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Celiac Disease and Nonceliac Gluten Sensitivity
A Review

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IMPORTANCE The prevalence of gluten-related disorders is rising, and increasing numbers of individuals are empirically trying a gluten-free diet for a variety of signs and symptoms. This review aims to present current evidence regarding screening, diagnosis, and treatment for celiac disease and nonceliac gluten sensitivity.

OBSERVATIONS Celiac disease is a gluten-induced immune-mediated enteropathy characterized by a specific genetic genotype (*HLA-DQ2* and *HLA-DQ8* genes) and autoantibodies (antitissue transglutaminase and antiendomysial). Although the inflammatory process specifically targets the intestinal mucosa, patients may present with gastrointestinal signs or symptoms, extraintestinal signs or symptoms, or both, suggesting that celiac disease is a systemic disease. Nonceliac gluten sensitivity is diagnosed in individuals who do not have celiac disease or wheat allergy but who have intestinal symptoms, extraintestinal symptoms, or both, related to ingestion of gluten-containing grains, with symptomatic improvement on their withdrawal. The clinical variability and the lack of validated biomarkers for nonceliac gluten sensitivity make establishing the prevalence, reaching a diagnosis, and further study of this condition difficult. Nevertheless, it is possible to differentiate specific gluten-related disorders from other conditions, based on currently available investigations and algorithms. Clinicians cannot distinguish between celiac disease and nonceliac gluten sensitivity by symptoms, as they are similar in both. Therefore, screening for celiac disease must occur before a gluten-free diet is implemented, since once a patient initiates a gluten-free diet, testing for celiac disease is no longer accurate.

CONCLUSIONS AND RELEVANCE Celiac disease and nonceliac gluten sensitivity are common. Although both conditions are treated with a gluten-free diet, distinguishing between celiac disease and nonceliac gluten sensitivity is important for long-term therapy. Patients with celiac disease should be followed up closely for dietary adherence, nutritional deficiencies, and the development of possible comorbidities.

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Celiac disease is a chronic, small-intestinal immune-mediated enteropathy initiated by exposure to dietary gluten in genetically predisposed individuals and characterized by specific autoantibodies against tissue transglutaminase 2 (anti-tTG2), endomysium, and/or deamidated gliadin peptide.[1] Although up to 40% of the population carries the genotype *HLA-DQ2* or *HLA-DQ8*, which is required for the development of celiac disease, only 2% to 3% of *HLA-DQ2* or *HLA-DQ8* carriers subsequently develop celiac disease.[2] Celiac disease, once considered a relatively rare gastrointestinal condition affecting almost exclusively young white children, can develop at any age and can affect almost any race. Celiac disease was first described by Samuel Gee in 1887. Wheat was hypothesized as the possible offending agent by William Dicke in 1941.[3]

The epidemiology, clinical presentation, pathophysiology, and management of the disease have changed since its initial description. There is strong evidence that celiac disease is an autoimmune disease triggered by the ingestion of gluten present in wheat, barley, and rye in genetically predisposed individuals. The prevalence of celiac disease in the general population is 1%, with regional differences (**Table 1**).[4] Celiac disease can affect any human organ or tissue (Table 1 and **Table 2**).[6]

Nonceliac gluten sensitivity is a term used to describe individuals who have intestinal signs or symptoms, extraintestinal signs or symptoms, or both, related to ingestion of gluten-containing grains (Table 2), with improvement when these are removed from a patient's diet. The frequency of nonceliac gluten sensitivity is unknown owing to the lack of validated biomarkers, but it is thought to be more common than celiac disease. Wheat allergy, the third gluten-related disorder, which will not be addressed in this review, is defined as an adverse type-2 helper T-cell immunologic reaction to wheat proteins and typically presents soon after wheat

Table 1. Prevalence of Celiac Disease in the General Population and in At-Risk Groups[a]

	Prevalence, %
General Population	
Algeria	5.6
Argentina	0.6
Australia	0.4
Brazil	0.5
Burkina Fasu	0
Egypt	0.5
Finland	1.0-2.4
Germany	0.2
India	0.3-1.0
Iran	0.5-1.0
Ireland	0.8
Italy	0.9-1.0
Libya	0.8
The Netherlands	0.5
New Zealand	1.2
Portugal	0.7
Russia	0.2
Spain	0.3-1.4
Sweden	0.5-2.9
Tunisia	0.6
Turkey	0.6-1.0
United Kingdom	0.9-1.5
United States	0.3-0.9
Mean (weighted)	1.0
At-Risk Groups	
Type 1 diabetes	3-12
Autoimmune thyroid disease	3
Autoimmune liver disease	13.5
Down syndrome	5.5
Turner syndrome	6.5
Williams syndrome	9.5
IgA deficiency	3
IgA nephropathy	4
Juvenile idiopathic arthritis	1.5-2.5

[a] Modified from Husby et al.[4] Data on at-risk groups were collected from different, Western populations.[5] A prevalence range indicates that more than 1 study is available.

ingestion, with signs of anaphylaxis such as swelling or itching of the mouth, throat, and skin; nasal congestion; watery eyes; and difficulty breathing. Wheat allergy is more common in children, with reported prevalence between 2% and 9% in children and 0.5% and 3% in adults.[8]

This review provides an evidence-based update of the pathophysiology, diagnosis, treatment, and implications of celiac disease and nonceliac gluten sensitivity.

