Who Should Be Gluten-Free? A Review for the General Practitioner

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INTRODUCTION

Gluten is composed of a protein network that contributes to the elasticity and extensibility in bread and other commonly consumed products that contain wheat, rye, or barley.1,2 Following a gluten-free diet (GFD) has become one of the most popular trends over the past decade. In a survey conducted by the National Restaurant Association in 2014, the GFD was voted 1 of the top 5 food trends. Gluten-free (GF) products may cost as much as 240% more than similar gluten-containing products,3 and, despite this added cost, population surveys suggest that most of those endorsing a GFD do not have a formal diagnosis of celiac disease (CD).4 Historically, GFDs were

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KEYWORDS

- Celiac disease
- Wheat allergy
- Nonceliac gluten sensitivity
- Nutritional deficiencies
- Gastrointestinal symptoms

KEY POINTS

- A strict gluten-free diet is necessary in those with celiac disease and IgE-mediated wheat allergy.
- The prevalence of celiac disease is increasing and there are a significant number of individuals who remain undiagnosed.
- Following a gluten-free diet has become a popular fad diet in individuals who are trying to lose weight.
- Nonceliac gluten sensitivity is a poorly understood disorder in which patients have both intestinal and extraintestinal symptoms in response to gluten, although gluten exposure does not cause intestinal damage.
- Providers should understand how to evaluate for celiac disease and nonceliac gluten sensitivity and be aware of differences in the long-term risks and management options.

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Gluten is composed of a protein network that contributes to the elasticity and extensibility in bread and other commonly consumed products that contain wheat, rye, or barley.1,2 Following a gluten-free diet (GFD) has become one of the most popular trends over the past decade. In a survey conducted by the National Restaurant Association in 2014, the GFD was voted 1 of the top 5 food trends. Gluten-free (GF) products may cost as much as 240% more than similar gluten-containing products,3 and, despite this added cost, population surveys suggest that most of those endorsing a GFD do not have a formal diagnosis of celiac disease (CD).4 Historically, GFDs were
only recommended for those with a diagnosis of CD or IgE-mediated wheat allergy (WA), but more recently, as gluten-related disorders have come to the forefront of popular culture, people are following a GFD for numerous other reasons. As the number of GFD consumers increases, it is imperative that health care providers understand how to differentiate medical fact from popular fiction to effectively counsel their patients and limit potential complications.

Although a small percentage of individuals may be harmed by ingestion of particular foods due to food poisoning, food allergies, immune-mediated reasons, and food intolerances or sensitivities, food consumption is required for survival and benefits the vast majority of people. It is important to make a clear distinction among these various food-related entities because each one is associated with specific implications. Food poisoning, food allergy, and immune-mediated diseases cause significant complications and require strict avoidance, whereas intolerances and sensitivities result in less severe symptomology and thus do not require strict dietary avoidance. Beyond infectious etiologies, adverse food reactions are characterized as either immune mediated or non–immune mediated. Immune-mediated food reactions include those that are IgE mediated (hives and anaphylaxis), non–IgE mediated (food protein–induced enterocolitis syndrome and CD), cell mediated (allergic contact dermatitis), or mixed (eosinophilic esophagitis). Non–immune-mediated food reactions include metabolic (lactose intolerance and inborn errors of metabolism) and pharmacologic (reactivity to vasoactive amines in tyramine). Approximately 1% of Americans have CD and 0.4% of Americans have WA. Based on the National Health and Nutrition Examination Survey diet study in 2009, which included 7798 persons, 0.63% followed a GFD although many of these individuals had neither CD nor WA.

Not all gastrointestinal symptoms are considered true adverse food reactions. For example, it is physiologically normal to feel abdominal bloating after ingestion of a large meal, legumes, and/or cruciferous vegetables or high-fat foods because these foods enhance intestinal gas production or delay gastric emptying. Although these gastrointestinal symptoms may cause discomfort, none of these responses is considered pathologic.

CELIAC DISEASE: A HISTORICAL PERSPECTIVE

Wheat grain has been recognized as a human food source for thousands of years and has become a dietary staple in much of the world. Approximately one-third of the foods found in an American supermarket contain some component of wheat. Adverse symptoms attributed to gluten ingestion date as far back as the first century AD. Despite the long hypothesized dietary link, it was not until the 1940s when Dutch physicians discovered that children with CD symptomatically improved when wheat and rye were scarce but subsequently deteriorated once bread was reintroduced into the diet by Allied forces. A majority of American foods are regulated by the US Food and Drug Administration (FDA) but these exclude foods regulated by the US Department of Agriculture, such as meat, and also products, such as alcohol, tobacco, and cosmetics.

