

Review



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Advances in Celiac Disease and Gluten-Free Diet

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ABSTRACT

Celiac disease is becoming an increasingly recognized autoimmune enteropathy caused by a permanent intolerance to gluten. Once thought to be a rare disease of childhood characterized by diarrhea, celiac disease is actually a multisystemic disorder that occurs as a result of an immune response to ingested gluten in genetically predisposed individuals. Screening studies have revealed that celiac disease is most common in asymptomatic adults in the United States. Although considerable scientific progress has been made in understanding celiac disease and in preventing or curing its manifestations, a strict gluten-free diet is the only treatment for celiac disease to date. Early diagnosis and treatment, together with regular follow-up visits with a dietitian, are necessary to ensure nutritional adequacy and to prevent malnutrition while adhering to the gluten-free diet for life. The purpose of this review is to provide clinicians with current updated information about celiac disease, its diverse clinical presentation and increased prevalence, the complex pathophysiology and strong genetic predisposition to celiac disease, and its diagnosis. This review focuses in detail on the gluten-free diet and the importance of intense expert dietary counseling for all patients with celiac disease. Recent advances in the gluten-free diet include food allergen labeling as well as the US Food and Drug Administration's proposed definition of the food-labeling term *gluten-free*. The gluten-free diet is complex

and patients need comprehensive nutrition education from a skilled dietitian.

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Celiac disease is becoming an increasingly recognized disorder. This disease is a complex autoimmune enteropathy caused by a permanent intolerance to gluten in genetically susceptible individuals. Gluten is the main storage protein of wheat. The alcohol-soluble fraction (prolamin) of gluten, gliadin, is toxic in celiac disease, as are similar proteins in barley (hordein) and rye (secalin) (1). Celiac disease is associated with maldigestion and malabsorption of nutrients, vitamins, and minerals in the gastrointestinal tract. Epidemiological studies in Europe and the United States indicate that celiac disease is common and that the prevalence of celiac disease is approximately 1% in the general population (2-7). Long delays between onset of symptoms and diagnosis often occur (8), and the condition remains underdiagnosed. Currently, the only available treatment is lifelong adherence to a gluten-free diet (4).

CLINICAL PRESENTATION

Samuel Gee, MD, described the classical features of celiac disease in 1887 as diarrhea, lassitude, and failure to thrive (9). At that time, Gee believed regulation of food was the main part of the treatment and noted that the disease was not age-specific. In 1953, Willem Karel Dicke demonstrated in a controlled study, that wheat, rye, and barley triggered celiac disease, and that the condition could be reversed after their exclusion from the diet (10). The first accurate description of the celiac lesion, however, was by Paulley, in 1954, when he examined full-thickness biopsy specimens taken at laparoscopy from a patient with celiac disease. He described broad flat villi and a dense chronic lymphoepithelial inflammatory cell infiltrate in the small intestinal mucosa (11). A staging of mucosal injury, first described by Marsh, demonstrated the pathological spectrum of celiac disease, and described the progression of the abnormalities of the intestinal mucosal response to gluten. Five interrelated lesions have been characterized that range from minimal injury of the mucosa with an increase in intraepithelial lymphocytes to total villous atrophy (12). The classic celiac lesion is characterized by infiltration of lymphocytes in the epithelium and the lamina propria, with crypt hyperplasia and villous atrophy (12-15).

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The clinical presentation of celiac disease varies greatly, depending on a patient's age, the duration and extent of the disease, and presence of extraintestinal manifestations (16). Celiac disease primarily affects the proximal small intestine, but can involve the entire small intestine in some individuals. This proximal location of celiac disease often results in overt malabsorption of vitamins and minerals. Diarrhea in celiac disease presentation is due to progression of the disease into the distal small bowel (3).

Classic symptoms associated with celiac disease in children are diarrhea, abdominal distension, and failure to thrive (3). Similarly, adolescents and adults present with diarrhea, constipation, weight loss, weakness, short stature, flatus, abdominal pain, and vomiting (8,17,18). Presence of obesity does not exclude the diagnosis of celiac disease (19,20). Atypical clinical manifestations of celiac disease are characterized by few or no gastrointestinal (GI) symptoms, instead, extraintestinal symptoms such as iron-deficiency anemia, reduced bone mineral density, chronic fatigue, irritable bowel, dyspepsia, infertility, miscarriage, hypertransaminemia, coagulopathy, short stature, pubertal delay, arthralgia, aphthous stomatitis, folate/zinc deficiency, dental enamel hypoplasia, and otherwise unexplained neurological disorders (primarily peripheral neuropathy and ataxia) predominate (14,15,17-19,21).

