

Celiac Disease

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AUDIENCE

This activity is designed for physicians, pharmacists, and managed care organization medical directors and administrators.

GOAL

To identify symptoms, diagnosis, and treatment of celiac disease, a systemic illness with varied manifestations and serious complications if untreated.

LEARNING OBJECTIVES

Upon successful completion of this educational activity, participants should be able to:

1. Describe risk factors for and clinical presentation of celiac disease.
2. Explain the rationale for early diagnosis of celiac disease.
3. Describe methods of screening and diagnosing celiac disease.
4. Discuss treatment modalities and resources for patients with celiac disease.

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Accreditation

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The estimated time to complete this activity is 1 hour.

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Celiac disease, a systemic illness characterized by an abnormal T-cell response to gluten, is more prevalent than previously thought. Because of its varied clinical manifestations and the serious complications that can occur if the condition is untreated, diagnosis is important but can be difficult. Recently developed, accurate serologic tests and the gold standard for diagnosing celiac disease, endoscopic small bowel biopsy, can lead to early detection. Besides a lifetime commitment to a gluten-free diet, management of celiac disease may include dietary supplementation, bone mineral density measurements, intravenous corticosteroid therapy, or other immunosuppressant agents. Symptoms, diagnosis, and treatment of celiac disease are presented.

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Celiac disease, also known as celiac sprue or gluten-sensitive enteropathy, is a multifactorial systemic disorder with its central component being an abnormal T-cell response to gluten in predisposed individuals.^{1,2} Although this disease has been recognized for more than a century, recent advances have improved our understanding of its prevalence, pathogenesis, and complications. There is a growing awareness in the general population, as well as in the medical

community, that celiac disease may be more common than previously suspected. With the advent of highly sensitive and specific serologic tests for celiac disease comes the possibility of prompt accurate diagnosis and treatment, leading to symptomatic relief and possible mitigation of the risk of a number of associated disorders such as cancer and osteoporosis.

EPIDEMIOLOGY

In the past, celiac disease was considered to be a rare disorder in the United States, with a prevalence ranging from 1 in 3000³ to 1 in 6000,⁴ and teachings in many American medical schools tended to reflect this belief. Although celiac disease is still considered to be uncommon among some Asian and African populations,⁵ in recent years the prevalence of celiac disease in the United States has been estimated at between 1 in 133⁶ and 1 in 250,⁷ which is similar to prevalence rates reported in western Europe.⁸⁻¹⁰ Further, populations with a prevalence of celiac disease similar to or greater than these rates have been found across the globe.^{11,12} Consistent reports of the high prevalence of celiac disease, together with new means of diagnosis and the recognition of the potentially severe consequences of untreated celiac disease, has led a number of European countries to consider national screening programs. While this tactic has not yet been adopted in the United States, a broad, up-to-date understanding of the wide spectrum of celiac disease is needed by all physicians.

Outside the general population, certain groups have markedly elevated risks of celiac disease. It has long been known that individuals with first-degree relatives diagnosed with celiac disease have a 10% to 20% risk of developing celiac disease.^{13,14} Additional populations known to have a high prevalence of celiac disease include those with Down's syndrome¹⁵⁻¹⁷ and patients with autoimmune disorders such as type 1 diabetes mellitus,¹⁸ autoimmune thyroid disease,¹⁹ rheumatoid arthritis,²⁰ systemic lupus erythematosus,²¹ autoimmune liver disease,^{22,23} sarcoidosis,²⁴ and immunoglobulin A (IgA) deficiency.²⁵