Methods

The Cochrane Library (January 15, 2010, to April 10, 2017), MEDLINE (January 15, 2010, to April 10, 2017), and Google Scholar (January 15, 2010, to April 18, 2017) were searched using the search terms *coeliac*, *celiac*, *non-celiac*, *non-coeliac*, *gluten*, and *wheat sensitivity*, alone and in combination. Publications in the past 5 years were selected in addition to commonly referenced and highly regarded older publications. Reference lists of articles identified by this search strategy were selected. Review articles and book chapters were cited to provide readers with additional details and sources of additional references.

Results

Pathophysiology

Gluten as Environmental Trigger of Gluten-Related Disorders

Gluten is a mixture of gliadins and glutenins, complex proteins unusually rich in prolines and glutamines that are not completely digestible by intestinal enzymes.[9] The final product of this partial digestion is a mix of peptides that can trigger host responses (increased intestinal permeability and innate +/− adaptive immune response) that closely resemble those instigated by the exposure to gastrointestinal pathogens[10-13] (**Figure 1**).

Normal Phsyiologic Events That Contribute to the Pathogenesis of Celiac Disease and Nonceliac Gluten Sensitivity

Gluten Translocation From Lumen to Lamina Propria (Paracellular vs Transcellular) | Previous studies have shown that gliadin can cause an immediate and transient increase in gut permeability.[9,13] This permeating effect is secondary to the binding of specific undigestible gliadin fragments to the CXCR3 chemokine receptor with subsequent release of zonulin, a modulator of intercellular tight junctions (Figure 1).[14] This process takes place in all individuals who ingest gluten. For the majority, these events do not lead to abnormal consequences. However, these same events can lead to an inflammatory process in genetically predisposed individuals when the immunologic surveillance system mistakenly recognizes gluten as a pathogen. Thus, this normal physiologic process is also essential to the development of celiac disease and nonceliac gluten sensitivity in at-risk individuals. Additionally, there is evidence that during the acute phase of celiac disease, gluten can also cross the intestinal barrier through the transcellular pathway via transferrin receptor CD71, once tolerance to gluten has been lost[15] (Figure 1).

The Innate Immune Response | Innate immunity plays a critical role in initiating celiac disease and possibly nonceliac gluten sensitivity. Cytokines such as interleukin (IL) 15 and interferon alfa can prime the innate immune response by polarizing dendritic cells and intraepithelial lymphocyte function.[15,16] These mucosal events, along with the breach of the epithelial barrier function secondary to the gliadin-mediated zonulin release,[14] lead to the passage of undigested peptides from the gut lumen to the lamina propria. Once gliadin crosses the epithelial barrier, neutrophil recruitment through IL8 production[11,12,17] or a direct neutrophil chemoattractant effect[18] causes a loss of tolerance to gluten in genetically susceptible individuals (Figure 1).

Specific Events in Celiac Disease Pathogenesis

The Celiac Disease Adaptive Immune Response

The adaptive immune response is the consequence of a highly specific interplay between selected gluten peptides and major histocompatibility complex class II HLA-DQ2/8–restricted T-cell antigens and plays a role in celiac disease pathogenesis.[19,20] The contact of $CD4^+$ T cells in the lamina propria with gluten induces their activation and proliferation, leading to production of proinflammatory cytokines, metalloproteases, and keratinocyte growth factor, which induces cryptal hyperplasia and villous blunting secondary to intestinal epithelial cell death induced by intraepithelial lymphocytes.[20,21] Celiac disease crypt hyperplasia has been hypothesized to be the consequence of an imbalance between continuous tissue damage due to the mucosal autoimmune insult described above and inability of the stem cells to compensate (Figure 1).

Specific Events in Nonceliac Gluten Sensitivity Pathogenesis

The pathophysiology of nonceliac gluten sensitivity remains largely undetermined. In addition to gluten, α-amylase/trypsin inhibitors are suggested to play a key role in the innate immune response of gluten-related disorders.[22] A study by Sapone et al[23] found that gluten-sensitive individuals without celiac disease have a significant reduction in T-regulatory cell markers compared with control patients and patients with celiac disease and an increase in the α and β classes of intraepithelial lymphocytes, with no increase in adaptive immunity-related gut mucosal gene expression. These findings suggest an important role of the intestinal innate immune system in the pathogenesis of nonceliac gluten sensitivity without an adaptive immune response.[24] This hypothesis is also supported by the lack of enteropathy with villous blunting in nonceliac gluten sensitivity, a feature detected in celiac disease as a sign of HLA-driven adaptive immune response.