Patients who have a subclinical form of celiac disease are unaware of it because outwardly they have no physical symptoms, yet they have positive serological test results for celiac disease and villous atrophy on intestinal biopsy (19). Subclinical celiac disease is identified as a result of screening at-risk groups or by recognition on biopsies obtained for another indication (ie, dyspepsia or reflux) (22,23). At-risk groups include first-degree relatives of patients with celiac disease (2,24); people with Down syndrome (25); and those with an autoimmune disease, such as type 1 diabetes (24,26) and Hoshimoto's thyroiditis (27,28). Autoimmune disorders occur 3 to 10 times more frequently in those with celiac disease than in the general population (29-31). Evidence exists that the risk of developing other autoimmune conditions increases with length of exposure to gluten (31). Conditions that are associated with an increased prevalence of celiac disease are rheumatoid arthritis (32), systemic lupus erythematosus (33), autoimmune liver disease (34,35), Turner syndrome (19), Williams syndrome, Addison's disease (36), alopecia areata, Sjögren's syndrome (28), cholangitis, primary biliary cirrhosis, autoimmune hepatitis, peripheral neuropathy, psoriasis, and cardiomyopathy (35,37). An increased incidence of small bowel malignancies, adenocarcinoma, and enteropathy-associated T-cell lymphoma has been reported in untreated celiac disease (8,38).

One unique presentation of celiac disease is dermatitis herpatiformis, an uncommon skin manifestation that affects about 10% to 20% of patients with celiac disease (39,40). This extremely pruritic, blistering, chronic skin rash is classically characterized by symmetrical papulovesicular lesions frequently affecting the knees, elbows, buttocks, and back (41). Although patients with dermatitis herpatiformis are unlikely to have GI symptoms or features of malabsorption (42), serological antibody pro-

| | |
|--|----------|
| In the general population: | 1 in 133 |
| In symptomatic children: | 1 in 322 |
| In symptomatic adults: | 1 in 105 |
| In first-degree relatives of people with CD: | 1 in 22 |
| In second-degree relatives of people with CD: | 1 in 39 |
| In chronic diseases (such as type 1 diabetes): | 1 in 60 |
| In African-, Hispanic-, and Asian-Americans: | 1 in 236 |
| World-wide prevalence: | 1 in 266 |

Figure 1. Estimated prevalence of celiac disease (CD) (2,15,16).

files are similar and inflammatory small intestinal mucosal damage is identical to those seen in celiac disease (42). Manifestations of dermatitis herpatiformis are responsive to gluten-free diet (41) and dosages of Dapsone, a medication used to treat the rash, may be decreased with the gluten-free diet.

Currently, celiac disease is thought to resemble a multisystem immunological disorder rather than a disease restricted to the GI tract (17,20). Studies confirm (17,18,43) that fewer patients present with severe GI symptoms, and the clinical face of celiac disease in the United States is diverse. Adult presentations are now more common than pediatric presentations (3); females predominate over males in a ratio of 3:1; and 25% of newly diagnosed celiac disease occurs in patients older than 60 years of age (8). Subclinical or atypical presentations are more frequently encountered (19,20,43), and more cases are being diagnosed as a consequence of widespread serological testing and increased awareness.

PREVALENCE

Much of the data on the prevalence of celiac disease has come from European countries, where celiac disease was previously thought to be more common than in other parts of the world. Recent studies (2-7) have estimated that in the United States, celiac disease occurs in approximately 1% of the general population (Figure 1), which is similar to that reported in Europe (2,5,7). Recently, several authors have reported data on the prevalence of celiac disease in Asia (44,45), the Middle East (46,47), North Africa (48), and South America (49). Prevalence of celiac disease has increased sharply in recent years because of better recognition of the disease and its associated disorders (2,16).

GENETIC PREDISPOSITION

Celiac disease is one of the most common genetically based diseases (3). Approximately 97% of individuals with celiac disease have genetic markers on chromosome 6p21, called class II human leukocyte antigen (HLA), specifically HLA-DQ2 and HLA-DQ8. However, up to 40% of the general population also carries these HLA haplotypes (19). Their presence is necessary for the development of celiac disease, but the absence of these alleles virtually excludes the diagnosis. HLA-DQ2 is expressed in >90% of patients with celiac disease and HLA-DQ8 is found in most of the remainder (8).

PATHOGENESIS

Under normal physiologic conditions, the intestinal epithelium, with its intact intercellular tight junctions, serves as the main barrier to the passage of macromolecules, such as gluten proteins. These proteins have been classified into two major solubility fractions, the gliadins and glutenins, both of which contain disease-activating peptides (50,51). The alcohol-soluble fraction of gluten, prolamins (namely gliadins, glutenins, hordeins from barley, and secalins from rye), are rich in proline and glutamine, and undergo partial but incomplete digestion in the small intestine. The result is an accumulation of relatively large peptide fragments, as many as 50 amino acids in length (such as a recently described 33mer sequence in celiac disease) (52,53). Patients experience compromised epithelial function when the integrity of the tight junction system is compromised, as occurs in an enteric infection, surgery, or in celiac disease (54,55); and also as a result of upregulation of zonulin (56), an intestinal protein involved in tight junction regulation (57). Large peptides are able to cross the epithelial barrier and reach antigen-presenting cells in the lamina propria.