PATHOPHYSIOLOGY

The familial clustering of celiac disease along with its association with autoimmune disorders has contributed to the current understanding of the disease's pathophysiology as a primary immune disorder. Gluten is the major protein constituent of many grains. The pivotal step of gluten sensitivity appears to be the alteration of

the gliadin peptides in gluten by tissue transglutaminase.²⁶ These altered gliadin peptides are then presented to local intestinal T cells and recognized as foreign, thereby stimulating an immune response.²⁷ The gliadin peptides are preferentially presented by a limited number of human leukocyte antigen (HLA) haplotypes, with more than 90% of patients with celiac disease sharing the HLA DQ2 haplotype (DQA1*0501, DQB1*0201 heterodimer) and most of the remainder carrying DQ (alpha 1*0301, beta 1*0302) (DQ8).^{28,29} Along with abnormal antigen presentation of gliadin, predisposition to developing celiac disease and a number of related autoimmune phenomena appears to be mediated by T cells,³⁰ although the mechanisms behind this T-cell mediation are not well understood. A combination of genetic and environmental factors likely leads to the immune reaction to gliadin peptides, causing inflammation with characteristic intestinal histology and systemic changes.

CLINICAL PRESENTATION

The clinical manifestations of celiac disease are extremely varied and, in many cases, differentiating these manifestations from those of associated disorders can be difficult. Clinical manifestations of celiac disease tend to differ by age group. Infants and children with celiac disease typically present with gastrointestinal manifestations including diarrhea, abdominal distention, or symptoms of malnutrition such as short stature, anemia, defects in dentition, failure to thrive, or developmental delay.³¹ Extraintestinal manifestations are less common in this patient group. For adults, nonspecific gastrointestinal complaints are common and include abdominal pain, flatulence, diarrhea, and, in severe cases, steatorrhea. Nevertheless, most adults with celiac disease present with extraintestinal features.

One of the most common extraintestinal features among adults is fatigue and malaise, which may occur independently of anemia. Anemia has also been shown to be a strong predictor of celiac disease in all populations, leading some to argue that celiac testing is indicated for anyone with anemia of unknown origin.³² Although anemia in celiac disease may be due to a number of factors including folate or vitamin B₁₂ deficiency or chronic disease, iron deficiency is the most common cause. Iron deficiency anemia in celiac disease may be compounded by bleeding from the gastrointestinal tract, as almost half of patients in 1 study were found to have positive fecal occult blood tests.³³

Osteoporosis and increased risk of fractures are also common among patients with undiagnosed or subclini-

Table 1. Celiac Disease and Related Disorders

Gastrointestinal Features	Extraintestinal Features	Associated Conditions	Associated Malignancies
Diarrhea, abdominal pain, abdominal distention, steatorrhea, anemia, failure to thrive, flatulence, aphthous ulcers	Osteopenia/osteoporosis, neuromuscular disorders, psychiatric disturbances, infertility, dermatitis herpetiformis, fatigue and malaise, anemia	IgA deficiency, type 1 diabetes mellitus, thyroid dysfunction, rheumatoid arthritis, Down syndrome, vitiligo, systemic lupus erythematosus	Small bowel lymphoma, small bowel adenocarcinoma, large bowel carcinoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, oropharyngeal carcinoma, primary liver carcinoma, esophageal lymphoma

Source: Data from references 2, 3, 31-40.

cal celiac disease.^{34,35} The etiology of increased osteopenia in celiac disease relates to impaired calcium and vitamin D malabsorption from the small intestine. Interestingly, celiac-related osteopenia in some individuals appears to be caused by an antibody immune process with antibodies targeting a number of normal skeletal constituents.³⁶ Skin lesions, most commonly dermatitis herpetiformis, occur in approximately 10% of patients with celiac disease.³⁷ Additional clinical presentations of celiac disease are varied and include psychosis,³⁸ neuromuscular abnormalities,³⁹ infertility,⁴⁰ and aphthous ulcers⁴¹ (Table 1).