Clinical Presentation

Celiac Disease

Historically, the classic presentation of celiac disease had been malabsorption manifesting as diarrhea and poor growth in childhood.[25] It was presumed that the disease appeared when gluten was introduced, and the timing of the presentation of symptoms varied according to the intensity of the immune response. However, the development of highly sensitive and specific noninvasive tests[6,26] facilitated a more accurate measurement of celiac disease prevalence, identified at-risk individuals and groups, and helped to establish that celiac disease is a systemic autoimmune disease and that onset can occur at any age,[27] presenting with gastrointestinal manifestations, extraintestinal manifestations, or both (Table 2).[28,29]

Table 2. Gastrointestinal and Extraintestinal Manifestations of Celiac Disease and Nonceliac Gluten Sensitivity[a]

Symptoms	Presence of Symptoms	
	Celiac Disease[b]	Nonceliac Gluten Sensitivity
Intestinal		
Abdominal pain, %	+ (27.8)	+
Anorexia	+	–
Bloating	+	+
Constipation, %	+ (20.2)	+
Diarrhea, %	+ (35.3)	+
Flatulence	+	+
Lactose intolerance	+	–
Nausea	+	–
Gastroesophageal reflux	+	–
Weight loss	+	–
Vomiting	+	–
Extraintestinal		
Anemia, %	+ (32)	+
Anxiety	+	+
Arthralgia, %	+ (29.3)	+
Arthritis, %	+ (1.5)	+
Ataxia	+	+
Dental enamel hypoplasia	+	–
Delayed puberty	+	–
Dermatitis herpetiformis	+	–
Depression	+	+
Elevated liver enzymes	+	–
Rash (eg, eczema)	+	+
Fatigue, %	+ (26.3)	+
Cloudiness of consciousness	+	+
Headache	+	+
Infertility	+ (1.5)	–
Irritability	+	+
Iron-deficiency anemia	+	–
Mouth sores	+	–
Myalgias	+	+
Osteoporosis, %	+ (5.5)	–
Pancreatitis	+	–
Peripheral neuropathy, %	+ (0.7)	+
Short stature, %	+ (1.0)	–

[a] Sources: Lionetti and Catassi[5] and Fasano et al.[6]

[b] Prevalence of celiac disease at presentation indicated in parentheses where available.[5,7]