Data from Maiuri and colleagues clearly show that certain gluten peptides elicit an innate immune response, while others drive adaptive immunity (58-60). The adaptive immune response involves CD4⁺ T cells in the lamina propria that recognize specific immunogenic gluten peptides processed and presented by antigen-presenting cells (61). Gluten antigens are modified enzymatically by tissue transglutaminase (tTG). This intracellular enzyme is ubiquitous in cells and is involved in several processes in celiac disease. tTG is the target of endomysial autoantibodies (62), and, in an acidic pH that occurs with inflammation, it deamidates glutamine residues in gliadin by converting them to negatively charged glutamic acid residues. These deamidated peptides are more antigenic than native gluten peptides and usually adhere to the binding grooves of HLA-DQ2 and HLA-DQ8 molecules with a higher affinity than native peptides (63). HLA-DQ peptide complexes trigger inflammatory T cells, which in turn stimulate production of autoantibodies in the form of anti-tTG and antiendomysial antibodies (64); the presence of these antibodies is a specific indication of celiac disease. Subsequently, CD4⁺ T lymphocytes infiltrate the lamina propria, T cells produce proinflammatory cytokines, and consequently destruction of the surface epithelium occurs. Flattening of the mucosa ensues (60,61).

Although the importance of the adaptive immune response to gluten has been well-established, observations now also point toward a central role for the gluten-induced innate stress response in the pathogenesis of celiac disease and its malignant complications (65).

The innate immune response is the initial activation step induced by α -gliadin peptides and is mediated primarily by CD8⁺ T cells, enterocytes, macrophages, and dendritic cells. These cells trigger production and proliferation of proinflammatory cytokines, interleukin-15, which induce expression of natural killer receptor NKG2D and its ligand MIC molecules on epithelial cells that arm the cytolytic NKG2D pathway to destroy stressed epithelial cells (66). Infiltration by CD4⁺ T lymphocytes into the lamina propria and CD8⁺ T lympho-

cytes into the intestinal epithelium are characteristic of active celiac disease (60).

Along with genetic susceptibility, environmental factors may play a role in the development of celiac disease. Timing of the introduction of gluten in infancy was demonstrated to be a considerable factor (67). A recent study showed that introduction of gluten-containing foods within the first 3 months or after 7 months of age conferred an increased risk of developing celiac disease-associated antibodies as compared with gluten exposure between 4 and 6 months of age. Ivarsson and colleagues (68) found that gradual introduction of gluten-containing foods into the diet of infants while they are still being breastfed had a protective effect; reducing the risk of celiac disease in early childhood and probably also during the subsequent childhood period (68). D'Amico and colleagues reported that children who were exclusively breastfed for the first 6 months of life (69) presented later and differently than those who were not breastfed exclusively; they had less diarrhea, growth disturbance, vomiting, and abdominal pain or distension.

As a common autoimmune disorder, celiac disease represents a unique model of autoimmunity (70) because of the identification of (a) a close genetic association with HLA-DQ2 and HLA-DQ8, (b) a highly specific humoral autoimmune response (autoantibodies against the autoantigen, tTG), and, most important, (c) the external trigger, gluten peptides (63,70). Because of the genetic predisposition to celiac disease, an individual's intolerance to gluten is lifelong and self-perpetuating (71,72). The amount of gluten ingested, the gene dose of HLA-DQ2 and HLA-DQ8 (homozygous individuals appear to be at highest risk of celiac disease), and the local expression of tTG appear to be important determinants of celiac disease manifestation and severity.

DIAGNOSIS

No single test exists that can definitively diagnose or exclude celiac disease in every individual (19). Serological testing, used as an initial noninvasive screen, is the first step in pursuing a diagnosis of celiac disease. Widely available serological tests used for detecting celiac disease include antigliadin antibodies, anti-endomysium antibodies (EmA) and anti-tTG antibodies (73). The most sensitive and specific tests are the EmA and anti-tTG (74); antigliadin antibodies tests are no longer routinely recommended because of their low specificity and sensitivity. The IgA anti-tTG has 95% to 97% specificity and approximately 90% to 96% sensitivity. The serological gold standard is IgA EmA with its virtual 100% specificity, though a somewhat lower sensitivity than anti-tTG (75), and reports exist of lower sensitivity and specificity in the clinical practice setting (24,73,76). This is because of lower titers of these antibodies in the presence of lesser degrees of mucosal damage (73,77). In fact, celiac disease patients with lesser degrees of villous atrophy are less likely to have positive celiac serologies (76). Children younger than 2 years of age lack EmA and tTG antibodies (78); for this reason, serological testing in children younger than 5 years of age may be less reliable and requires additional study (19). In individuals who are IgA-deficient, the measurement of IgG EmA and anti-tTG offers reliable results. It appears that the specificity of