The association between celiac disease and malignancy is of special concern because of the potential to prevent the development of cancer through maintenance of a gluten-free diet. The incidence of malignancies, which may occur either before or after the diagnosis of celiac disease is made, are significantly increased.^{42,43} Malignancies that have been reported with higher frequency in patients with celiac disease include small bowel lymphoma and small bowel adenocarcinoma,⁴² primary liver cancer, both Hodgkin's and non-Hodgkin's lymphoma, and oropharyngeal, esophageal, and large intestine carcinoma.⁴³ Further, there is some evidence that maintenance of a gluten-free diet can, over time, return the risk of malignancy in patients with celiac disease to baseline.^{43,44}

A specific manifestation of celiac disease worth mention is refractory sprue, also known as intractable celiac disease. This condition is defined as symptomatic, severe villous atrophy of the small intestine with increased intraepithelial lymphocytes despite maintenance of a strict gluten-free diet.⁴⁵ The prevalence of the condition in patients with celiac disease has been estimated to be between 7% and 30%.⁴⁶ Refractory sprue is by definition resistant to treatment and has been associated in the past with a number of entities including ulcerative jejunoileitis,

lymphoma, and collagenous sprue.⁴⁷ Poorly understood for many years, refractory celiac disease has been convincingly linked by recent studies to an abnormal clonal proliferation of intraepithelial T-cell population, the likely precursor to enteropathy-associated T-cell lymphoma.^{47,48}

Diagnosis

Accurate serologic tests are now available for the diagnosis of celiac disease. Whereas multiple tests have been introduced, 3 main categories of antibodies are currently available for diagnostic tests: anti-endomysial antibody (EMA), anti-tissue transglutaminase antibody (tTG), and anti-gliadin antibody (AGA). These tests differ in their sensitivity and specificity and in their average cost (Table 2). The IgA anti-endomysial antibody assay is 85% to 98% sensitive and 96% to 100% specific.⁴⁹ Although this high specificity makes this assay the gold standard serologic test in ruling out celiac disease, its lower sensitivity means that results can be falsely negative in patients with celiac disease,⁵⁰ particularly if the villous atrophy is only mild or partial.⁵¹ This immunofluorescence assay involves binding of endomysial antibody to connective tissue surrounding smooth muscle cells and identification of a characteristic staining pattern.⁵² Monkey esophagus and now, more commonly, human umbilical cord are used as substrates. The EMA is a qualitative assay, whereby results are reported as either positive or negative, in contrast to tTG or AGA, which are quantitative assays, whereby results are reported as titers.⁵³

Tissue transglutaminase is now recognized to be the autoantigen bound by anti-endomysial antibody.⁵² A highly sensitive enzyme-linked immunosorbent assay (ELISA) is available that identifies this antigen. IgA anti-tTG testing is more sensitive than EMA but less specific.² However, as ELISA tests are less cumbersome and costly than direct immunofluorescence and less subject to interob-

server variation, anti-tTG testing may become the favored method of diagnosing and screening for celiac disease.⁵⁰

Anti-gliadin testing remains a useful tool; however, the sensitivity and specificity of anti-IgA and anti-IgG anti-gliadin testing is significantly lower than for EMA or tTG assays.⁵¹ In addition, the positive predictive value of the tests in the general population is relatively poor, as more than one third of the general population will have a positive AGA test result.⁵² While the anti-IgA AGA assay is marginally more sensitive and specific than IgG AGA, the IgG AGA assay is useful in detecting the 2% to 5% of patients with celiac disease who have concomitant IgA deficiency, in whom IgA EMA, tTG, and AGA test results will be falsely negative.⁵³

Although serologic testing allows for noninvasive screening, the gold standard for diagnosing celiac disease remains endoscopic small bowel biopsy.⁵⁴ As depicted in the **Figure**, serology is most useful in patients who carry a low clinical suspicion for celiac disease, as positive results identify individuals who warrant further evaluation with endoscopic biopsy. In patients in whom there is a moderate-to-high clinical suspicion, serologic testing alone cannot make the diagnosis. For these patients, concurrent serologic and endoscopic evaluation should comprise the initial work-up.

