Chapter 59: Celiac Disease

Priti N. Patel; Robert A. Mangione

KEY CONCEPTS

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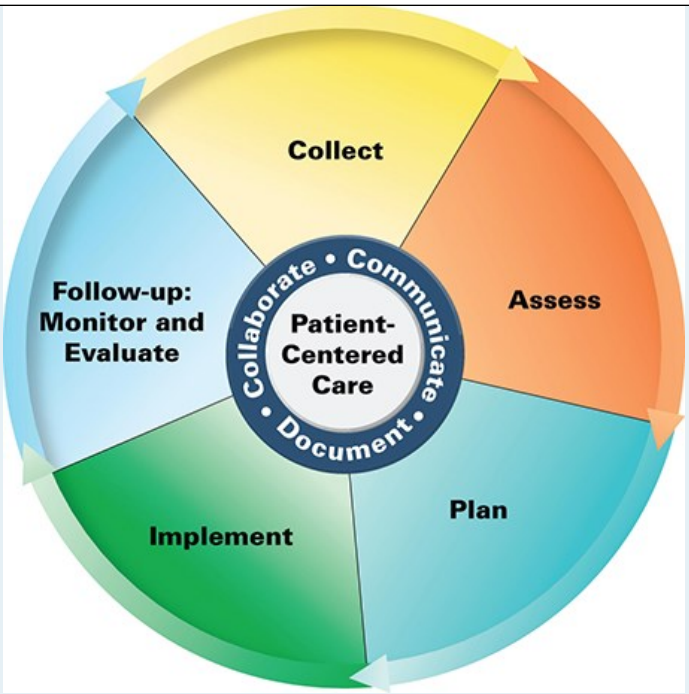
1. Celiac disease is a chronic, small intestinal immune-mediated enteropathy caused by intolerance to gluten found in wheat, barley, rye, and other foods when a genetically predisposed person is exposed to the environmental trigger, gluten.
2. The prevalence of celiac disease is 0.7% in America and is increasing in prevalence worldwide.
3. The integrity of the tissue junctions of the intestinal epithelium is compromised in patients with celiac disease; this enables gluten to reach the lamina propria. The presence of gluten in the lamina propria and an inherited combination of genes contribute to the heightened immune sensitivity to gluten that is found in patients with celiac disease.
4. The classic presenting symptom is diarrhea, which may be accompanied by abdominal pain or discomfort; however, during the past decade diarrhea has been reported as the main presenting symptom of celiac disease in less than 50% of cases.
5. Dermatitis herpetiformis is a skin manifestation of small intestinal immune-mediated enteropathy caused by exposure to dietary gluten.
6. The frequency of diagnosis of patients with celiac disease has increased; however, the majority of patients with this condition remain undiagnosed.
7. The confirmation of a diagnosis of celiac disease should be based on a combination of findings from the medical history, physical examination, serology, and duodenal biopsy. The recommended serologic marker that is used for screening patients is serum antitissue transglutaminase antibody.
8. Strict, lifelong adherence to a gluten-free diet is the only treatment for celiac disease that is available.
9. Clinicians must evaluate the patient with celiac disease for nutritional deficiencies (including folic acid, vitamin B_{12}, fat-soluble vitamins, iron, and calcium) due to malabsorption.

PATIENT CARE PROCESS

Patient Care Process for Celiac Disease



Collect

- Patient characteristics (eg, age, sex, height, weight)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use) and dietary habits including intake of gluten-containing grains (see Table 59-1)
- Current medications including nonprescription, herbal products, dietary supplements
- Objective data
  - Results of diagnostic testing (HLA typing, serology, and/or biopsy)
  - Results of testing for nutritional deficiencies (eg, iron, folic acid, vitamin D, vitamin B_{12})
  - Results of other testing (eg, DEXA)

Assess

- Presence of signs and symptoms of malnutrition or nutrient deficiency
- Ability/willingness to follow gluten-free diet
- Ability/willingness to pay for treatment options (gluten-free food, dietary supplements)
- Emotional status (eg, presence of anxiety, depression)
- Family/caregiver support

Plan*

- Patient education (purpose of treatment, dietary and lifestyle modification)

- Self-monitoring for symptoms of celiac disease (intestinal and extra-intestinal)
- Referral to dietician
- Dietary supplement regimen including specific product(s), dose, route, frequency, and duration
- Medication regimen including identification of gluten-free oral medications

Implement

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, adherence assessment)

Follow-up: Monitor and Evaluate

- Resolution of celiac disease symptoms (eg, intestinal and extra-intestinal)
- Patient's adherence to treatment plan
- Resolution of nutritional deficiencies
- Repeat testing as needed (serology, biopsy, labs for nutritional deficiencies, DEXA)

**Collaborate with patients, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

BEYOND THE BOOK

Read "Gluten in Medicine, Vitamins & Supplements" from the Celiac Disease Foundation at https://celiac.org/gluten-free-living/gluten-in-medicine-vitamins-and-supplements/. This provides a patient-centered guide for understanding the risks of gluten in medications and how patients with celiac disease may identify drugs that could pose problems for them. This is important information for pharmacists as well.