| Gluten-free Grains, Flours, and Starches | Gluten-containing Grains, Flours, and Starches |
|---|---|
| Amaranth | Barley |
| Arrowroot | Bulgar |
| Bean flours (garbanzo, fava, romano) | Cereal binding |
| Buckwheat | Chapatti flour (atta) |
| Corn | Couscous |
| Fava | Dinkel |
| Flax seed | Durum |
| Garbanzo beans | Einkorn |
| Garfava ^a flour (garbanzo + fava bean) | Emmer |
| Hominy | Farina |
| Mesquite flour | Farro |
| Millet | Fu |
| Montina ^b flour | Gluten, gluten flour |
| Nut flour and nut meals | Graham flour |
| Oats (uncontaminated) | Kamut |
| Peas flour | Malt (malt extract, malt flavoring, malt syrup, malt vinegar) |
| Potato flour, potato starch | Matzoh meal |
| Quinoa | Oats (most commercial brands, oat bran, oat syrup) |
| Rice, all forms (brown, white, sweet, wild, jasmine, basmati, glutinous rice, rice polish, rice bran) | Orzo |
| Sago | Rye |
| Sorghum flour | Seitan (aka wheat meat) |
| Soy flour | Semolina |
| Tapioca (manioc, cassava, yucca) | Spelt |
| Teff (or tef) flour | Triticale |
| | Wheat (bran, germ, starch) |

Figure 2. Gluten-free and gluten-containing grains, flours, and starches. ^aOriginally developed by Authentic Foods Company, Gardena, CA. ^bAmazing Grains Grower Cooperative, Ronan, MT. Adapted from Case S. *Gluten-Free Diet: A Comprehensive Resource Guide*. Regina, Saskatchewan, Canada: Case Nutrition Consulting; 2006, with permission, and Raymond N, Heap J, Case S. The gluten-free diet: An update for health professionals. *Pract Gastroenterol*. 2006;30:67-92, with permission.

IgG EmA and anti-tTG are nearly 100% in IgA-deficient patients with celiac disease (78-80).

Although positive test results can be supportive of a diagnosis, a small intestinal biopsy is the gold standard for the diagnosis of celiac disease, and is used to confirm positive antibody test results (73,74). Diagnosis depends on the finding of characteristic changes of intraepithelial lymphocytosis, crypt hyperplasia, and various degrees of reduced villous height, identified by intestinal biopsies, together with symptomatic and histologic improvement when gluten is withdrawn (73,81,82). Patients must adhere to a gluten-containing diet until after biopsy results are obtained, as a gluten-reduced diet may impact serologic analyses and pathologic interpretation of biopsy specimens (73). With concordant positive serology and biopsy results, a presumptive diagnosis of celiac disease can be made; a definitive diagnosis is confirmed when symptoms resolve. It is important to note that if gluten is reintroduced to the diet, a relapse of the disease will occur.

Clinical-based evidence concludes that in certain high-risk symptomatic groups (eg, unexplained iron-deficiency anemia), individuals who initially have a negative serological test result may later develop a positive result (with repeat testing every few years) and subsequently have a biopsy compatible with celiac disease (3). Diagnosis of celiac disease is often delayed for many years when disease progression in the small intestine is slow or mild. Investigators have noted a long duration of extraintestinal symptoms before diagnosis (83,84). Studies report that symptoms are

present for an average of 11 to 12 years (8,85) prior to diagnosis. The delay is thought to be due to physicians failing to diagnose the disease rather than patients not seeking medical care (85,86). Absence of specific symptoms and the high variability in clinical presentation associated with celiac disease have led to the misconception that it is a rare condition and physicians are not likely to suspect celiac disease as a cause (15,16,21). In national surveys (8,85,86), patients reported having received one or more different diagnoses before a definitive diagnosis of celiac disease was made.

TREATMENT

Currently, the only scientifically proven treatment for celiac disease is strict lifelong adherence to a gluten-free diet. All foods and medications containing gluten from wheat, rye, and barley, and their derivatives (Figure 2) are eliminated, as even small quantities of gluten may be harmful. Complete removal of gluten from the diet in a patient with celiac disease will result in symptomatic, serologic, and histologic remission in the majority of patients (15,81,82). Growth and development in children returns to normal with adherence to the gluten-free diet and, in adults, many disease complications are avoided. Green and colleagues (8) found that 70% of patients reported an improvement in symptoms within 2 weeks of initiating the gluten-free diet. With strict dietary control, antibody levels may revert to normal during 6 to 12

months of instituting the diet, complete histologic resolution may take up to 2 years (87). In a small percentage of patients, it has been reported that small intestinal recovery and resolution of symptoms is incomplete (88). Some patients have been found to suffer from refractory celiac disease, a complicated form of celiac disease in which patients may not respond entirely to the gluten-free diet (89,90). Researchers have found that a noncompliance rate of >50% accounted for symptoms in patients with nonresponsive celiac disease (91).