Biopsy of the distal duodenum in affected patients classically shows blunted small intestinal villi, enlarged and hyperplastic crypts of Lieberkuhn, and inflammatory cells in the lamina propria, as well as increased intraepithelial lymphocytes.⁵⁵ Although endoscopic findings may reveal atrophic duodenal folds, scalloping of duodenal folds, mucosal grooves, and mosaic-appearing mucosa, none of these macroscopic findings are specific for celiac disease, thus making duodenal biopsy necessary for definitive diagnosis.⁵⁶

TREATMENT

The cornerstone of treatment of celiac disease is a lifetime commitment to a gluten-free diet. Patients with celiac disease need to avoid gluten, which is contained in wheat and related barley and rye proteins.² Because of the widespread use of gluten in commercial and processed foods wherein wheat flour is used as a thickener in the processing of some meat, vegetable, fruit, and dairy products, patients must be educated about the less obvious sources of gluten and counseled to read labels meticulously. A number of resources on the World Wide Web may aid in this endeavor, eg, <http://www.celiac.com>; however, direct patient counseling with a registered dietician is recommended.

Dietary avoidance of gluten leads to symptom improvement in 70% of patients within 2 weeks.⁵⁷ Titers of EMA, tTG, and AGA can be used to monitor compliance and response to therapy because they decrease after initiation of a gluten-free diet.² Within 3 to 6 months, antibody levels should become undetectable with strict gluten withdrawal.² Although resolution of small bowel inflammation also occurs with the institution of a gluten-free diet, in some individuals complete histological resolution may take up to 2 years.⁵⁸

In addition to gluten restriction, patients should be screened and treated for iron, folate, B₁₂, calcium, and vitamin D deficiencies.⁵⁴ Dietary supplementation with a multivitamin, iron, calcium, and vitamin D is important at the initiation of a gluten-free diet; all patients should have bone mineral density measurements to assess their need for bisphosphonate therapy.⁵⁵

The role of oats in celiac disease remains controversial.⁵⁹ Although oats do not contain gliadin, they are often processed with wheat and may become contaminated. Short-term and long-term studies have demonstrated that adults can consume up to 50 g of oats per day without developing symptoms or evidence of

injury on small intestinal biopsy.⁶⁰ Because oats are often grown or processed with other cereals leading to cross-contamination, the American Dietetic Association does not endorse the use of oats as part of a gluten-free diet. Because of concerns pertaining to possibly contaminated oats, a recommendation that patients with newly

Table 2. Serologic Tests for Celiac Disease

Assay	Sensitivity (%)	Specificity (%)	Cost (\$)
IgA anti-endomysial antibody	85-98	96-100	45-99
IgA anti-tissue transglutaminase antibody	90-98	95-97	85-164
IgA anti-gliadin antibody	80-90	85-95	45
IgG anti-gliadin antibody	75-85	75-90	45-90

Source: Data from references 2, 47, and 49.

diagnosed celiac disease avoid oats initially is prudent. Only after complete resolution of symptoms may oats from reliable sources be reintroduced into the diet in small quantities (ie, less than 50 g per day).²

While diet regulation is the mainstay of treatment, occasionally intravenous corticosteroid therapy is required for critically ill patients who present with acute celiac crisis manifested by severe diarrhea, dehydration, weight loss, acidosis, hypocalcemia, and hypoproteinemia,⁶¹ and for the rare patients who present with gliadin shock after a gluten challenge.⁶² Patients with refractory celiac disease may also require treatment with corticosteroids and other immunosuppressant agents, including azathioprine and cyclosporine.^{63,64} Total parenteral nutrition may become necessary for patients in whom immunosuppressant therapy fails.