Read "Questions and Answers on the Gluten-Free Food Labeling Final Rule" from the Food and Drug Administration (FDA) at https://www.fda.gov/food/food-labeling-nutrition/questions-and-answers-gluten-free-food-labeling-final-rule. This question-and-answer format guide provides information on the FDA's gluten-free food-labeling regulation.

INTRODUCTION

1 Celiac disease is a small intestinal immune-mediated enteropathy caused by intolerance to ingested gluten, a storage protein found in wheat, barley, and rye. Genetic, environmental, and immune factors all play a role in the development of celiac disease. The mainstay of treatment of the disease is strict, lifelong adherence to a gluten-free diet.[1]

A disease resembling celiac disease was first described by a Greek physician in the second century AD. In the mid-1900s, the connection between the ingestion of cereals and celiac disease was made. For many years, celiac disease was considered a disease of childhood with primarily gastrointestinal (GI) symptoms. It is now recognized as a disease of all ages with varied presentations.

Celiac disease has been known as celiac sprue, nontropical sprue, and gluten-sensitive enteropathy; however, these terms are not recommended. The nonspecific use of celiac disease-related terminology may lead to misunderstandings. Accepted terms associated with celiac disease should be used

and understood when engaging in patient consultations or discussions with other healthcare providers. The publication of the Oslo Definitions of celiac disease helped to address this concern and further refining of appropriate terminology continues as new information is learned.[1] The Oslo classification used terminology such as “classic” and “non-classic” symptoms while more recent literature cites intestinal and extra-intestinal symptoms.[1]

The disease is characterized by both GI and extra-intestinal symptoms. Chronic inflammation caused by exposure to gluten leads to GI discomfort, nutrient malabsorption, and systemic complications. GI symptoms, including diarrhea, cramping, bloating, and flatulence, are the “classic” symptoms; however, a patient with celiac disease may initially present with a variety of extra-intestinal symptoms. Patients with subclinical celiac disease have no or minimal symptoms but manifest mucosal damage on biopsy and have positive serologic testing. Patients with celiac disease classified as potential are asymptomatic patients who may show positive serology and have the human leukocyte antigen (HLA)-DQ2 and/or DQ8 haplotype, but have normal mucosa on biopsy.[1,3]

Adherence to a gluten-free diet is essential because it improves symptoms and prevents long-term complications of celiac disease, which include T-cell lymphomas, small bowel adenocarcinoma, and esophageal and oropharyngeal carcinomas.[4]

EPIDEMIOLOGY

2 Originally thought to be a pediatric disease, celiac disease is now being diagnosed in increasing numbers of both adult and pediatric patients due to increased awareness and improved diagnostic techniques.[5] Celiac disease is common in Europe and North America. The prevalence of the disease is 0.71% to 0.79% in the United States, affecting up to 1% of White patients.[6] The prevalence of celiac disease is higher in females than in males at a rate of 1.5:1.[7] In Finland and the United States, the prevalence of celiac disease has increased fivefold during the past 50 years.[8]

Celiac disease has been less well studied in other parts of the world. Previously believed to rarely occur in racial groups other than White patients, improved screening and diagnostic techniques prove that the prevalence of celiac disease in many non-Western nations is similar to that in Europe and North America.[9] The common and increasing use of wheat in diets, coupled with the prevalence of HLA-DQ2, may lead to an increase in the prevalence of celiac disease in the global population in coming years in areas where celiac disease is rarely diagnosed.[10,11]

ETIOLOGY

Celiac disease is known to occur when a genetically predisposed person ingests gluten. Wheat gluten proteins exist in two fractions: gliadins and glutenins. Wheat, barley, and rye are all derived from the Triticeae tribe of the grass (Gramineae) family. Proteins similar to glutenins, called hordeins and secalins, are found in barley and rye, respectively. Table 59-1 refers to grains and other foods that do and do not contain gluten and related proteins. Ingestion of any of these proteins will lead to an autoimmune response in patients with celiac disease. Oats, from the Aveneae tribe, are distantly related and therefore contain fewer disease-activating proteins.[13] One concern with oats is that they may be contaminated with gluten during the manufacturing process.[13]

TABLE 59-1

Grains and Other Foods That Do and Do Not Contain Gluten

Contain Gluten	Do Not Contain Gluten
Wheat	Amaranth
Barley	Buckwheat
Rye	Corn
Bran	Flax
Graham flour	Millet
Spelt	Potato flour
Wheat germ	Quinoa
Triticale	Rice
Oats[a]	Sorghum
	Soybeans
	Tapioca
	Teff

[a]Oats are in a different plant family, but they have also been regarded as problematic, although the ingestion of certified pure gluten-free oats is safe in most patients with celiac disease.[12] Due to the continued difference of opinion regarding the safety of oats, patients are generally advised to discuss the risks and benefits associated with consuming oats with their healthcare provider before they include oats in their diet.