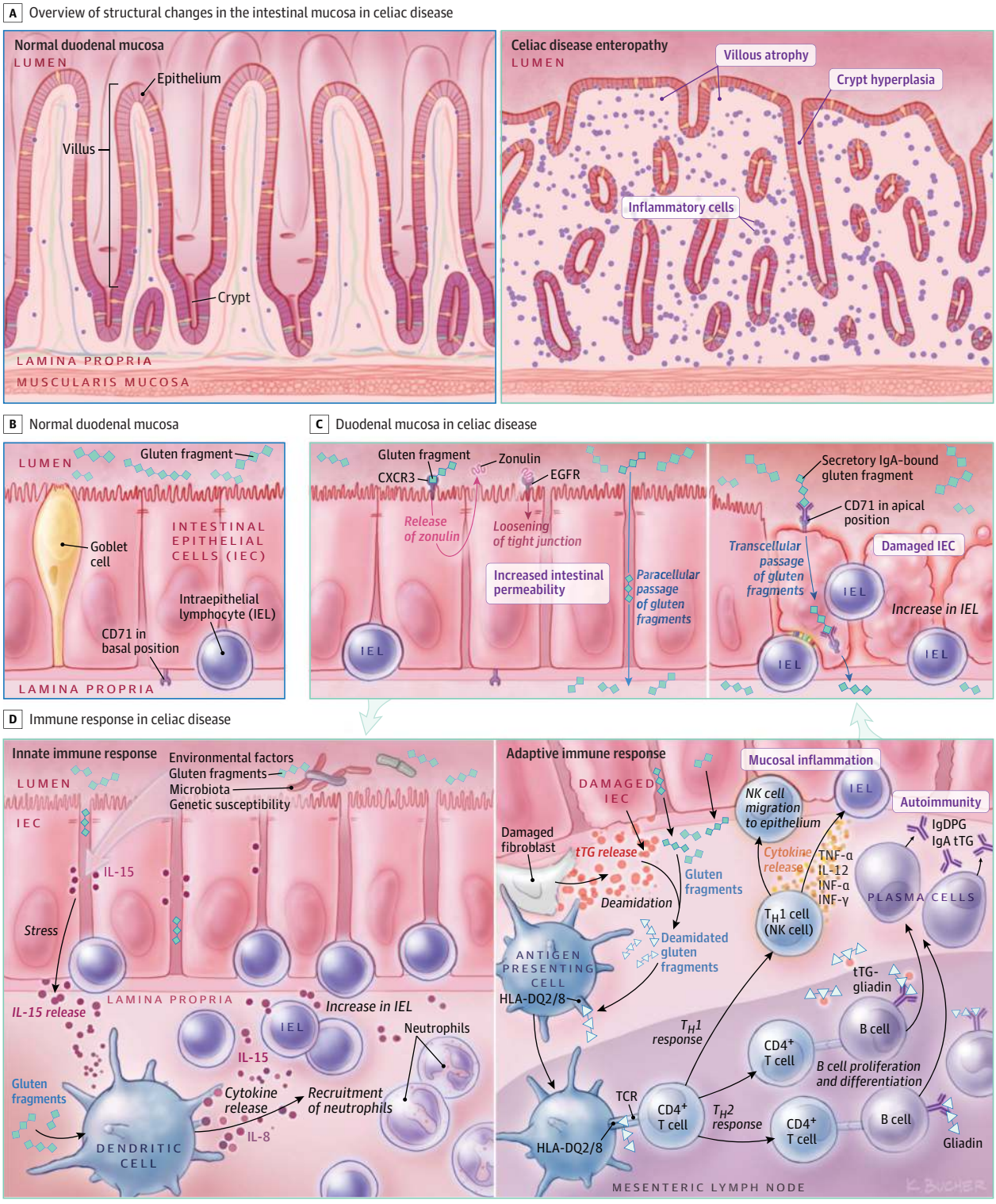
Intestinal Manifestations

Gastrointestinal symptoms are more common in the pediatric age group. Children younger than 3 years are likely to present with diarrhea, loss of appetite, abdominal distention, and poor growth.[30] Older children and adults may present with diarrhea, bloating, constipation, abdominal pain, or weight loss.[31,32]

Extraintestinal Manifestations

The etiology of extraintestinal manifestations is attributable to a combination of chronic inflammation, nutrient deficiencies, and possibly an adaptive immune response spreading from the intestinal mucosa to other tissues and organs. Poor growth, short stature, or delayed puberty may be the only presenting symptoms of pediatric celiac disease.[6] Dental enamel defects are common in children who develop celiac disease before age 7 years.[33] Iron-deficiency anemia is a common presentation of celiac disease and is seen in 32% of adults and 9% of children.[7,34,35] In women, studies suggest an increased risk of miscarriage.[36,37] In addition to dermatitis herpetiformis, dermatologic conditions such as urticaria, psoriasis, and dry skin are more frequent in patients with celiac disease.[38] Up to 22%

Figure 1. Mucosal Innate and Adaptive Immune Responses Involved in Celiac Disease Pathogenesis



A, Mucosa with normal 3:1 villous-crypt ratio (left) and with structural features of celiac disease (right). B, Competent tight junctions and CD71 receptor expressed on IEC basal membrane. C, Specific undigested gluten fragments bind to CXCR3 receptor with subsequent release of zonulin and increased paracellular passage of gluten fragments. D, In genetically susceptible individuals, the presence of gluten fragments in the lamina propria triggers an innate immune response (left), culminating in tissue transglutaminase (tTG) release from damaged cells. Deamidated gluten fragments are presented to CD4+ T cells (right), with subsequent activation of both T_H2 response leading to B-cell proliferation and T_H1 response leading to the release of proinflammatory cytokines, migration of natural killer (NK) cells to the gut epithelium, and increased IELs, and ultimately to the insult of IEC and CD71 expression on the apical side of IEC with subsequent additional passage of gluten fragments through the transcellular pathway. EGFR, epidermal growth factor receptor; IL, interleukin; INF, interferon; KGF, keratinocyte growth factor; TCR, T-cell receptor.

Table 3. Range of Sensitivity and Specificity and Use of Current Serologic Tests for Celiac Disease[a]

Serologic Study	% Sensitivity	% Specificity	Application in Clinical Practice
IgA tTG	73.9-100	77.8-100	First-line testing to screen for celiac disease[b]
IgG DGP	80.1-96.9	86.0-96.9	First-line testing for celiac disease in patients with IgA deficiency
IgA EMA	82.6-100	94.7-100	Second-line confirmatory test to screen for celiac disease
IgG tTG	12.6-99.3	86.3-100	Not recommended for routine use because of poor sensitivity compared with IgG DGP
IgA DGP	80.7-95.1	86.3-93.1	Not recommended for routine use because of poor sensitivity and specificity compared with IgA tTG and IgA EMA

Abbreviations: EMA, antiendomysial antibody; DGP, deamidated gliadin peptide; tTG, tissue transglutaminase.

