The nomenclature for diabetes mellitus has changed during the past 40 years. In the 1970s, age was the main characteristic by which diabetes was classified. This classification was based on the concept that type 1 diabetes mellitus (T1DM) affected children with insulin insufficiency but no insulin resistance, whereas type 2 diabetes mellitus (T2DM) affected adults with insulin resistance but no initial insulin insufficiency.
Table 1
Baseline Characteristics of Patient

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient’s Value</th>
<th>Reference Range/Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HgA1c, %</td>
<td>5.8</td>
<td>4.0-5.9</td>
</tr>
<tr>
<td>TSH/Free T4</td>
<td>1.28/1.54</td>
<td>0.50-4.55/0.58-1.64</td>
</tr>
</tbody>
</table>

Lipid Profile, mg/dL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient’s Value</th>
<th>Reference Range/Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>226</td>
<td>125-200</td>
</tr>
<tr>
<td>LDL-C</td>
<td>114</td>
<td>&lt;100</td>
</tr>
<tr>
<td>HDL-C</td>
<td>101</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>53</td>
<td>40-184</td>
</tr>
</tbody>
</table>

Abbreviations: HgA1c, glycosolated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid stimulating hormone; T4, thyroxine.

Table 2
Results of Patient’s Endocrine and Autoimmune Laboratory Tests

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient’s Value</th>
<th>Reference Range/Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-peptide, ng/mL</td>
<td>1.2</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Autoantibodies, U/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAD</td>
<td>85.6</td>
<td>0-1.5</td>
</tr>
<tr>
<td>Insulin</td>
<td>2.8</td>
<td>0-5.0</td>
</tr>
<tr>
<td>Islet cell</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: GAD, glutamic acid decarboxylase.

It later became clear that the incidence of T1DM in patients older than 30 years was greater than previously thought. New findings led to the classification of diabetes mellitus by the need to take insulin. Years ago, T1DM was classified as insulin-dependent diabetes mellitus, and T2DM was classified as noninsulin-dependent diabetes mellitus. However, this classification was not accurate since most people with T2DM eventually have complete β-cell exhaustion and will then need to take insulin.

Currently, the classification of diabetes is based on pathogenesis. T1DM is characterized by the destruction of insulin-secreting β cells of the pancreas, resulting in severely deficient insulin production or no insulin production at all. If patients with diabetes have measurable autoantibodies, they have type 1A diabetes mellitus. If they have no measurable autoantibodies, they are classified as having type 1B diabetes mellitus.

T2DM is characterized by insulin resistance, abnormal hepatic glucose production and a relative deficiency in insulin secretion. Approximately 10% of people with newly diagnosed T2DM have autoantibodies directed against pancreatic β cells, which will eventually result in absolute insulin insufficiency. This reclassification of diabetes led to the designation of latent autoimmune diabetes of adulthood (LADA) as a separate clinical entity. The term was introduced by Paul Zimmet, MD, PhD, in 1995 to describe cases of adult-onset T1DM in which patients do not have an immediate need for insulin. This condition has also been coined type 1.5 diabetes mellitus or a slowly progressive T1DM. The case presentation reported in this article provides a typical example of a patient with LADA.

Case presentation

A woman aged 43 years visited her physician to discuss her diabetes mellitus. She had been diagnosed with T2DM three years previously, when she experienced frequent urination and unintentional weight loss. She was found to have a urinary tract infection and was treated for this condition. However, her glucose level at that time was 300 mg per deciliter. As a result, she was told that she had diabetes mellitus as well.

After beginning to take glyburide, the patient initially responded well. However, within a couple of months she found that very high glucose levels developed anytime she ate food containing carbohydrates. Her glucose logs revealed that her morning glucose level was usually normal to slightly high (90-130 mg/dL), but the glucose level shot up to the 200-300 mg/dL range after eating carbohydrate-containing meals. It would then take her the rest of the day to get her glucose levels back within an acceptable range. To help keep her glucose levels under control, she started to eat a diet very low in carbohydrates.