Genetic factors, in combination with exposure to gluten, are necessary for the development of celiac disease. There is a concordance rate of 85% in monozygotic twins indicating that genetics play a large role in the disease, but other factors also are likely to involved.[13,15]

Most patients with celiac disease have variants of HLA-DQ2 or HLA-DQ8 molecules that are expressed on the surface of antigen-presenting cells.[3,4] Other non-HLA genes may also play a role in enhancing genetic susceptibility to celiac disease.[16]

Various infections and compounds may contribute to the development of celiac disease. There is an association between change in the gut microbiome and celiac disease; however, experts caution against suggesting that the gut microbiome causes celiac disease since many environmental factors that play a role in celiac disease also affect the gut microbiome.[1,17] GI, upper respiratory, and lower respiratory infections are risk factors for the development of celiac disease. Various drugs, such as olmesartan, azathioprine, methotrexate, as well as others, may play a role in the development of sprue-like bowel disease.[2]

In Sweden, increased rates of diagnosis of celiac disease in the mid-1980s was thought to correspond to a change in infant feeding practices. However, the timing of gluten introduction or duration of breastfeeding did not avoid the eventual diagnosis of celiac disease, even at children at higher risk due to the presence of one of the high-risk HLA haplotypes.[16]

PATHOPHYSIOLOGY

During normal digestion, peptides that remain from gastric or pancreatic digestion are broken down into amino acids, dipeptides, or tripeptides by the small intestinal brush-border membrane enzymes.[16] These GI proteases that are found in the intestinal lumen are one of the body's first defenses against potentially toxic dietary proteins.[18] The intestinal epithelium, with its intact intercellular tight junctions, functions as the primary barrier to the passage of macromolecules into the lamina propria. Gluten is unusually rich in the amino acids glutamine and proline, which enable part of the molecule to withstand the digestive processes. These peptides are kept within the GI tract and are primarily excreted before they can illicit an immune reaction. Small fractions of gluten do cross this important defense barrier in patients without celiac disease; however, the quantity of gluten that passes across the GI lining is generally insufficient to illicit a significant response from a normally functioning immune system.[18]

Pathophysiology of celiac disease is associated with an interaction between gluten and immune, genetic, and environmental factors.[18] In celiac disease, the integrity of the tissue junctions of the intestinal epithelium is compromised, enabling gluten to reach the lamina propria through different routes. The presence of gluten in the lamina propria and an inherited combination of genes contribute to the heightened immune sensitivity to gluten found in patients with celiac disease (Table 59-2).[18] The notable immune response to gluten consists of both adaptive and innate immune responses that occur only in individuals who carry the HLA type DQ2 or DQ8.[18] The precise mechanism by which the immune system leads to damage of the intestinal lining of patients with celiac disease continues to be studied.

TABLE 59-2

Proposed Pathophysiology of Celiac Disease

- Enterocytes release the protein zonulin in response to the presence of indigestible fragments of gluten in the intestine.
- Zonulin loosens the intercellular tight junctions.
- Abundant quantities of gluten fragments cross the intestinal lining and accumulate under the enterocytes (epithelial cells).
- Gluten induces the enterocytes to secrete interleukin-15 (IL-15).
- IL-15 induces an immune response of intraepithelial lymphocytes against the enterocytes.
- The damaged cells release the enzyme tissue transglutaminase (tTG), which modifies the gluten.
- Antigen-presenting cells of the immune system join the modified gluten to HLA molecules and display the resulting complexes to other immune cells (ie, helper T cells).
- Helper T cells that recognize the complexes secrete molecules that attract other immune cells, which may result in damage to the enterocytes.
- Helper T cells spur killer T cells that directly attack the enterocytes.
- B cells release antibody molecules that are targeted to gluten and tTG (the role that these antibodies play remains to be further clarified; however, they may cause further damage when they contact their targets on or near the enterocytes).
- Enterocytes are disabled or killed.

Data from Reference 18.