[a] Adapted from Thawani et al.[41]

[b] Should be sent with a baseline IgA level initially to ensure there is no IgA deficiency.

of patients with celiac disease have neurologic manifestations, psychiatric manifestations, or both.[39,40] Peripheral neuropathy is frequent, compared with healthy controls. The etiology may be attributable to nutritional deficiencies such as deficient vitamin B_{12}, chronic inflammation, or an immune-based mechanism.[40] In one study, neuropathy was diagnosed in 0.7% of patients with celiac disease, compared with 0.3% of controls.[41]

Refractory celiac disease is defined as persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet for at least 6 to 12 months. Patients with refractory celiac disease may go on to develop uncommon but severe complications such as ulcerative jejunitis and enteropathy-associated T-cell lymphoma.[42]

Nonceliac Gluten Sensitivity

The clinical symptoms of nonceliac gluten sensitivity begin after the ingestion of gluten-containing grains. Symptoms improve or disappear with withdrawal of these grains from the diet, and symptoms reappear after gluten challenge, usually within hours or days. The clinical gastrointestinal presentation of nonceliac gluten sensitivity is characterized by abdominal pain, bloating, bowel irregularity (diarrhea, constipation, or both), while extraintestinal manifestations include patient report of a "foggy brain," which is described as slowed thinking, memory disturbance, or reduced level of alertness, along with headache, joint and muscle pain, fatigue, depression, leg or arm numbness, dermatitis (eczema or skin rash), and anemia (Table 2).[8,43]

Assessment and Diagnosis

Celiac Disease

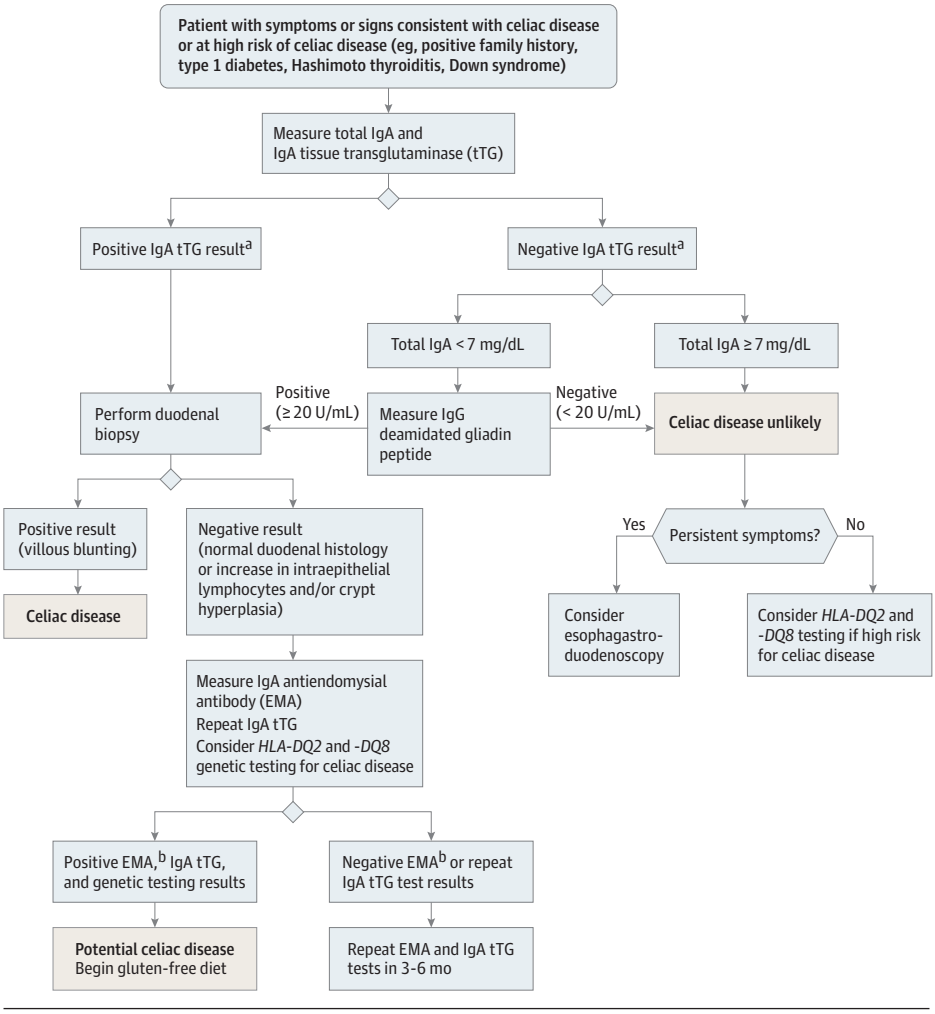
There has been an increase in the availability and use of accurate noninvasive tools for the diagnosis of celiac disease in the last 20 years. Their performance has been recently and comprehensively reviewed.[44,45] Recommendations for the use of each test and the sensitivity and specificity are summarized in **Table 3**. In practice, measurement of serum IgA antibodies to tissue transglutaminase (anti-tTG) (or IgG class in patients with IgA deficiency) is an excellent screening procedure with high sensitivity and specificity and is considered the first screening test that should be ordered in patients in whom celiac disease is suspected. The IgA antiendomysial antibody determination is 98% specific for active celiac disease, but it should be used only as a confirmatory test because of cost and subjective interpretation, which may contribute to the more variable sensitivity.[44] Deamidated gliadin peptides—antibodies of the IgG class—have a sensitivity and specificity close to IgA anti-tTG antibodies and should be used as the initial screening test for patients with IgA deficiency. Given the highly accurate tests available, the first-generation antinative gliadin antibody test should no longer be used to evaluate for celiac disease.[44] *HLA-DQ2* and *HLA-DQ8* determination may be useful when there is discrepancy between serologic studies and histologic findings to better assess whether celiac disease is possible, because the disease, except in rare cases, cannot develop in individuals who are negative for *HLA-DQ2* and *HLA-DQ8*.[44] **Figure 2** provides a diagnostic approach to celiac disease.

