

# Case Study: Celiac Disease: An Important Comorbidity Associated With Type 1 Diabetes

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## PRESENTATION

A.M. is a 33-year-old white woman with a history of type 1 diabetes diagnosed at 19 years and complicated by microalbuminuria. She was treated with multiple insulin injections until 2003, when she started on insulin pump therapy. Her hemoglobin A<sub>1c</sub> (A1C) levels have ranged between 7.0 and 7.5% during the past 3 years. She has history of anxiety disorder and tobacco use.

During a clinic visit, A.M. complained of a slow, steady weight loss of 20 lb during the past year. She admitted to rare postprandial bloating and some early satiety, but no diarrhea. She reported no significant changes in her diet or exercise and denied any changes in her bowel movements, nausea, fever, night sweating, skin hyperpigmentation, lightheadedness, or dizziness after standing.

Her physical examination revealed a thin, well-nourished young woman. She had no goiter, no ophthalmopathy, no hyperhidrosis, and no tremor. Laboratory tests, including hematocrit and hemoglobin, creatinine, potassium, and sodium measurement were all normal. She had no evidence of iron deficiency anemia and a normal complete blood count. Her liver function tests were normal, as were levels of vitamin B<sub>12</sub>, folate, and calcium. Her thyroid function tests revealed a morning cortisol of 10.3 mg/dl, thyroid-stimulating hormone (TSH) level of < 0.01 mU/ml (normal range: 0.6–3.3), total triiodothyronine (TT3) level of 1.9 nmol/l (normal range: 1.0–1.7), and thyroxine (T4) level of 9.2 µg/dl (normal range: 5.5–11).

The patient was started on 50 mg propylthiouracil (PTU) three times daily. After 4 months of therapy, her TSH level was 0.32 mU/ml, TT3 was 1.6 nmol/l, and TT4 was 8.6 µg/dl. She has continued on PTU.

A.M. was still concerned about her difficulties gaining weight. She reported a good appetite. Because of her persistent weight loss despite improvement in thyroid function studies, immunoglobulin A (IgA) antiendomysial antibodies were checked, with a titer of 1:1280. She underwent a small bowel biopsy, which confirmed the diagnosis of celiac sprue, also known as gluten-associated enteropathy.

The patient was started on a gluten-free diet, which resulted in less abdominal bloating and a 3-lb weight gain during the next 3 months. Her A1C decreased from 7.2 to 6.3% with dietary modifications. Her thyroid function studies remained stable on 50 mg of PTU three times daily, with a TSH level of 0.41 mU/ml, TT3 of 1.4 nmol/l, and T4 of 8.2 µg/dl.

## QUESTIONS

1. What are common clinical features of celiac disease?
2. What is the relationship between celiac disease, type 1 diabetes, and Graves' disease?
3. What are the screening recommendations for celiac disease and thyroid autoimmunity in patients with type 1 diabetes?

## COMMENTARY

Celiac disease, also referred to as gluten-sensitive enteropathy, is characterized by

immune-mediated damage to the jejunal mucosa, which is triggered by gluten, a protein complex found in wheat, rye, and barley. The diagnosis is based on classic findings on small bowel biopsy of villous atrophy and crypt hyperplasia. With maintenance of a gluten-free diet, multiple studies have documented reversal of the mucosal changes. There has been conflicting data on whether the duration of exposure to gluten in those not following a gluten-free diet or with undiagnosed celiac disease correlates with a higher risk for subsequent autoimmune diseases, such as type 1 diabetes and thyroid disease.<sup>1</sup>

Many cases of celiac disease are asymptomatic, or, as with this case, have features that are only recognized retrospectively. Classic symptoms of celiac disease generally include steatorrhea, flatulence, and the consequences of malabsorption, such as growth failure in children, weight loss, severe iron deficiency anemia, neurological disorders from vitamin B deficiencies, and osteopenia from vitamin D and calcium deficiencies. Although our patient had unexplained weight loss, she had no other complaints.

Because of the availability of serological screening, more cases of mild celiac disease are now being diagnosed. In one study estimating the prevalence of celiac disease in adults with type 1 diabetes, patients who were screened and found to have positive antibodies and positive findings on small bowel biopsy typically had no symptoms.<sup>2</sup> Patients often have nonspecific complaints, such as fatigue. They may have borderline

iron deficiency, elevations in aminotransferases, or no symptoms at all. Once patients are placed on a gluten-free diet, they report objective and subjective improvement in well-being regardless of whether they recognized symptoms before diagnosis.

Celiac disease has a prevalence of 0.1–0.02% in the general Western population. The prevalence rates of celiac disease in children with type 1 diabetes are estimated to be between 1.7 and 12%. Screening studies have shown the prevalence among adults with type 1 diabetes to be similar, between 1.3 and 6.4%, which is 10 times the prevalence in the general population.