Nutritional status of the newly diagnosed person with celiac disease depends on the length of time that a person has lived with active but undiagnosed disease, extent of damage to the GI tract, and degree of malabsorption. At the time of diagnosis, some patients present with substantial weight loss, anemia, and evidence of overt vitamin/mineral deficiencies. Malabsorption of iron, folate, and calcium is common, as these nutrients are absorbed in the proximal small bowel. As the disease progresses along the intestine, malabsorption of carbohydrates, fat, and fat-soluble vitamins A, D, E, and K, and other micronutrients occurs (15). Secondary lactose intolerance resulting from decreased lactase production by the damaged villi is also common (92). A comprehensive nutritional assessment by a dietitian who is experienced in celiac disease will determine the degree of malnutrition that exists (93-99). Patients who present with nutrient deficiencies may require temporary or long-term nutrient supplementation with gluten-free vitamins, minerals and protein to correct deficiencies and replenish nutrient stores (15,93-101), although studies have not specifically looked at the efficacy of nutrient supplementation in the treatment of celiac disease.

Anemia may be treated with iron, folate, or vitamin B-12, depending on the origin of the anemia. However, studies have shown that 78% and 94% of adults, respectively, recovered from anemia while being treated with a gluten-free diet alone (102). Because the proximal small intestine is the predominant site of inflammation and also the site of iron absorption, the association of celiac disease to refractory iron deficiency anemia is well-established (95,97,102). Frequency of iron-deficiency anemia in celiac disease varies from 12% to 69% (103), and is reportedly higher in patients with long-standing, untreated disease (104). Incidence of vitamin B-12 deficiency in untreated patients ranges from 8% to 41% (103-105), though there is a relative sparing of villous atrophy in the ileum where vitamin B-12 is absorbed. While the mechanisms inducing deficiency are unclear, mucosal changes are considered the most likely cause of vitamin B-12 deficiency (97,106). Folic acid is absorbed in the jejunum, the proximal segments of which can be inflamed and damaged in active celiac disease. Folate supplementation is recommended to ensure that the goal daily allowance is consumed until the damaged, functionally impaired villi heal in the absence of gluten in the diet (93-101).

Fat-soluble vitamin deficiencies (vitamins A, D, E, and K) are encountered in patients with classic malabsorption. Recommended repletion dosages of fat-soluble vitamins are individually based; however, newly diagnosed patients may benefit from a water miscible form (eg, ADEKs; Axcan Pharma, Birmingham, AL) (95). Calcium, phosphorus, and vitamin D deficiencies may occur due to

malabsorption or a decreased intake of milk and dairy products in an effort to avoid lactose. In many cases, lactose intolerance resolves naturally with time on the gluten-free diet (107). Given the considerable risk for bone disease in celiac disease, measurement of bone density, serum calcium, alkaline phosphatase, and parathyroid hormone levels is recommended at the time of diagnosis (108), and adequate dietary intake of calcium and vitamin D is essential. Gluten-free sources of calcium and vitamin D include most milk and dairy products (eg, calcium-fortified soy milk, rice milk, and juices); tofu; beans; canned salmon and sardines with bones; and cooked spinach, kale and broccoli (93-95,97-100). Some patients may not be able to meet the Recommended Daily Intake for calcium and vitamin D by diet alone (107,108), and supplements may be indicated.

Rea and colleagues assessed the nutritional status of 23 Italian children with celiac disease at diagnosis and after 1 year of adherence to a gluten-free diet. Using anthropometry, biochemistry, and bone densitometry measurements, the authors found that although patients were clearly malnourished at the time of diagnosis, their body mass composition was virtually restored and they experienced a complete recovery after 1 year of a gluten-free diet (109). Similarly, another study found that strict adherence to the gluten-free diet promotes a rapid increase of bone mineral density that leads to a complete recovery of bone mineralization in children and adolescents after approximately 1 year of a gluten-free diet. In adults with celiac disease (110), diet treatment with calcium and vitamin D supplementation induced a decrease in bone turnover activity, and strict gluten avoidance promoted a substantial increase in bone mineral density (110). The overall goal of the treatment plan for celiac disease is to relieve symptoms, heal the intestine, and reverse the consequences of malabsorption, while enabling the patient to maintain a healthful, nutritionally diverse gluten-free diet (95).

At the time of diagnosis, patients may express fear, anger, anxiety, and sadness. Anger can worsen the patient-clinician relationship and has been correlated with dietary compliance (111). Twenty-three percent of children studied felt angry all or most of the time about following a gluten-free diet (112). Both men and women express bitterness over not being diagnosed earlier, believing that this could have led to better outcomes (113). Depression appears to be the most common neuropsychiatric complication among treated adults (81), which may ultimately affect compliance. Clinicians need to be sensitive to the emotional and psychological effects the diagnosis and treatment have on an individual (111). It is important to assess the patient's acceptance and willingness to change. Patients who have long been searching for a cause of their symptoms or who suffer with severe symptoms may be relieved to have a diagnosis. Asymptomatic individuals who have been diagnosed with subclinical celiac disease might consider the diagnosis a burden and might be reluctant to adhere to a strict gluten-free diet (113). Some patients may need additional compassion and encouragement; along with more frequent follow-up (95).