Villous blunting on the small-intestinal biopsy can definitively establish the diagnosis of celiac disease and is recommended by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the American College of Gastroenterology (ACG).[46,47] The characteristic histologic changes associated with celiac disease include an increased number of intraepithelial lymphocytes (>25 per 100 enterocytes), elongation of the crypts, and partial to total villous atrophy.[48] The European Society for Pediatric Gastroenterology and Hepatology (ESPGHAN) has proposed an algorithm for children who meet specific criteria, for whom biopsy is not recommended.[4] For the biopsy to be omitted, children must have signs and symptoms suggesting celiac disease, a positive anti-tTG antibodies finding with a level greater than 10 times the upper limit of normal, a positive antiendomysial antibody finding obtained at a different time than the anti-tTG antibodies finding, and a HLA genotype compatible with celiac disease.[4] Specific diagnostic procedures such as double-balloon enteroscopy, videocapsule endoscopy, or magnetic resonance imaging are rarely used and may be indicated in the workup of complicated celiac disease when there are discrepancies between serology and histology results or when a patient with celiac disease has persistent or worsening symptoms despite following a gluten-free diet.

Nonceliac Gluten Sensitivity

No specific biomarkers have yet been identified and validated for nonceliac gluten sensitivity. Clinicians should suspect nonceliac gluten sensitivity in a patient who presents with gastrointestinal or extraintestinal symptoms (Table 2) that appear to improve with a gluten-free diet. Since these symptoms also can be seen with celiac disease and, to a lesser extent, with wheat allergy, these conditions need to be preliminarily excluded with serologic and histologic evidence to focus on the suspicion of nonceliac gluten sensitivity. Until biomarkers are identified and validated, the diagnosis of nonceliac gluten sensitivity is confirmed in a research setting with a double-blind crossover gluten challenge.[49] In a clinical setting, clinicians may suggest a blinded gluten challenge during which a patient is given approximately 8 g of gluten (corresponding to approximately 2 slices of bread) or placebo for 1 week each, separated by a 1-week gluten-free washout period. Symptoms are monitored throughout the challenge.[49] A blinded challenge is not generally feasible in a clinical setting; therefore, for patients with fluctuating symptoms,

Figure 2. Proposed Screening Algorithm for Celiac Disease



[a] Reference values for IgA tTG vary depending on the source of the tTG used (recombinant tTG vs tTG purified from human red blood cells) and kit-specific range (cutoff ranging from <4 U/mL to <20 U/mL).

[b] Cutoff for EMA is 1:5 dilution (subjective immunofluorescence method).

symptomatic assessment of a patient adhering vs not adhering to a gluten-free diet for at least 1 week is suggested.[49]

Treatment

Currently, a strict gluten-free diet remains the only available treatment for gluten-related disorders, but the time frame is different according to the specific disorder. It has been suggested that nonceliac gluten sensitivity may be a transient condition.[49] Therefore, expert recommendation is that the gluten-free diet should be followed for a given period, eg, 12 to 24 months, before testing gluten tolerance again. Based on severity of symptoms, some gluten-sensitive patients without celiac disease may choose to follow a gluten-free diet indefinitely.[49] For patients with celiac disease, lifelong implementation of a strict gluten-free diet is the only option; however, adhering to such a diet can be difficult, owing to minute amounts of gluten that may be present on gluten-free foods. These trace amounts can be as harmful as lack of adherence to a gluten-free diet. According to expert opinion, patients diagnosed with a gluten-related disorder should be monitored by a gastroenterologist and an experienced dietician to counsel the patient and family in navigating the gluten-free diet.[50,51]

Acute and Long-term Management: Follow-up and Outcomes in Patients With Celiac Disease