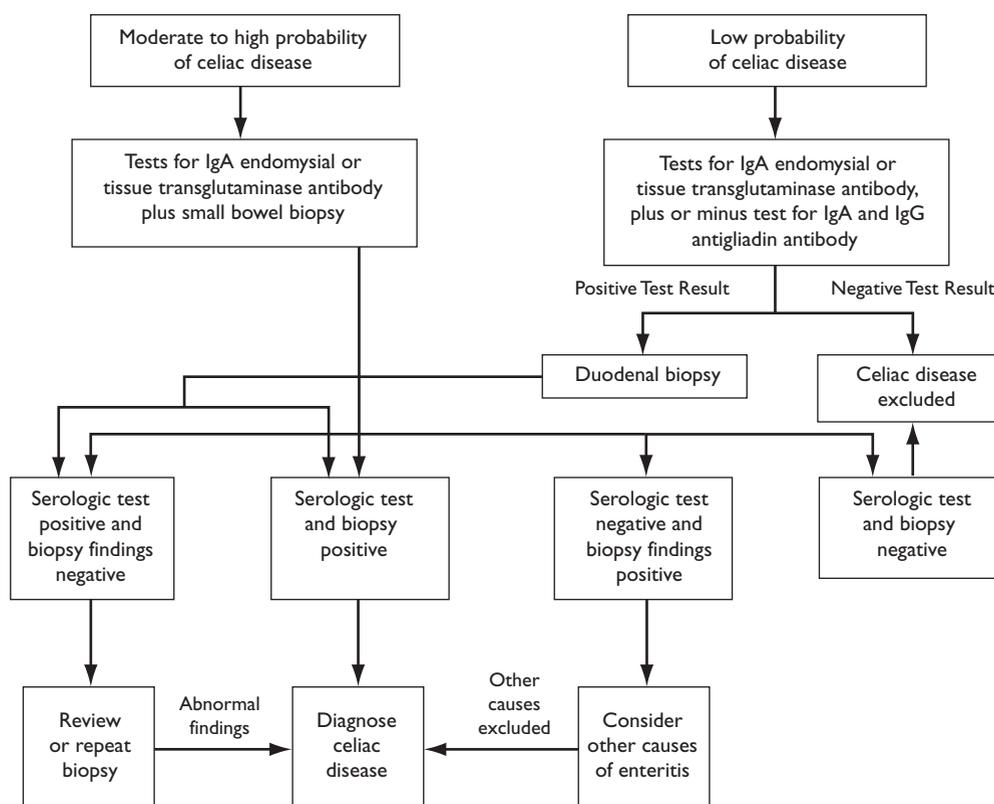
Additionally, as our understanding of the pathophysiology of celiac disease increases, new modalities for treatment are coming to light. One of the most promising areas of current research is peptidases, including a bacterial prolyl endopeptidase, which can degrade

gluten into nontoxic components,⁶⁵ analogous to the use of lactase in individuals with lactose intolerance.

SUMMARY

Timely diagnosis and treatment of celiac disease is important not only to improve the immediate quality of life of the patient but also to decrease the long-term risks of untreated celiac disease. A large Finnish study showed that the 5-year survival among patients who strictly adhered to a gluten-free diet was similar to that of the general population.⁶⁶ Growth and development in infants and children proceed normally with continued gluten avoidance, and in adults many of the disease complications including osteopenia are avoided.⁶⁷ However, peripheral neuropathy, ataxia, and severe osteopenia, particularly in the setting of secondary hyperparathyroidism, usually persist.⁶⁸ Enteropathy-associated T-cell lymphoma is widely recognized as a complication of celiac disease, and gluten restriction has been shown to significantly decrease the risk of this malignancy to the level of the general population.⁶⁷

Figure. Algorithm for the Diagnosis of Celiac Sprue



Adapted from reference 2.

Whether gluten restriction is beneficial or should be recommended for patients with asymptomatic disease remains controversial. However, the available evidence suggests that this treatment is always indicated in patients showing celiac enteropathy, at least to prevent the possible long-term complications of this condition. Despite a dearth of evidence presently to support population-wide screening for celiac disease, patients at high-risk for celiac disease should be screened based on symptoms, family history, and associated conditions, as morbidity from subclinical disease in young patients has been demonstrated.

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