Surveys of patients in the United States (114-116) recognized that the gluten-free diet imposes a large number of restrictions on a patient. The diet has both lifestyle and

financial implications (4) and thus studies have evaluated the impact of the gluten-free diet on patients' health-related quality of life (8,85,112,113,115-117). With regard to compliance, 90% of adults (85,116) and 95% of children (112) described their diets as strictly GF; and 83% of adults (85,116) and 89% of children (112) reported their health "improved a lot." Several factors have been identified as being associated with a reduced health-related quality of life in adult patients with celiac disease: female sex (113,116,118), younger age at diagnosis (111,117), newly diagnosed patients (116), latency of diagnosis (119), poor adherence to a gluten-free diet (8,117,119), somatic as well as psychiatric morbidity (119), and dissatisfaction with information provided by health care professionals (117). Also, the additional financial burden of the gluten-free diet in the United States may be a negative influence on quality of life (120). Areas of negative impact in maintaining the gluten-free diet affect lifestyle changes, such as dining out, traveling, family life, and career or work (8,115,116). Although evidence supports the need to treat celiac disease with a gluten-free diet, a change in lifelong dietary patterns, especially in adults, can be challenging (121).

Patient education and maintenance of dietary adherence are of paramount importance. Causes of nonadherence include insufficient education and misinformation and the restrictive nature of the diet (8). Even the most motivated and highly educated patients can have difficulty adjusting to the gluten-free diet (95). Ideally, a team approach, consisting of the patient, physician, dietitian, and local support groups, should be used when educating the newly diagnosed celiac disease patient (93-100). Numerous resources including books, periodicals, and Web sites are available to patients who are in need of support and information (Figure 3). Based on its assessment of an extensive collection of medical literature and expert presentations, the National Institutes of Health Consensus Development Panel (19) on celiac disease identified six elements essential to managing individuals affected by celiac disease:

- C: Consultation with a skilled dietitian;
- E: Education about celiac disease;
- L: Lifelong adherence to a gluten-free diet;
- I: Identification and treatment of nutritional deficiencies;
- A: Access to an advocacy group; and
- C: Continuous long-term follow-up.

It is essential that patients be referred immediately to a dietitian who specializes in celiac disease for complete nutrition assessment and intervention. A dietitian with such expertise can educate patients about the complexities of the gluten-free diet; sources of hidden gluten; balanced meal planning; label reading; shopping for foods; dining out and traveling, benefits of exercise and relaxation; appropriate vitamin and mineral supplementation; and credible resources and support groups. Patients need to learn to integrate the gluten-free diet into their school or work schedules, as well as family life (93-100).

Another important role of the dietitian is to educate family members who can support the patient when they face the challenges of the gluten-free diet. Family members must understand the importance of taking precau-

tionary measures to prevent cross-contamination of foods. Gluten-free foods must be stored and prepared separately, cooking and serving utensils must be cleaned carefully prior to use, and a separate toaster must be purchased for the person with celiac disease. Collectively, these practices support the patient's adherence to the gluten-free diet.

Several visits should be scheduled with a dietitian because follow-up is necessary to assess knowledge, competence, and compliance, as well as to provide reinforcement (95). Without such support, a patient is more likely to obtain inaccurate information from health food stores, alternative health practitioners, family, friends, and other sources, often resulting in confusion, frustration, and insufficient knowledge regarding celiac disease and the gluten-free diet (94). Patients should be encouraged to join a celiac disease support group because patients who are active members are usually more knowledgeable and adherent to their diet (93-100). Ongoing support, education, and attention to changing nutritional needs are critical factors in the patient's successful adaptation to this new diet and lifestyle.

EATING GLUTEN-FREE

When a patient begins to eat gluten-free, there is often much concern and confusion as to which foods are allowed and which are not. Many foods are gluten-free, such as milk, butter, and cheese; fresh, frozen or canned fruits and vegetables; fresh meats, fish, poultry, eggs, beans, seeds, nuts; corn, and rice. Gluten is predominantly present in breads, cereals, and pastas, but is, surprisingly, found in seasonings, sauces, marinades, soy sauce, soups, salad dressings, and conveniently packaged flavored rice. It is critical that a patient ensures that each product is gluten-free by carefully reading food labels or by contacting food companies.

Eating and baking gluten-free has become easier in recent years, with increases in the number and quality of gluten-free food products that are available on-line and in some food stores today, albeit at a greater expense than gluten-containing foods (120). Consumers can purchase premade gluten-free breads, buns, rolls, pizza crusts, donuts, pastas, pretzels, cereals, and desserts. Baking mixes and flours are available to bake breads, pancakes, muffins, desserts, and more. Gluten-free cookbooks provide recipes and helpful tips for successful gluten-free baking. The availability of gluten-free foods increases a patient's food choices and improves diet variety while allowing patients to feel "normal" when eating among their peers.

Common ingredients in gluten-free breads and baking mixes are cornstarch, potato flour/starch, tapioca flour/starch, and brown/white rice flour. Although flours from wheat, rye, and barley are fortified with vitamins and minerals, such as B vitamins and iron, gluten-free flours are not fortified (122). Gluten-free baked goods tend to be high in fat and calories to enhance flavor, texture, appearance and overall acceptability of the gluten-free products, which may be of concern for those patients who do not wish to gain any weight (123,124).