In patients with celiac disease, nutritional markers should be evaluated at diagnosis, and abnormal findings should be reassessed after 1 year of adherence to a gluten-free diet. Up to 28% of children presenting with celiac disease have a nutritional deficiency, such as iron (28%), folate (14%), vitamin B_{12} (1%), or vitamin D (27%) deficiency at diagnosis.[35] Adults presenting with celiac disease are likely to have a nutritional deficiency, such as folate (20%), B_{12} (19%), or zinc (67%); 32% had iron-deficiency anemia in 1 study.[7] Children's growth should be routinely monitored. Current guidelines recommend follow-up serologic testing to assess dietary adherence and for use as a surrogate marker of mucosal recovery in children and adults.[4,46,47] Recommendations also support a baseline dual-energy x-ray absorptiometry scan for women and men older than 30 years diagnosed with celiac disease.[52]

Serologic Follow-up in Patients With Celiac Disease

Celiac-specific autoantibody levels should be measured every 6 to 12 months after initiation of the gluten-free diet until they normalize.[4,46,47] Once levels have normalized, it is presumed that

mucosal recovery, secondary to dietary adherence, has occurred. Although current guidelines according to the ACG, NASPGHAN, and ESPGHAN endorse and recommend the use of serology as a marker of dietary adherence and mucosal recovery, these tests have not been validated for this purpose.[4,46,47] Furthermore, recent work has reported that the sensitivity of IgA tTG to identify persistent enteropathy after a patient with celiac disease has started a gluten-free diet is 43% to 83%.[53,54]

Intestinal Biopsy in Patients With Celiac Disease

Currently available serologic tests may be inadequate to predict mucosal recovery in patients with celiac disease who follow a gluten-free diet.[54,55] In the United States, the Food and Drug Administration has prioritized the need to develop accurate surrogate end points to assess mucosal recovery in patients with celiac disease. Although data evaluating pediatric mucosal recovery are limited, previous data suggested a more complete and faster healing time in children compared with adults.[56] More recent data suggested that 5% to 19% of children with celiac disease who follow a gluten-free diet may have persistent enteropathy despite treatment with a gluten free diet for at least 1 year.[53,54] Irrespective of IgA tTG levels, 25% to 40% of adults did not achieve mucosal recovery after 2 years of following a gluten-free diet.[57,58] Persistent villous blunting was more common in older and male patients and less common in patients with higher educational attainment.[59] Given these findings, a follow-up endoscopy to ensure mucosal recovery in adult patients is recommended in some celiac centers. More studies are needed to evaluate the long-term complications associated with persistent villous blunting in adults and children with celiac disease before universal follow-up and treatment regimens are described. At this time, available treatment options for patients diagnosed with celiac disease with persistent villous blunting despite a gluten-free diet include implementation of the gluten contamination elimination diet, which offers only fresh fruits, vegetables, meat, and limited condiments or medical therapy with immunosuppressants, such as budesonide.[60,61] These interventions should be offered and monitored by a gastroenterologist with expertise in celiac disease, because both symptom improvement and resolution of the enteropathy are considered in the response to treatment.

Prognosis of Celiac Disease

Implementation of the gluten-free diet is the only treatment for celiac disease and therefore acts to prevent possible morbidity and possible mortality associated with untreated celiac disease.

Morbidity

Research by Cosnes et al[62] suggested that the implementation of a gluten-free diet in patients with celiac disease may be associated with a protective effect against autoimmune disease such as thyroid disease. Researchers reported a lower cumulative risk of developing subsequent autoimmune disease in patients following a gluten-free diet compared with patients diagnosed with celiac disease not following a gluten-free diet for at least 10 years (6% [±2%] vs 15.6% [±5.9%], respectively).[62] Additionally, 2 Italian studies[63,64] suggest that a gluten-free diet may decrease the prevalence of thyroid autoantibodies; however, whether it protects against hypothyroidism or hyperthyroidism remains to be established. Men with undiagnosed celiac disease have an increased rate of osteoporosis and hypothyroidism and had a lower body mass index and lower levels of ferritin and cholesterol compared with women with undiagnosed celiac disease.[65] Last, infertility and recurrent abortion are reported as possible adverse pregnancy outcomes.[66]

Mortality

A number of studies have examined mortality in undiagnosed celiac disease. Some showed increased mortality, while others did not.[67-69] A recent meta-analysis suggested that the overall malignancy risk in patients with diagnosed celiac disease was not elevated, compared with the risk in general population–based controls.[70] However, individual cancers, such as lymphoproliferative cancer and gastrointestinal cancers,[71,72] may still be positively associated with celiac disease.

Practical Questions

Should Family Members of People With Celiac Disease Be Tested?

