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Celiac Disease and Metabolic Bone Disease

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Abstract

Celiac disease is a common autoimmune gastrointestinal disorder affecting multiple organs, precipitated in genetically vulnerable persons by the ingestion of gluten. Gluten is poorly digested and is presented to the intestinal mucosa as a large polypeptide. Binding to human leukocyte antigen-DQ2 and human leukocyte antigen-DQ8 molecules on antigen-presenting cells stimulates cellular and humeral immune reactions. Although common serological tests are available to diagnose celiac disease, the diagnosis of celiac disease is often delayed or missed because of lack of recognition as the disease presentation in adults is highly variable and may be asymptomatic. Celiac disease is a common secondary cause of metabolic bone disease and delayed treatment with gluten-free diet affects bone mineral density and fracture risk, so it is crucial to diagnose and treat celiac disease promptly. In this article, we will review recent studies of celiac disease in adults and provide practical, easily accessible information for busy clinicians.

Key Words: Antigliadin antibody; bone mineral density; dual-energy X-ray absorptiometry; endomysial antibody; tissue transglutaminase.

Definition, Epidemiology, and Nonceliac Gluten Sensitivity

Celiac disease, also known as celiac sprue, is a common autoimmune gastrointestinal disorder that is precipitated, in genetically disposed persons, by the ingestion of gluten, the major protein of wheat, rye, barley, titracale (hybrid of wheat and rye), and spelt.

Celiac disease is estimated to occur in approximately 1% of the US population; the disease is not only recognized in individuals of European ancestry but is also present in individuals from the Middle East, North Africa, South America, and Asia. The frequency of celiac disease is increasing in many developing countries because of westernization of the diet, changes in wheat production and preparation, and increased awareness of the disease. Originally considered a pediatric disease, celiac disease is now diagnosed at any age and affects many organ systems. Although the evaluation of celiac disease is usually uncomplicated, the signs and symptoms of celiac disease are often nonspecific, making diagnosis difficult and often delayed. Celiac disease is a secondary cause of reduced bone mineral density (BMD) and is associated with impaired quality of life and increased overall mortality. Therefore, clinicians should appropriately investigate possible cases and diagnose and treat celiac disease promptly.

Nonceliac gluten sensitivity also exists *(1)*. Patients with nonceliac gluten sensitivity experience intestinal and extraintestinal symptoms after eating gluten while having negative results on serum anti-tissue transglutaminase (tTG) or anti-endomysial antibody (EMA) testing and have a normal small bowel biopsy. The etiology is not clear, and multiple mechanisms are postulated.

Pathogenesis

Celiac disease is an autoimmune disorder induced by ingestion of gluten in a genetically vulnerable population. Gluten is the major protein in wheat, barley, rye, and similar grains. Gluten proteins can be divided into 2 major fractions according to

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their solubility in alcohols: the soluble gliadins and the insoluble glutenins. Both components have high proline and glutamine content. However, gliadin is considered to be the important molecule triggering the autoimmune process.

tTG is present in the cytoplasm and can be released extracellularly, particularly in response to tissue injury and stress. In the submucosa of the intestine, gliadin's additional γ-carboxamide group is deamidated by tTG to glutamic acid that adds a negative charge to the molecule. The change of shape and its negative charge allows glutamic acid to bind with higher affinity to human leukocyte antigen (HLA)-DQ2 or HLA-DQ8 on antigen-presenting cells such as macrophages or dendritic cells. Deamidated gliadin is presented to gliadin-reactivated CD4+ T cells through a T-cell receptor, activating T cells and B cells to produce cytokines and autoantibodies (Fig. 1). There are 2 theories about how dietary gliadin stimulates the immune system. One theory postulates that an immune response to tTG develops because tTG is physically proximal to gliadin. An alternative theory is that antibodies to deamidated gliadin peptide have cross-reactivity with the tTG antigen *(2)*. Activated gluten-specific CD4+ T cells provide signals to preactivated epithelial cells and upregulate the expression of interleukin-15, HLA-E, and major histocompatibility complex class I polypeptide-related sequence. Subsequently, intraepithelial cytotoxic T lymphocytes can be activated by self or microbial peptide signals and kill epithelial cells, which is responsible for gut epithelial damage.