The patient was not overweight, with a body mass index of 22. In addition, she had normal results on her physical examination.

The patient’s medical history consisted of hypothyroidism (resulting from Hashimoto’s thyroiditis), which was diagnosed about 10 years previously. She was currently taking levothyroxine (88 mcg daily) and was euthyroid (ie, had normal thyroid gland function) for the past five years. She had no family history of diabetes mellitus. She smoked 1.5 packs of cigarettes daily. She did not drink alcohol or use recreational drugs. She did not get regular exercise. She had not lost weight recently. The patient had no health complaints other than the previously mentioned glucose problems.

The patient underwent laboratory tests two weeks prior to her physician’s appointment. Results of these tests are shown in Table 1.

In light of her history and her laboratory test results, the possibility...
Furthermore, she had a personal history of autoimmune disease (Hashimoto’s thyroiditis). Autoimmune diseases tend to “travel together.” Thus, this patient was at increased risk of other autoimmune diseases, such as T1DM.

Another clue that this individual may not have had T2DM was the fact that she did not have diabetic dyslipidemia. Diabetic dyslipidemia—present in people with insulin resistance, metabolic syndrome and T2DM—is characterized by low levels of high-density lipoprotein cholesterol (HDL-C) and high levels of triglycerides. By contrast, this patient had high levels of HDL-C and normal levels of triglycerides—even though she had hyperglycemia. Behaviors that could have raised her HDL-C level were regular exercise and drinking alcohol. She did neither of these.

### Case discussion

The case reported in this article is unique in a number of ways. Most people with T2DM have a family history of that condition or of obesity. However, this patient had a family history of neither condition—nor was she herself obese, unlike the great majority of people with T2DM. Furthermore, she had a personal history of autoimmune disease (Hashimoto’s thyroiditis). Autoimmune diseases tend to “travel together.” Thus, this patient was at increased risk of other autoimmune diseases, such as T1DM.

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### Latent autoimmune diabetes of adulthood

Latent autoimmune diabetes of adulthood is believed to be a form of T1DM resulting from an autoimmune process. Although LADA does not have a single definition, it is most often characterized as a condition in which an adult has autoimmune diabetes mellitus that is not immediately insulin dependent. As previously mentioned, this condition is sometimes referred to as type 1.5 diabetes mellitus or slowly progressive T1DM.

Most people with T1DM have one or more of the following autoantibodies: tyrosine phosphatase-like insulinoma-associated protein 2 (IA-2); tyrosine phosphatase-like IA-2β; glutamic acid decarboxylase (GAD); islet cell cytoplasmic; islet cell complement-fixing; and insulin antibodies. The autoantibody titer most commonly used to identify LADA in patients is the GAD autoantibody. The presence of GAD autoantibodies has been associated with rapid decline of β-cell function, resulting in absolute insulin deficiency.

People with T2DM do not exhibit these GAD antibodies and typically can maintain their β-cell function for more than 12 years after diagnosis. The antibodies seen in patients with type 1A diabetes mellitus and LADA are believed to be only markers of the disease—and not necessarily pathogenic. Fewer than half of patients with LADA have positive results in titers of T1DM autoantibodies—raising the question of whether LADA is a unique disease with a separate pathogenesis from T1DM or merely a variant of T1DM.

A patient with LADA typically has the phenotype of a person with T1DM. However, the patient may appear to be more like a person with T2DM at clinical presentation, because β-cell destruction in LADA is typically slower and more subtle than in T1DM. Unlike most people with T1DM, individuals with LADA do not immediately lose all β-cell function.