Recently, the quality of the gluten-free diet was challenged by Thompson (123,124), who rationalized that in the general population, enriched fortified wheat-based

Online Resources

Quick Start Diet Guide: Celiac Disease Foundation (CDF) & Gluten Intolerance Group (GIG)

www.celiac.org, www.gluten.net

American Celiac Disease Alliance

www.americanceeliac.org

American Dietetic Association (ADA)

www.eatright.org

Canadian Celiac Association (CCA)

www.celiac.ca

Celiac Disease and Gluten-Free Diet Support Center

www.celiac.com

Celiac Disease Center at Beth Israel Deaconess Medical Center

www.bidmc.harvard.edu/ceciaccenter

Celiac Disease Center at Columbia University

www.celiacdiseasecenter.columbia.edu

Celiac Disease at Mayo Clinic

www.mayoclinic.org/ceciac-disease

Celiac Sprue Association (CSA)

www.csaceliacs.org

Center for Celiac Research at University of Maryland

www.celiaccenter.org

Children's Digestive Health and Nutrition Foundation: Celiac Disease Resources

www.celiachealth.org

Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA)

www.cfsan.fda.gov/~dms/alrgact.html

Gluten Free Living: National Newsletter for People with Gluten Sensitivity

gfliving@aol.com

Living Without Magazine

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National Institutes of Health Celiac Awareness Campaign

<http://celiac.nih.gov/>

National Institutes of Health Consensus Development Conference on Celiac Disease

<http://consensus.nih.gov/2004/2004celiacdisease118html.htm>

University of Chicago Celiac Disease Program

www.celiacdisease.net

University of Southern California Keck School of Medicine

Center for Celiac Research-West

www.glutenfreemd.com

University of Virginia Digestive Health Center of Excellence-Celiac Disease

www.healthsystem.virginia.edu/internet/digestivehealth/nutrition/ceciacsupport.cfm

Wm. K. Warren Medical Research Center for Celiac Disease

Clinical Celiac Disease Center at the University of California, San Diego

www.celiaccenter.ucsd.edu

Books

Celiac Disease: A Hidden Epidemic

by Peter Green, MD, and Rory Jones. Harper Collins Publishers, 2006.

www.harpercollins.com

Celiac Disease Nutrition Guide, American Dietetic Association: 2nd ed., 2006.

by Tricia Thompson, MS, RD

www.eatright.org

Gluten-Free Diet: A Comprehensive Resource Guide, Regina, Saskatchewan, Canada

by Shelley Case, RD. Case Nutrition Consulting, 2006.

www.glutenfreediet.ca

Guidelines for a Gluten-free Lifestyle, 3rd ed. Celiac Disease Foundation.

www.celiac.org

(1) *Kids with Celiac Disease: A Family Guide to Raising Happy, Healthy, Gluten-Free Children*;

(2) *Wheat-Free, Worry-Free: The Art of Happy, Healthy, Gluten-Free Living*

by Danna Korn. Hay House, Inc.

www.glutenfreedom.net

Pocket Dictionary: Acceptability of Foods and Food Ingredients for the Gluten-Free Diet.

Canadian Celiac Association. www.celiac.ca

Figure 3. Sources of information on celiac disease and gluten-free diet. Adapted from Raymond N, Heap J, Case S. The gluten-free diet: An update for health professionals. *Pract Gastroenterol.* 2006;30:67-92, with permission, and from Case S. *Gluten-Free Diet: A Comprehensive Resource Guide.* Regina, Saskatchewan, Canada: Case Nutrition Consulting; 2006, with permission.

cereal products contribute a large percentage to the daily intake of thiamin, riboflavin, niacin, iron, and folic acid. Thompson found that many gluten-free cereal products contain inferior amounts of thiamin, riboflavin, niacin, folate, and iron compared with the enriched wheat products that they are intended to replace.

A recent dietary survey in the United States assessed the diets of adults with celiac disease who were following a strict gluten-free diet (125). An analysis of 3-day food records suggested inadequate intakes of fiber, iron, and calcium in >50% of females studied. People with celiac disease should be encouraged to consume adequate amounts of these nutrients. Fiber can be obtained from gluten-free whole grains such as amaranth, buckwheat, corn bran, flax seed, millet, oats, quinoa, brown/wild rice, sorghum, and teff; beans, lentils, peas, nuts, seeds; fruits and vegetables; and fiber-enriched gluten-free breads, pastas, cereals, and energy bars (100,122). Aside from meeting their daily fiber needs, it is also important that people with celiac disease consume adequate daily amounts of thiamin, riboflavin, niacin, folate, iron, calcium, and fiber (123).

