WebLog Journal of Endocrinology and Diabetes

Case Presentation
Published: 15 Jan, 2026

Celiac Disease in Patients with Type 1 Diabetes and Negative Serology: About Two Cases and Literature Review

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Abstract

Introduction: Celiac disease (CD) is an autoimmune enteropathy triggered by gluten ingestion in genetically predisposed individuals. It is frequently associated with type 1 diabetes (T1D), with a prevalence significantly higher than that observed in the general population. Diagnosis usually relies on positivity of specific autoantibodies and histological confirmation. However, seronegative forms can be observed, notably in T1D patients, making diagnosis more complex.

Observation: We report two cases of type 1 diabetic patients in whom the diagnosis of celiac disease was confirmed based on histological arguments despite negative serology.

Discussion: The negativity of specific CD antibodies does not exclude the diagnosis, particularly in T1D patients presenting suggestive signs such as anemia, unexplained glycemic disorders, or signs of malabsorption. Duodenojejunal biopsy remains the reference examination in these situations.

Conclusion: In patients with T1D, celiac disease can evolve silently or atypically, with negative serology. Increased clinical vigilance and early use of digestive histology are essential to prevent metabolic and nutritional complications.

Keywords: Celiac Disease; Type 1 Diabetes; Negative Serology; Duodenal Biopsy; Malabsorption

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Received Date: *29 Dec 2025*
Accepted Date: *13 Jan 2026*
Published Date: *15 Jan 2026*

Citation:
K. Gorgi, M. Chaouche. Celiac Disease in Patients with Type 1 Diabetes and Negative Serology: About Two Cases and Literature Review. WebLog J Endocrinol Diabetes. wjed.2026.a1504. https://doi.org/10.5281/zenodo.18368161

Introduction

Celiac disease (CD) is a chronic inflammatory autoimmune enteropathy induced by gluten exposure occurring in genetically predisposed subjects carrying HLA-DQ2 and/or HLA-DQ8 haplotypes [1, 2]. It is characterized by involvement of the small intestine mucosa, causing variable malabsorption.

The association between CD and type 1 diabetes (T1D) is well established, as these two pathologies share a common autoimmune background. The prevalence of CD in T1D patients is estimated between 4 and 10%, nearly 20 times higher than that of the general population [3, 4]. In most cases, CD associated with T1D is asymptomatic or pauci-symptomatic, justifying systematic screening.

Diagnosis traditionally relies on detection of anti-tissue transglutaminase (anti-tTG IgA) and anti-endomysium antibodies, followed by histological confirmation. However, seronegative forms of CD exist and pose a real diagnostic challenge [5].

Here, we report two cases of T1D patients presenting histologically confirmed celiac disease despite negative serology.

Observations

Case 1

A 17-year-old female patient, followed in dermatology for vitiligo, referred to endocrinology for management of recently diagnosed type 1 diabetes. Initial workup revealed severe hypochromic microcytic anemia (Hb: 7.8 g/dL, MCV: 65 fL, MCHC: 26 g/dL), without associated digestive symptoms.

Digestive autoimmune workup, including anti-tissue transglutaminase IgA (anti-tTG) and anti-gliadin antibodies (AGA), was negative. Given unexplained anemia and autoimmune background, upper digestive endoscopy with jejunal biopsies was performed. Histological examination favored celiac disease. The patient was referred to gastroenterology and started on a gluten-free diet with

favorable clinical evolution.

Case 2

A 20-year-old female patient with type 1 diabetes for 8 years and irregular follow-up was hospitalized for marked glycemic imbalance, associated with repeated episodes of unexplained severe hypoglycemia. Biological investigations showed signs of malabsorption.

Despite absence of gastrointestinal symptoms, celiac disease was suspected. Celiac serology (IgA anti-tTG) was negative. Upper digestive fibroscopy with duodenal biopsies (D3) revealed total villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes, corresponding to Marsh IIIc classification.

Implementation of a strict gluten-free diet led to marked improvement in glycemic control and reduction in hypoglycemia episodes.

Discussion

The association between celiac disease and type 1 diabetes is frequent and well documented [3, 6]. This coexistence is explained by common autoimmune mechanisms involving shared genetic susceptibility, notably HLA-DQ2 and HLA-DQ8 haplotypes predisposing to both diseases [1, 2]. The prevalence of CD in T1D patients is significantly higher than in the general population, justifying systematic screening [4, 6].

Although serological tests have excellent sensitivity and specificity, seronegative forms of CD are described, representing up to 5–10% of cases [5, 7]. These forms are more frequent in patients with other autoimmune diseases, notably T1D [8]. Seronegativity complicates diagnosis and may delay management.

In our two cases, absence of specific antibodies could have delayed diagnosis. However, the presence of indirect signs such as severe iron-deficiency anemia or unexplained glycemic disorders justified performing duodenojejunal biopsy, which remains the diagnostic gold standard [9]. Histology showed villous atrophy, crypt hyperplasia, and intraepithelial lymphocytic infiltration characteristic of CD.

Late diagnosis of CD in T1D patients exposes them to increased risk of complications, including severe hypoglycemia, nutritional deficiencies (iron, vitamins, calcium), osteoporosis, and increased risk of intestinal lymphoma and adenocarcinoma [10, 11]. These complications worsen morbidity and mortality in these patients.

These elements highlight the importance of increased clinical vigilance, especially in T1D patients with unexplained biological abnormalities or unusual glycemic imbalance, even in the absence of specific antibodies. Early use of digestive histology is therefore essential. Systematic and repeated screening is recommended to limit morbidity associated with this association [6, 9].

Conclusion

Celiac disease associated with type 1 diabetes may evolve silently and manifest as seronegative forms. In any T1D patient presenting unexplained biological abnormalities or unusual glycemic imbalance, CD should be suspected, even in the absence of specific antibodies. Duodenojejunal biopsy remains an essential diagnostic tool. Systematic and repeated screening is recommended to reduce associated morbidity and mortality.

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