T2DM is most often diagnosed based on results of screening laboratory tests. Symptoms of T2DM are usually nonspecific in nature, such as fatigue or increased rate of infections. Many people first discover that they have T2DM when a complication develops. For example, 30% of people who suffer

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**Table 3**

Comparison of Mean Characteristics of Type 1A Diabetes Mellitus, Latent Autoimmune Diabetes of Adulthood, and Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1DM</th>
<th>LADA</th>
<th>T2DM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, y</td>
<td>44.5</td>
<td>59.0</td>
<td>63.0</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>C-peptide, ng/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>0.46</td>
<td>0.53</td>
<td>1.23</td>
<td>.02†</td>
</tr>
<tr>
<td>1-10 years postdiagnosis</td>
<td>0.03</td>
<td>0.4</td>
<td>0.68</td>
<td>.03*</td>
</tr>
<tr>
<td>BMI</td>
<td>23.1</td>
<td>23.5</td>
<td>29.1</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>1.2</td>
<td>1.4</td>
<td>1.1</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>1.4</td>
<td>1.2</td>
<td>6.0</td>
<td>.001†</td>
</tr>
</tbody>
</table>

* LADA vs T1DM
† LADA vs T2DM

**Abbreviations:** BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LADA, latent autoimmune diabetes of adulthood; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

from an acute myocardial infarction discover that they have diabetes at the time of the heart attack. Only those individuals with decompensated T2DM and extreme hyperglycemia will have weight loss, polydipsia and polyuria at presentation. This collection of symptoms represents absolute insulin deficiency and is the hallmark of T1DM.

Clinical criteria for LADA are loosely defined. The key features are: adult onset, lack of initial need for insulin therapy, low C-peptide levels and the presence of antibodies directed against pancreatic islet cells. However, there is no clear age that defines typical age of onset of LADA. Most clinical studies use a mean age of onset of 30 years, but some studies avoid defining a typical age of onset. In addition, the presence of autoantibodies is not specific to T1DM/LADA, because these autoantibodies are also present in other autoimmune disorders.

Nora Hosszufalusi et al reported significant differences between mean characteristics of patients with T1DM, LADA and T2DM. These differences are highlighted in Table 3.

**Treatment of patients with LADA**

Individuals with LADA should ultimately be treated like those with T1DM—using insulin as the primary therapy. Studies have demonstrated that residual β-cell function in patients with LADA is extended with the use of insulin therapy and shortened with the use of insulin secretagogues. Evidence also suggests that exogenous insulin administration slows the loss of β cells by reducing glucose toxicity—providing an important reason for early diagnosis and treatment.

**Who to screen?**

Spiros Fourlanos et al suggested a set of clinical criteria for determining which patients should get tested for anti-GAD autoantibody titers as a way of screening for LADA. These criteria include diagnosis before age 50 years, acute symptoms of insulin deficiency (ie, “the polys”), body mass index less than 25, and a personal or family history of autoimmune disease. If a patient meets two or more of these criteria, it is recommended that he or she be tested for anti-GAD autoantibodies.

**Take home messages**

It is important to distinguish LADA from T1DM and T2DM. Because LADA may be present in as many as 10% of people with presumed T2DM, a clinician is likely to encounter cases of LADA. Most patients with LADA do not receive the correct diagnosis at initial presentation. Typically, a patient with LADA presents with an episode of the “polys” that is responsive to intermediate treatment options, such as administration of fluids and correction of hyperglycemia with insulin or oral agents. Such responsiveness, however, is believed to be temporary and can follow a widely variable course.

People with LADA are more likely than people with T2DM to have complications at the time of diagnosis, and they may also have microvascular complications earlier in the course of the disease. In addition, people with LADA have an autoimmune disease process and are more likely than people with T2DM to have other autoimmune conditions.

If a patient was initially diagnosed with T2DM, he or she may be rediagnosed as having LADA when the condition deteriorates to diabetic ketoacidosis. However, such patients are sometimes considered to have “brittle type 2” diabetes mellitus, in which case they may never be properly diagnosed.
Final notes
In summary, the clinician should consider LADA when a patient with
presumed diabetes mellitus has any of the following clinical characteristics:

- age >30 years
- lack of family history of T2DM
- personal or immediate family history of autoimmune disorders
- body mass index <25
- lipid panel results not showing diabetic dyslipidemia
- period during which patient had “the polys” and weight loss

References