The likely explanation for the frequent association between celiac disease and type 1 diabetes is the shared genetic susceptibility of the HLA DR3-DR2 haplotype. A well-defined cohort of celiac patients without diabetes was studied prospectively to assess the prevalence of coexisting thyroid disease and positive thyroid autoantibodies. Overall, 14% of the celiac patients had thyroid disease: 10.3% were hypothyroid and 3.7% hyperthyroid, both of which were significantly more than expected. Patients with type 1 diabetes and known celiac disease appear to have a higher prevalence of autoimmune thyroid disease. However, patients with type 1 diabetes and autoimmune thyroid disease do not appear to have a higher incidence of celiac disease compared to patients with type 1 diabetes alone.<sup>3</sup>

Autoimmune thyroid disorders are the most common immunological disorders in patients with type 1 diabetes. Cross-sectional studies have reported a prevalence of hypothyroidism in 12–24% of females and ~6% of males. Hyperthyroidism has been reported in 1–2% of patients with diabetes. Positive thyroid peroxidase (TPO) antibodies have been reported in 80% of patients with type 1 diabetes and elevated TSH levels and in 10–20% in patients with normal TSH levels. In a prospective longitudinal study of 58 patients participat-

ing in the Diabetes Control and Complications Trial (DCCT), 33% of patients developed thyroid dysfunction, all with hypothyroidism. In this study, patients with TPO antibodies were 17.91 times more likely to develop hypothyroidism than patients who were TPO negative.<sup>4</sup> The majority of participants were diagnosed with type 1 diabetes ~13 years before being diagnosed with thyroid disease at an average age of 33 years.

The American College of Physicians guidelines state that screening in women <50 years of age and in men is not warranted because of the low frequency of thyroid dysfunction. However, in patients with type 1 diabetes in whom thyroid dysfunction can present a decade or more after the diabetes diagnosis, it appears reasonable to recommend TSH screening in the long term. Despite the association between positive TPO antibodies and subsequent development of thyroid dysfunction, the annual measurement of TSH is considered the preferred screening test. If TPO antibodies had been used as the single diagnostic tool in the DCCT follow-up study, 28% of cases of subclinical hypothyroidism would have been missed.

Screening for celiac disease is initiated with serological evaluation using IgA anti-tissue transglutaminase and IgA endomysial antibodies (EMA), with documentation of normal IgA levels. These tests have a higher sensitivity and specificity than previously used anti-gliadin antibody tests. Patients should be maintained on a gluten-containing diet during serological testing.

Of children with type 1 diabetes, 16% have been shown to have positive antibodies, and of these, 6.2% had definitive biopsy changes consistent for celiac disease despite being asymptomatic. Barera et al. reported in an Italian pediatric population that 41.2% of patients with celiac disease and type 1 diabetes experienced seroconversion of EMA and villous atrophy on biopsy during a 6-year follow-up period. All new cases of celiac disease developed within

4 years of the onset of diabetes.<sup>5</sup> Thus, the recommendation for children with type 1 diabetes is to screen at the time of diabetes diagnosis and annually for several years thereafter.

The 2008 American Diabetes Association clinical practice recommendations state that antibody screening should be performed in patients with type 1 diabetes with suggestive symptomatology, such as iron deficiency anemia, weight loss, or unexplained fatigue. Patients with type 1 diabetes who become symptomatic for celiac disease should be tested by measuring tissue transglutaminase or anti-endomysial antibodies, with documentation of normal serum IgA levels. Patients with positive antibodies should be referred to a gastroenterologist for confirmation and to a dietitian for instruction on a gluten-free diet.<sup>6</sup>

Adherence to a gluten-free diet has been shown to significantly reduce the risk of small bowel lymphoma and nutritional deficiencies of iron, vitamin B<sub>12</sub>, zinc, calcium, magnesium, and fat-soluble vitamins in patients with celiac disease.<sup>7</sup> However, only a handful of small prospective studies have addressed the issue of the glycemic benefits of a gluten-free diet. Short-term prospective studies in children with type 1 diabetes and celiac disease have demonstrated no significant change in A1C when started on a gluten-free diet, despite improvements in growth. Observational data have suggested a reduction in hypoglycemic events in children after initiation of a gluten-free diet.<sup>8</sup> One prospective clinical trial of 22 adults with type 1 diabetes and celiac disease demonstrated no significant differences in A1C, insulin dosage, BMI, or hypoglycemic episodes between those who were following a strict gluten-free diet and those who were not.<sup>9</sup>

## CLINICAL PEARLS

- Individuals with type 1 diabetes and celiac disease often do not have overt gastrointestinal complaints. They

often present with mild constitutional symptoms of weight loss and fatigue with the development of celiac disease. Because of the high prevalence and minimal symptomatology of celiac disease in patients with type 1 diabetes, health care providers should have a low threshold for screening for IgA anti-tissue transglutaminase and IgA endomysial antibodies.

- Evidence of celiac disease is present in a high percentage of children at the time of diagnosis of type 1 diabetes, and these individuals typically develop celiac disease within 4 years of their diabetes diagnosis. In contrast, autoimmune thyroid disease typically follows the diagnosis of diabetes by an average of 10 years. Thus, screening for celiac disease should be considered early in young individuals with diabetes, whereas screening for thyroid disease should be considered for decades after diabetes diagnosis.

- Dietary management of celiac disease improves symptomatology, increases weight, and decreases the risk of osteopenia and malignant lymphoma without any significant change in glycemic control.

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