Nonceliac gluten sensitivity is a condition in which the ingestion of gluten results in morphological or symptomatic manifestations in the absence of celiac disease.[19] This disorder must therefore be considered in the differential diagnosis of celiac disease. Symptoms alone cannot reliably differentiate celiac disease from nonceliac gluten sensitivity. Therefore, a diagnostic evaluation including celiac serology and small-intestinal biopsy (while the patient is including gluten in their diet) is needed. If these tests are negative, HLA-DQ typing is required to differentiate between the two disorders. Differentiating between these disorders is important as it will impact the implications of the level of adherence to the gluten-free diet, approach to continued disease-state monitoring and evaluation, and the counseling of family members (as nonceliac disease sensitivity does not have a strong hereditary basis).[4]

The primary toxic components of wheat gluten are a family of closely related proteins called gliadins.[18] The gliadin peptides induce changes in the epithelium through innate immunity and in the lamina propria through adaptive immunity.[18]

Tissue transglutaminase (tTG), a ubiquitous enzyme that catalyzes posttranslational modification of proteins and is released during inflammation, may play at least two crucial roles in celiac disease by serving as the main target autoantigen for antiendomysial enzymes and as a deaminating enzyme that raises the immunostimulatory effect of gluten. This enzyme, by deaminating glutamine to glutamic acid, makes the gliadin peptides become negatively charged and therefore more capable of fitting into pockets of the HLA-DQ2 (or HLA-DQ8) antigen-binding groove on the antigen-presenting cells.[21] Gliadin is presented to gliadin-reactive CD4 T cells through a T-cell receptor, which then results in the production of cytokines that cause tissue damage. This then leads to villous atrophy, crypt hyperplasia, and the expansion of antibody-producing B cells found in celiac disease.[21]

CLINICAL PRESENTATION

4 The recognition of celiac disease may be quite challenging due to the wide range of presenting symptoms, which includes patients who are asymptomatic.[1] Clinical manifestations of celiac disease significantly vary with age group (Table 59-3) in that pediatric patients are more likely to experience classic GI symptoms while adults are more likely to have extra-intestinal symptoms.[2] Infants and young children generally experience diarrhea, abdominal distention, and failure to thrive. Vomiting, irritability, anorexia, and even constipation are also common in these young patients. Extra-intestinal manifestations such as short stature, neurologic findings (eg, peripheral neuropathy, ataxia, seizure, migraine, and dementia), or anemia are often found in older children and adolescents.[23] The classic presenting symptom in adults is diarrhea, which may be accompanied by abdominal pain or discomfort; however, during the past decade diarrhea has been reported as the main presenting symptom of celiac disease in less than 50% of cases.[19,20] Adults may exhibit iron-deficiency anemia or osteoporosis. Less common presentations of celiac disease in adults include abdominal pain, constipation, weight loss, neurologic symptoms, dermatitis herpetiformis, hypoproteinemia, hypocalcemia, and elevated liver enzymes. Patients with celiac disease without GI symptoms often experience symptoms for a long period of time before celiac disease is diagnosed.[24]

TABLE 59-3

Selected Signs and Symptoms of Celiac Disease

Children	Adults
Symptoms • Fatigue • Bloating • Constipation • Abdominal pain • Chronic diarrhea • Irritability • Vomiting **Signs** • Muscle wasting • Failure to thrive/weight loss • Short stature • Delayed puberty • Osteopenia/osteoporosis • Hepatitis • Dental anomalies • Anemia	**Symptoms** • Abdominal pain • Chronic diarrhea • Abdominal distension • Recurrent spontaneous abortion • Peripheral neuropathy • Depression • Fatigue/malaise • Ataxia **Signs** • Weight loss • Infertility • Dermatitis herpetiformis • Hepatitis • Anemia • Aphthous ulcers • Alopecia • Malignancy • Seizures • Osteopenia/osteoporosis • Arthritis

Data from Reference 22.

5 Dermatitis herpetiformis is a skin manifestation of small intestinal immune-mediated enteropathy caused by the ingestion of gluten.[25] This extremely pruritic, bullous skin rash should prompt testing for celiac disease.[25]

6 The diagnosis of celiac disease is based on clinical suspicion and confirmation with laboratory tests and duodenal biopsy.[4] Although the prevalence of celiac disease has increased, many patients with this condition remain undiagnosed.[4] This is particularly concerning as undiagnosed celiac disease has been associated with a nearly fourfold increased risk of death compared with subjects without serologic evidence of disease.[12]

Healthcare providers should recognize the many and diverse possible symptoms of celiac disease.[19] A delay in diagnosis is often reported, with longer times to diagnosis in patients who primarily exhibit extra-intestinal symptoms.[24] Clinicians can help reduce the time from the onset of symptoms to the diagnosis of celiac disease by being aware of the common diseases that may also coexist with celiac disease (Table 59-4).[24]

TABLE 59-4

Selected Common Misdiagnoses

- Irritable bowel syndrome
- Viral gastroenteritis
- Lactose intolerance
- Amoebic/parasitic infection
- Inflammatory bowel disease
- Psychological dysfunction
- Gallbladder disease
- Chronic fatigue syndrome
- Gastroesophageal reflux disease
- Allergies
- Ulcers
- Cystic fibrosis
- Colitis

Data from Reference 4.