Oats appear to be safe for use by most individuals with celiac disease but their inclusion in a gluten-free diet is limited by potential contamination with gluten during milling and processing (19,126-128). Several studies in Europe and the United States, which have revealed that when consumed in moderation, long-term consumption of pure uncontaminated oats is well-tolerated by most children and adults with celiac disease and does not contribute to abdominal symptoms, serological or mucosal relapse, nor prevent small bowel healing (129-133). Oats add variety, taste, satiety, dietary fiber, and other essential nutrients to the diets of individuals with celiac disease. Pure uncontaminated oats are processed in dedicated facilities, which conduct onsite testing for gluten contamination and have recently become available from several companies in the United States and Canada (93,100).

LABEL READING AND THE DESIGNATION OF GLUTEN-FREE

People with celiac disease must read all food labels to ensure the gluten-free status of a food item. This process has become easier since the enactment of the Food Allergen Labeling and Consumer Protection Act of 2004 (134). It requires that all food products manufactured after January 1, 2006, be clearly labeled to indicate the presence of any of the top eight food allergens (milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, soybeans, and wheat). This act has simplified label reading by identifying those foods that contain hidden wheat gluten. Because barley and rye are not among the top eight allergens, it is possible that they could be sources of hidden gluten in flavorings or other additives. This is more likely to occur with barley because of its use in barley-malt flavorings and extracts. However, most companies declare barley-based flavorings on their ingredient lists (93,100).

Worldwide, there is a debate regarding the accepted definition for what constitutes "gluten-free." Studies have found that gluten contamination in gluten-free products cannot totally be avoided. Each study determined a different safe threshold for which gluten-contamination should be set: 100 parts per million (ppm) per day (equiv-

alent of 30 mg gluten) (135); between 10 and 100 mg intake daily (136); and <50 mg per day in the treatment of celiac disease (137). A unanimous view is that gluten-free dieting should be as strict as possible, a diet completely devoid of gluten would be difficult if not impossible to maintain (135-137). Experts continue to work toward an agreeable safe threshold for gluten contamination in gluten-free products.

Currently, in the United States, there is no federal regulation that defines the term *gluten-free* used in the labeling of foods. However, the US Food and Drug Administration (138) is proposing to define the food-labeling term *gluten-free* to mean that a food bearing this claim does not contain any one of the following:

An ingredient that is a "prohibited grain," which refers to any species of wheat (eg, durum wheat, spelt wheat, or kamut), rye, barley, or their crossbred hybrids;

An ingredient (eg, wheat flour) that is derived from a "prohibited grain" and that has not been processed to remove gluten;

An ingredient (eg, wheat starch) that is derived from a "prohibited grain" that has been processed to remove gluten, if the use of that ingredient results in the presence of 20 ppm (6 mg equivalent) or more gluten in the food;

20 ppm or more gluten.

A food that bears the claim gluten-free or a similar claim (eg, free of gluten, without gluten, no gluten) in its labeling and fails to meet the conditions specified in the proposed definition of gluten-free would be deemed misbranded (138). The Food and Drug Administration believes that establishing a definition for gluten-free, along with uniform conditions for its use in food labeling, will ensure that people with celiac disease are not misled and are provided with truthful and accurate information (138).

Most European countries have accepted the definition of gluten-free designated by CODEX Alimentarius (139), a United Nations commission appointed to establish international food standards and food-trade guidelines. CODEX states that the content of gluten in gluten-free products (free of wheat, rye, and barley) should not exceed 20 ppm (6 mg equivalent), while those food products containing ingredients from wheat, rye, or barley that have been rendered gluten-free must contain <200 ppm gluten (60 mg equivalent).

Because there are no federal standards, the Gluten Intolerance Group has developed a voluntary program of testing and monitoring gluten-free food products. The Gluten-Free Certification Organization was created in August 2005 and identifies qualifying foods with a "gluten-free" certification mark. The Gluten-Free Certification Organization uses strict standards to certify that a gluten-free product contains <10 ppm gluten (3 mg equivalent) and enables people to easily identify gluten-free foods with confidence. This new independent food-processing inspection program will verify that food products meet the highest standards for gluten-free ingredients and safe processing environment (140,141).

Future Therapeutic Options

The quality of life for patients with celiac disease could potentially be improved if a treatment was available that

would allow patients to consume gluten, even in small amounts or over a short period of time. Effective treatments for celiac disease, other than dietary restrictions, are being developed (142-151).

CONCLUSION

Celiac disease is recognized as a common multisystemic disorder that may be diagnosed at any age. At this time, the gluten-free diet remains the only available treatment. The gluten-free diet is a complex and challenging diet, but recent advances in the food industry are making it easier to follow. With more patients being diagnosed, there is a greater need for health care professionals who are knowledgeable about celiac disease and the gluten-free diet. Expert dietitians are responsible for nutrition assessment, treatment of nutritional deficiencies, and education of patients with celiac disease. Patients who understand the long-term consequences of celiac disease will make informed choices in managing their disease. Dietitians provide the tools that patients need to successfully understand the diet and integrate it into every aspect of their lives, leading to overall improvements in the physical and emotional challenges of the disease.

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