First-degree family members of patients with celiac disease have up to a 15- to 25-fold higher frequency of developing celiac disease based on their genetics, compared with individuals without a first-degree family member with celiac disease.[6,73] For that reason, the ACG, NASPGHAN, and ESPGHAN suggest screening first-degree family members with or without signs or symptoms concerning for celiac disease.[4,46,47] Recommendations include initiation of testing by age 3 years and, if serologic testing results are negative, repeating testing throughout a patient's lifetime. The US Preventive Services Task Force recently released recommendations that screening asymptomatic patients with or without a known increased risk of celiac disease, inclusive of family members, is not recommended, based on inadequate evidence regarding benefits and risks of this screening.[74,75]

When Should Clinicians Check for *HLA-DQ2* and *HLA-DQ8*?

Clinically, genetic testing for *HLA-DQ2* and *HLA-DQ8* may be helpful to determine whether patients in high-risk groups, such as family members or patients with comorbid conditions such as autoimmune thyroid disease, need screening for celiac disease. It also may be used for patients already following a gluten-free diet who have not been accurately assessed for celiac disease and are hesitant to reintroduce gluten into their diet for an accurate diagnostic reevaluation. In these cases, if patients do not carry the *HLA-DQ2* or *HLA-DQ8* genes, they would not require further diagnostic workup to evaluate for celiac disease. Celiac genetic testing may be useful in complicated cases such as in patients with signs and symptoms suggestive of celiac disease and with compatible histology but seronegative serology to solidify a diagnosis.[2] If patients are found to have compatible celiac genetics but other test results are normal, this places them among the nearly 40% of the general population that carries one of these genes. These patients should continue to follow a gluten-containing diet unless they are diagnosed with a gluten-related disorder.

How Does One Make a Diagnosis of Celiac Disease? What Serologic Tests Should Be Used?

Clinicians should start with serologic testing in patients presenting with signs and symptoms compatible with celiac disease or those who belong to a high-risk group (Table 2). Signs, symptoms, family history, and serologic results should be considered according to the

algorithm shown in Figure 2 to make a diagnosis. At the time that celiac disease serology is tested, patients should have been following a gluten-containing diet for at least some months.

What Are the Most Common Manifestations at Celiac Disease Presentation?

The clinical presentation of celiac disease is heterogeneous; thus, there is not a "typical" presentation. Testing for celiac disease should be considered in patients who have gastrointestinal manifestations such as abdominal pain, bloating, diarrhea, and constipation. Extraintestinal manifestations such as anemia, joint pain, osteoporosis, peripheral neuropathy, fatigue, and headache are frequent (Table 2). In pediatric patients, testing should be considered for those with slow or poor growth, delayed puberty, or tooth enamel defects.

How Common Is Iron-Deficiency Anemia or Osteoporosis the Presenting Sign or Symptom? Which Patients With Iron-Deficiency Anemia or Osteoporosis Should Be Screened for Celiac Disease?

At the time of diagnosis, approximately 28% and 9% of children may present with iron deficiency and iron-deficiency anemia, respectively.[35] Up to 32% of adults present with iron-deficiency anemia, making it the second most common clinical presentation after diarrhea.[7,76] Patients with otherwise unexplained iron-deficiency anemia, in those who do not respond to oral iron therapy, should be tested for celiac disease. In adults, osteoporosis may be present in 10% of patients at celiac disease diagnosis.[76] However, the frequency with which patients present with osteoporosis is likely underreported, since most cases of osteoporosis will not be apparent until a clinical complication such as a spontaneous fracture occurs. Therefore, physicians should have a low threshold for testing for celiac disease in children and adults with unexplained, spontaneous, or repetitive fracture.

Can a Gluten-Free Diet Be a Treatment for Situations That Do Not Belong to Gluten-Related Disorders?

There is no scientific evidence to suggest that a gluten-free diet is part of a healthier lifestyle or can be helpful to treat overweight or obesity. The incomplete digestibility of gluten (see "Pathophysiology" section) may explain why some people report nonspecific improvement in well-being after starting the gluten-free diet. Furthermore, gluten-containing cereals, particularly wheat, are also a primary source of FODMAPs (fermentable oligosaccharides, disaccharides, and monosaccharides and polyols), a group of highly fermentable but poorly absorbed short-chain carbohydrates and polyols. The reduction of FODMAPs associated with the gluten-free diet may explain, at least in part, why some patients affected with irritable bowel symptoms may report amelioration of their symptoms after starting a gluten-free diet.[77] Self-diagnosis of nonceliac gluten sensitivity should be discouraged to avoid misdiagnosis and inappropriate treatment.

Conclusions

Celiac disease and nonceliac gluten sensitivity are common. Although both conditions are treated with a gluten-free diet, distinguishing between celiac disease and nonceliac gluten sensitivity is important for long-term therapy. Patients with celiac disease should be followed up closely for dietary adherence, nutritional deficiencies, and the development of possible comorbidities.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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