Individuals with certain disorders are more likely to have celiac disease than the general population. Examples include other autoimmune diseases, such as thyroid disease, diabetes mellitus (type 1), multiple sclerosis, myasthenia gravis, Raynaud's disease, rheumatoid arthritis, Addison's disease, chronic active hepatitis, cystic fibrosis, scleroderma, and Sjögren's syndrome; Down's syndrome; neurologic conditions such as ataxia, epilepsy, and cerebral calcifications; and primary biliary cirrhosis. Although patients with these disorders are more frequently found to have celiac disease than the general population, these associated conditions are not believed to cause celiac disease.[26]

7 Diagnostic testing for celiac disease must be performed while the patient continues to consume gluten; patients who have already started on a gluten-free diet prior to diagnosis should consume three slices of wheat bread daily for 1 to 3 months before testing commences.[5,27] A confirmed diagnosis of celiac disease requires both a positive finding on duodenal biopsy and a positive response to a gluten-free diet.[4] The identification of villous atrophy with small bowel endoscopy and biopsy is generally regarded as the diagnostic gold standard (although according to the guidelines from the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition a small intestinal biopsy may not be required in children with typical symptoms, titers of anti-tTG greater than 10 times the upper normal limit and predisposing HLA genotype).[28] Although villous atrophy is associated with celiac disease, clinicians must consider that this may also be found in other diseases, including giardiasis, autoimmune enteropathy, tuberculosis, Crohn's disease, intolerance to food other than gluten, intestinal lymphoma, and Zollinger–Ellison syndrome.[4]

Histologic changes seen on biopsy are categorized according to one of several classification systems including the Marsh, Marsh modified, or the Corazza, all of which examine intraepithelial lymphocytes, crypt hyperplasia and villous atrophy.[4] Histologic findings lead to a diagnosis that is followed by placing the patient on a gluten-free diet. Dermatitis herpetiformis is diagnosed by skin biopsy.[29]

Serologic test results provide clinicians with a useful non-invasive tool that helps to determine if symptomatic patients, or patients who are at risk for celiac disease, require a biopsy.[4] Available tests include those for deamidated gliadin peptide (DGP) IgA or IgG antibodies, anti-endomysial antibodies, and antibodies against tTG. The American College of Gastroenterology recommends tTG IgA testing for patients 2 years and older and DGP IgA and IgG combined with IgA tTG for patients younger than 2 years.[4] Although serology is a good method to identify patients who will benefit from endoscopy and biopsy, negative serology should not preclude a biopsy examination in individuals for whom disease is suspected on clinical grounds.[4] Positive serology should be followed with confirmatory testing via biopsy, with the exception of some children who may be diagnosed based on serology alone.[4,28]

Genetic testing can be performed as a means of determining which family members of a diagnosed patient may develop the disease (the prevalence of

celiac disease is 10% to 12% in first-degree relatives and is also higher than that found in the general population in second-degree relatives).[4] Patients and their family members can be tested for HLA-DQ2 and HLA-DQ8 as HLA-DQ2 is found in up to 95% of patients with celiac disease, with most other patients being HLA-DQ8 positive.[4] Although nearly all patients with celiac disease carry one of these alleles, they are also found in 30% to 40% of the general population. When these alleles are absent, it is extremely unlikely that the individual has celiac disease (ie, the test has a high negative predictive value).[4] A patient-administered saliva-based test for HLA-DQ2/DQ8 was released for direct sale to consumers but is not recommended for use in the diagnosis of celiac disease.[4]

In 2017, the US Preventive Services Taskforce stated that the evidence on hand is "insufficient to assess the balance and harms of screening for celiac disease in asymptomatic persons."[30]

Forms of celiac disease that have been identified in practice since the publication of the Oslo classification include seronegative celiac disease, in which a patient experiences symptoms and positive findings in biopsy but is negative for serum markers, and gluten-free diet-nonresponsive celiac disease, in which a patient does not respond to 12 months of strict gluten-free diet.[2] Potential celiac disease is an additional new term indicating the presence of serum antibodies and HLA-DQ2/8 but normal intestinal mucosa.[31]

TREATMENT

Desired Outcomes

The main goals of treatment include relieving symptoms, healing the intestine, and prevent complications. In children, increases in height and weight are additional goals.[27]

General Approach to Treatment

The mainstay of treatment of celiac disease is the strict, lifelong adherence to the gluten-free diet. Supportive care of nutrient deficiencies should be addressed through drug therapy and preventive care, such as vaccines, should be recommended.