Family clustering has been observed, with the risk of celiac disease in first-degree relatives being 20−30 times higher than in the general population. The concordance rate between monozygotic twins is more than 75%. Celiac disease is associated with HLA-DQ2 in 95% of patients and with HLA-DQ8 in 5% of patients. Although 25%−30% of the general population possesses the HLA-DQ2 dimer, only a small percentage of the individuals who express this molecule will actually develop celiac disease.

HLA genes account for about 40% of the heritability of celiac disease. A variety of studies have attempted to identify new associated genes or loci. Recent studies suggest several non-major histocompatibility complex genes as susceptibility factors in celiac disease. Thirty-nine loci with 57 independent association signals have been described. Many of these loci harbor genes that are related to the immune response, particularly to B-cell and T-cell function *(2)*.

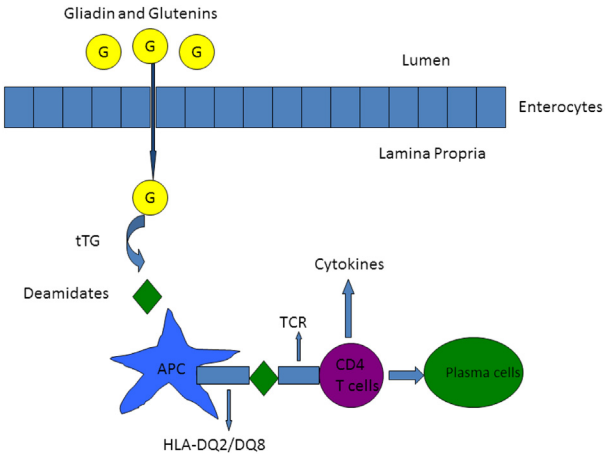

Fig. 1. Pathogenesis of celiac disease gliadin peptide enters from lumen to the lamina propria. Within the lamina propria, tTG deamidates the gliadin peptide, permitting it to bind into an HLA class II (e.g., HLA-DQ2/DQ8) molecule with high affinity. The deamidated gliadin peptide is then presented to a CD4+ T cell resulting in an immunologic signaling cascade. APC, antigen-presenting cell; HLA, human leukocyte antigen; TCR, T-cell receptor; tTG, tissue transglutaminase. (Modified from Dewar D, Pereira SP, Ciclitira PJ. 2004 The pathogenesis of celiac disease. Int J Biochem Cell Biol 36:17−24.)

Laboratory and Tissue Diagnosis

Figure 2 illustrates an algorithm created by authors for the diagnosis of celiac disease. Because celiac disease presents variably, deciding when to test for celiac disease is challenging. Historical risk factors that are highly predictive for celiac disease include chronic gastrointestinal symptoms with a family history of celiac disease or a history of autoimmune disease or immunoglobulin (Ig) A deficiency, biopsy-proven dermatitis herpetiformis, iron deficiency anemia refractory to oral iron supplementation, or failure to thrive in children *(3)*. The risk of disease in these high-risk populations is approximately 10% or higher.

In the mid-1980s, antigliadin antibody testing was developed, but the positive predictive value was only about 30% in a moderate risk group *(4)*. In the early 1990s, anti-EMA testing became available, but its use was limited by high cost and interpretability issues. Anti-tTG testing became available in 1997. The current IgA-anti-tTG test has a sensitivity of 90%, a specificity of 95%, a positive predictive value of 75%, and a negative predictive value of 99% in moderate risk population given a 5% pretest probability *(5,6)* (Table 1). Spurious positive anti-tTG tests can be seen in cirrhosis, congestive heart failure, and after enteric infections. IgA deficiency is 10 times more common in celiac disease than in

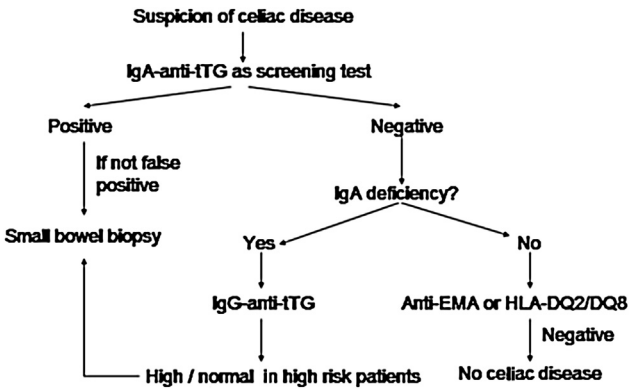

Fig. 2. Algorithm of diagnosis of celiac disease.