based physicians. During the 4-year DCCT observational study, nearly all participants were intensively managed. Armed with evidence-based knowledge regarding the benefits of diabetes management intensification, the patients who received conventional treatment in the DCCT reduced their mean A1C from 9.1% to 8.2% during the EDIC study (20); however, the mean A1C level rose from 7.2% to 8.0% in the cohort of patients who had been intensively managed in the DCCT, primarily because the level of personalized care available within the community setting was substantially less than that received during the original study. (20)

Despite the gradual rise in A1C levels during the EDIC study, patients who were intensively managed in the DCCT had a 57% reduction in first occurrence of stroke, myocardial infarction, or death from cardiovascular disease compared with patients who had received conventional treatment (18). Progression of retinopathy from the DCCT closeout examination to the eighth year of the EDIC follow-up was reduced by 63% in the original intensively managed cohort. (21) Finally, newly diagnosed cases of albuminuria, a clinical marker of nephropathy, were reduced by 84% in the DCCT intensively managed cohort. (20) EDIC has taught us that patients who are able to attain an A1C of 6.5% to 7% and maintain this level of glycemic control for ≥4 years will develop metabolic memory (21). In theory, once metabolic memory has been established, any future deterioration in glycemic control would be far less likely to be associated with significant long-term diabetes-related complications.

Two Japanese studies have also addressed the possibility of an effect of insulin therapy on the course of autoimmune diabetes. A pilot study performed in 10 patients diagnosed
with LADA determined that patients randomized to insulin therapy (n=5) were significantly less likely to experience significant, progressive beta-cell failure as compared to patients (n=5) randomized to treatment with sulfonylureas for 6 to 36 months (22).

In a subsequent randomized, multicenter study of 54 non–insulin-requiring patients positive for the GAD-65 autoantibody were randomized to receive either insulin or a sulfonylurea (23). In this study, insulin therapy again was found to prevent progressive beta-cell failure, specifically in patients with preserved beta-cell function and high GAD-65 autoantibody titers.

**Summary**

Patients who present with clinical features of type 2 diabetes may actually have LADA. Autoantibody screening, particularly for the GAD-65 autoantibody, should be performed in patients having ≥2 of the following clinical characteristics: (1) age younger than 50 years; (2) acute symptoms of hyperglycemia; (3) a BMI <25 kg/m²; (4) a personal history of autoimmune disorders; (5) a family history of autoimmune disease. Although treatment guidelines for LADA have not been published, theoretical advantages do exist to intensively manage these patients with insulin therapy. The goals for early intervention with exogenous insulin therapy are to preserve any remaining endogenous pancreatic beta-cell function and to minimize long-term complications via the induction of metabolic memory.
<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>T2DM</th>
<th>LADA</th>
<th>T1DM</th>
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<tbody>
<tr>
<td>Ketoacidosis</td>
<td>Usually absent</td>
<td>Absent at diagnosis, but may be present when patient becomes severely insulinopenic</td>
<td>Will develop rapidly unless patient receives insulin replacement therapy</td>
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<td>Cardiovascular complications</td>
<td>Risk 2–4 times higher than in individuals who are euglycemic</td>
<td>Same risk as patients with T2DM</td>
<td>Increased risk of cardiovascular morbidity and mortality related to strokes, acute coronary events, and coronary revascularizations. High incidence rates compared with euglycemic individuals, especially in women.</td>
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<tr>
<td>Risk of microvascular complications (retinopathy, nephropathy, neuropathy)</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
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<tr>
<td>Autoantibodies</td>
<td>Negative</td>
<td>Glutamic acid decarboxylase (GAD-65) autoantibodies Islet cell antibodies (ICA)</td>
<td>Glutamic acid decarboxylase (GAD-65) autoantibodies Islet cell antigen 2 (IA2) Insulin autoantibodies (IAA)</td>
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<td>Insulin requirements</td>
<td>Traditionally added later in treatment when remaining beta-cell mass and function no longer support acceptable glycemic control achieved by oral agents or incretin mimetics.</td>
<td>Should be initiated as soon as the patient develops autoantibodies.</td>
<td>From the time of diagnosis.</td>
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NOTE: Unlike in T1DM, in which patients typically test positive for all 3 antibodies, patients with LADA typically test positive only for the GAD-65 autoantibody.
References