Nonpharmacologic

Table 59-5 presents a mnemonic that summarizes the major principles of the treatment of celiac disease. Strict lifelong adherence to a gluten-free diet is the only proven treatment for celiac disease.[1] Patients must recognize that adhering to a gluten-free diet includes not ingesting anything that contains gluten or has been contaminated with gluten. Wheat, barley, and rye must be avoided.[3] Although oats are in a different plant family, they may be problematic; however, the ingestion of certified pure gluten-free oats is safe.[25] Due to the continued difference of opinion regarding the safety of oats, they should be added to the diet cautiously and with monitoring.[4] Patients must also commit to avoiding the ingestion of gluten found in nonfood items such as toothpaste, lip balm, lipstick, etc.[12] A list of gluten-free grains can be found in Table 59-1.

TABLE 59-5

Mnemonic for Celiac Disease

C	**C**onsultation with a skilled dietician
E	**E**ducation about the disease
L	**L**ifelong adherence to a gluten-free diet
I	**I**dentifying and treating nutritional deficiencies
A	**A**ccess to an advocacy group
C	**C**ontinuous long-term follow-up by a multidisciplinary team

Data from Reference 32.

Oral prescription drugs, nonprescription drugs, vitamin and mineral supplements, and health and beauty aids and cosmetics that have oral ingestion potential must not be overlooked as sources of gluten due to its presence in their formulation or due to contamination or contact.[12] Lack of reliable information can be confusing and although there are published lists of gluten-free drugs, it is often difficult to obtain information about the gluten content of medications.[33] Patients with celiac disease are concerned about the possibility of gluten in medications causing disease-related symptoms.[34] Also, the FDA issued draft guidance on "Gluten in Drug Products and Associated Label Recommendations" encouraging drug manufacturers to have accurate information about their products' gluten content available so they can respond to questions from consumers. Healthcare professionals and some researchers have advocated that all medications should be gluten-free.[35] Clinicians should realize that conflicting data regarding drug absorption requires careful selection and use of drugs in patients with celiac disease.[36]

The FDA determined the tolerable daily intake level for gluten in individuals with celiac disease to be 0.4 mg gluten/day for adverse morphologic effects and 0.015 mg gluten/day for adverse clinical effects and ruled that foods labeled on or after August 5, 2014 as gluten-free must contain less than 20 ppm gluten.[37,38] Although the ruling pertains to food only, the concerns regarding low-level exposure emphasize why healthcare providers must check to determine whether prescription drugs contain gluten in their formulation or have been contaminated with gluten before these drugs are provided to the patient with celiac disease.

9 Newly diagnosed patients should be evaluated for nutritional deficiencies associated with vitamin and mineral malabsorption, including folic acid, vitamin B_{12}, fat-soluble vitamins, iron, and calcium.[4] Monitoring for potential nutritional deficiencies should also continue during subsequent follow-up visits.

Most adults with celiac disease have some degree of bone loss. Therefore, all patients must be screened for osteoporosis or osteopenia.[39,40] Supplementing a gluten-free diet with calcium, magnesium, and vitamin D may arrest or reverse celiac-related bone loss. Although their use has not been extensively studied in patients with celiac disease, bisphosphonates and other drugs have been prescribed for patients with bone disease.[36]

Implementing a gluten-free diet presents some challenges. Consultation with a registered dietician is recommended for dietary evaluation and education.[4] Patients are advised to initiate a complete gluten-free lifestyle immediately after diagnosis. Partial adherence to this diet is not adequate. In order to accomplish this objective, patients must be aware of what foods are gluten-free and when in doubt must know how to confirm whether a food contains gluten. Reading labels is extremely important; however, it may be difficult to identify hidden sources of gluten listed among the ingredients. Patients with celiac disease must also determine whether products were processed on equipment shared with wheat, barley, or rye. It may be necessary to call the manufacturers or check their website to obtain the needed information.[41] Patients should seek guidance from a dietitian in order to avoid incurring nutritional deficiencies such as with fiber, vitamins and minerals, or overconsumption of fats, both of which can occur with gluten-free diets.[1]

Individuals with celiac disease must also be advised to maintain a gluten-free kitchen. A dedicated toaster, bread maker, waffle iron, and other appliances should be obtained for use in preparing gluten-free meals. Utensils and dishes must be carefully cleaned to avoid gluten contamination. Care must also be taken when dining in restaurants and homes of family and friends. The individuals who prepare and serve the food must be knowledgeable about gluten-free foods and food preparation.[12] The economic burden associated with maintaining a gluten-free diet may present some challenges.[42] The relatively low availability and high cost of these foods contribute to the challenges associated with adhering to the required strict diet and may lead to varying degrees of noncompliance.[43,44] Patients also find that the extra cost associated with the special diet is not reimbursed by healthcare plans, and most policies do not pay for consultations with a dietician.[44] These challenges with compliance are particularly concerning as noncompliance with the gluten-free diet is associated with an increased mortality rate and compromised quality of life.[43] Hypervigilance to a strict gluten-free diet may negatively impact upon the patient's quality of life and clinicians should therefore also promote the social and emotional well-being of the patient while counseling about the importance of adhering to the gluten-free diet.[45] Patients are also encouraged to investigate their personal circumstances as to whether some of the costs of maintaining a gluten-free diet are eligible for approval as a tax deduction.[44]

Pharmacologic

Dietary avoidance of gluten remains the mainstay of treatment of celiac disease. Novel pharmacologic treatment modalities are under investigation. Most reports related to pharmacotherapy for celiac disease focus on the treatment of refractory disease.

In case reports, corticosteroids, azathioprine, cyclosporine, tacrolimus, infliximab, and alemtuzumab have been reported as effective treatments for refractory celiac disease. Patients characterized to have refractory celiac disease have persistent or recurrent malabsorptive symptoms and signs with villous atrophy despite maintaining a gluten-free diet for more than 12 months.[1] Less than 5% of adult patients have refractory celiac disease.

Based on the pathophysiology of celiac disease, novel targets for the treatment of the disease have been identified: decreasing the antigenic load and modulation of the immune response. Methods of decreasing the antigenic load include blocking the activity of tTG, GI destruction of proline peptides via enzyme therapy, blocking the binding of deaminated proteins to HLA-DQ2 and HLA-DQ8, detoxification of gluten peptides, and decreasing intestinal permeability in patients with celiac disease, in particular through inhibition of zonulin.[2] A zonulin inhibitor, larazotide, was well tolerated and had efficacy in three phase-2 studies, allowing patients to tolerate small amounts of gluten through symptom control in patients who did not respond fully to a gluten-free diet.[1,47] Latiglutenase is a combination of recombinant proteases which aims to digest small amounts of gluten.[1]

EVALUATION OF THERAPEUTIC OUTCOMES

Clinical improvement will often be observed within days or weeks of instituting a strict gluten-free diet.[47] Repeat biopsy may be a helpful tool to monitor mucosal healing, particularly in patients with ongoing symptoms.[1,27]

Healthcare providers must also be mindful of conditions that are related to celiac disease and that are potential complications of the disease, including certain forms of cancer, neurologic manifestations, osteoporosis, depression, diabetes, infertility, as well as other autoimmune and related illnesses. Cancers that are of particular concern include thyroid cancer, adenocarcinoma of the small intestine, lymphoma (predominantly non-Hodgkin's lymphoma of any type), esophageal cancer, melanoma, and malignancies found in childhood.[3] Patients with celiac disease have an increased risk of developing certain infectious diseases, including pneumococcal infection.[48] Therefore, the pneumococcal vaccine should be recommended for all age groups, especially for those patients who did not receive the vaccine as a child.[48] Annual influenza vaccine is advisable as this will reduce the incidence of secondary bacterial infections.[49]

ABBREVIATIONS

DEXA	dual-energy X-ray absorptiometry
GI	gastrointestinal
HLA	human leukocyte antigen
IgA	immunoglobulin A
SIgA	serum immunoglobulin A
tTG	tissue transglutaminase

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SELF-ASSESSMENT QUESTIONS

1. Which of the following grains contains gluten?

   A. Sorghum

B. Buckwheat

C. Bran

D. Amaranth

2. Which drugs have been reported to play a role in the development of a sprue-like bowel disease?

A. Omeprazole

B. Olmesartan

C. Omalizumab

D. Octreotide

3. Regarding the role of breastfeeding and the risk of celiac disease, what is an appropriate recommendation?

A. Avoiding breastfeeding can delay the onset of celiac disease

B. Delaying the cessation of breastfeeding can avoid the onset of celiac disease

C. Early introduction of gluten during breastfeeding delayed the onset of celiac disease

D. The timing of gluten introduction in relation to breastfeeding does not avoid the eventual diagnosis of celiac disease

4. In active celiac disease, damaged cells release which enzyme that modifies gluten?

A. Interleukin-15

B. Tissue transglutaminase

C. Pancrease

D. Pepsin

5. Which symptom of celiac disease may appear more commonly in children than in adults?

A. Vomiting

B. Fatigue

C. Abdominal pain

D. Diarrhea

6. When should diagnostic measures occur?

A. Before a gluten-free diet is initiated

B. At the same time that a gluten-free diet is initiated

C. After a gluten-free diet is initiated

D. With no consideration to timing of initiation of a gluten-free diet

7. Which of the following disorders is more likely to be present in individuals with celiac disease?

A. Asthma

B. Cardiac hyperplasia

C. Dyslipidemia

D. Diabetes mellitus

8. A 45-year-old male patient with chronic diarrhea and a 10-lb (4.5 kg) weight loss over 3 months is tested for HLA-DQ2. The test is positive. Which of the following statements is correct?

A. The patient is confirmed to have celiac disease based on this serology test.

B. Based on this serology test, the patient does not have celiac disease.

C. The patient must undergo endoscopy with biopsy to confirm the diagnosis of celiac disease.

D. The test is inconclusive as the patient should have been tested for HLA-DQ8 as that is more common.

9. A patient is confirmed to have celiac disease after a positive biopsy. His two teenage sons wish to know if they are at risk for celiac disease as well. Which of the following tests can be used to his sons for celiac disease?

A. CD4 count

B. Antigliadin antibodies

C. Tissue transglutaminase

D. HLA DQ2 and DQ8

10. Which of the following nutritional deficiencies needs to be assessed in newly diagnosed patients with celiac disease?

A. Vitamin C

B. Zinc

C. Iron

D. Selenium

11. Within what period of time is clinical improvement often observed in patients with celiac disease after initiating a strict gluten-free diet?

A. Within days or weeks

B. 6 months to 1 year

C. 1 to 2 years

D. 2 to 3 years

12. What did the Food and Drug Administration (FDA) rule in 2014 in relation to gluten?

A. Foods labeled as gluten-free must contain less than 20 ppm gluten.

B. Both foods and drugs labeled gluten-free must contain less than 20 ppm gluten.

C. Drugs labeled gluten free must contain less than 20 ppm gluten.

D. The FDA issued a warning in 2014 and will revisit the issue in 2020.

13. A 13-year-old girl with celiac disease is being counseled on avoiding nonfood sources of gluten. Which of the following personal care items should they be warned of?

    A. Shampoo

    B. Body lotion

    C. Nail polish

    D. Lipstick

14. Which of the following recommendations is appropriate for patients with celiac disease?

    A. They should be screened for dyslipidemia annually.

    B. Patients of all ages should receive the pneumococcal vaccine.

    C. They must only use topical products that are gluten-free.

    D. All patients should undergo a skin biopsy to detect dermatitis.

15. A novel drug in development for the treatment of celiac disease, larazotide, targets which of the following?

    A. Tissue transglutaminase

    B. HLA-DQ2

    C. Proline peptides

    D. Zonulin

SELF-ASSESSMENT QUESTIONS ANSWER

1. **C.** Bran is a gluten-containing grain.

2. **B.** There are numerous reports in the published literature of olmesartan causing a sprue-like bowel disease.

3. **D.** While earlier reports supported the idea of introducing gluten during breastfeeding during a specific “window” between 4 and 6 months of age to minimize the risk of celiac disease, this does not seem to be the case based on newer studies. The timing of gluten introduction does not affect the risk of eventual celiac disease diagnosis.

4. **B.** Tissue transglutaminase is the enzyme that modifies gluten.

5. **A.** Vomiting is a symptom that may be seen more commonly in children than in adults.

6. **A.** The diagnosis of celiac disease should occur before a gluten-free diet is initiated; that is, while gluten is still being consumed.

7. **D.** Diabetes mellitus is more likely to be present in patients with celiac disease.

8. **C.** A positive serology test must be confirmed by a biopsy to properly diagnose celiac disease. A negative serology test can effectively rule out celiac disease, unless a patient’s symptoms warrant further investigation via endoscopy.

9. **D.** Family members can be screened for celiac disease using the serology tests HLA-DQ2 and HLA-DQ8. Negative tests for both of these can effectively rule out celiac disease in the absence of symptoms.

10. **C.** Calcium, vitamin D, and iron all need to be assessed upon diagnosis and addressed appropriately. Zinc, vitamin C, and selenium are less common nutritional deficiencies in celiac disease and do not need to be assessed upon diagnosis.

11. **A.** Clinical improvement can be seen in a patient with celiac disease days to weeks after instituting a gluten-free diet.

12. **A.** The FDA ruled that foods labeled on or after August 5, 2014 as gluten-free must contain less than 20 ppm gluten.

13. **D.** Gluten can be ingested orally through lipstick.

14. **B.** It is recommended for patients with celiac disease of all ages to receive the pneumococcal vaccine, particularly if they did not receive the vaccine as a child.

15. **D.** Larazotide is a zonulin inhibitor.