In 2004, the FDA Center for Food Safety and Applied Nutrition passed the 2004 Food Allergen Labeling and Consumer Protection Act, acknowledging the growing issue of food allergies and raising awareness. The FDA set goals for reporting on cross-contamination standards and GF labeling. Based on FDA standards, products may only be labeled GF if the product contains less than 20 parts per million of gluten. This facilitated both awareness of food allergies and CD to the general public and aided patients with CD and WA in disease management.
The possibility that gluten might also cause problems in other individuals without CD was first suggested in a small case series of 8 patients with chronic diarrhea and abdominal pain in the 1980s. These patients experienced a dramatic relief on a GFD; however, symptoms returned when gluten was reintroduced. Small bowel biopsies of these patients were unremarkable and, as a result, this study raised questions regarding the role of gluten as a trigger for irritable bowel syndrome (IBS). Given the wide overlap in nonspecific gastrointestinal symptoms between CD and IBS based on the Rome III criteria, many European countries began to recommend ruling out CD before diagnosing IBS. More recently, there has been increased attention to the individuals who seem to have an intolerance to gluten and improve on a GFD but do not otherwise meet criteria for CD. These individuals have been noted to have both intraintestinal and extraintestinal symptoms. Although this disorder is still not well elucidated, it is currently known as nonceliac gluten sensitivity (NCGS).

**POP CULTURE: GOING GLUTEN-FREE**

A major culture shift occurred with the publication of 2 best-selling self-help books, *Wheat Belly*, published by cardiologist William Davis, and *Grain Brain*, written by neurologist David Perlmutter. The vilification of wheat and gluten in these books seems to have created an empire founded on the premise that gluten is poison. Both books were extremely successful because they reinforce powerful myths and promise simple dietary solutions to numerous health problems despite lack of sound evidence. The common theme in these books and others reiterates the importance of limiting processed foods and refined sugars and thus raises the question on whether it is gluten or actually alternate ingredients and/or chemicals found in processed foods that are the culprit for disease. Unfortunately, with much of the science taken out of context, these books and others can make it difficult to determine which individuals truly benefit from a GFD.

**GLUTEN-RELATED DISORDERS: THE BASICS**

CD is a non–IgE immune-mediated condition that is triggered by dietary gluten ingestion in genetically susceptible individuals. NCGS is a disorder in which patients develop both intraintestinal and extraintestinal symptoms after gluten exposure but do not meet criteria for CD or WA. WA is a hypersensitivity reaction to wheat proteins mediated via mast cell activation and immune mechanisms that are both IgE mediated and non–IgE mediated and affects between 0.5% and 4% of the population. Additional diagnoses to consider in individuals who present with similar gastrointestinal symptoms include but are not limited to the following: NCGS, functional dyspepsia, eosinophilic gastroenteritis, IBS, inflammatory bowel disease, small intestinal bacterial overgrowth, connective tissue disorders, protein losing enteropathies (PLEs), common variable immune deficiency, microscopic colitis, and medication side effect.

**CELIAC DISEASE: BASIC PRINCIPLES AND PATHOPHYSIOLOGY**

The pathophysiology of CD is still not completely understood but is believed to result from a complex interplay among immunologic, genetic, and environmental factors. Ongoing research to study the pathophysiology of CD is essential to developing potential drug targets for treatment, particularly in those individuals who have refractory disease and do not respond to a strict GFD. Gluten is found in wheat, rye, barley, and crossbred hybrids of these 3 grains. Gluten is comprised of 2 peptides, glutenin and gliadin, which form a protein network and provide elasticity and extensibility in

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common food products and improve the texture and palatability. These peptides contain a high content of prolines and glutamines, which makes them resistant to degradation by gastric acid, pancreatic, and brush-border enzymes and allows them to remain in contact longer with mucosal surfaces and, in the setting of CD, cause intestinal damage. In those with CD, gluten ingestion causes an immune response to gliadin in the intestinal lumen, which promotes an inflammatory reaction, primarily in the proximal small intestine. The inflammatory cascade is characterized by infiltration of the lamina propria and epithelium with chronic inflammatory cells and villous atrophy. The response is mediated by the innate and adaptive immune systems. Increased intestinal permeability allows transport of intact gliadin molecules through the small intestinal epithelium into the lamina propria where tissue transglutaminase (TTG) deamidates the gliadin peptides and increases their immunogenicity.

CELIAC DISEASE: GENETIC FACTORS

CD has a strong genetic component. Epidemiologic studies report up to 20% of first-degree relatives are affected by the disease, with concordance rates of 75% to 80% with monozygotic twins and 10% in dizygotic twins. The best characterized genetic susceptibility factors are the HLA class II genes HLA-DQ2 and HLA-DQ8, which present antigens to immune cells. CD does not develop unless a person has alleles that encode for these proteins, although these alone are not sufficient to cause disease. The European Genetics Cluster on CD typed 1000 patients and found that 96% had either HLA-DQ2 or HLA-DQ8 genes. Although more advanced immunologic features of CD are beyond the scope of practice for most providers, these markers are believed to have an important role in screening because of their high negative predictive value. If a patient has obvious clinical disease in the setting of negative HLA-DQ2 or HLA-DQ8, however, this should not be ignored, given the potential for rare variants. The presence of these HLA gene variants changes geographically and may be used to assess CD risk and predict clinical course.

CELIAC DISEASE: ENVIRONMENTAL FACTORS

The primary trigger in CD is exposure to gluten, which activates both adaptive and innate immune responses in the host gut epithelium. Studies suggest several environmental factors that may influence the development of CD and include timing of gluten introduction, cesarean delivery, lack of breast feeding, recurrent childhood gastrointestinal infections, and the host microbiome, although all of these factors continue to be under investigation.

CELIAC DISEASE: SIGNS AND SYMPTOMS

Common presenting symptoms in children include vomiting, constipation, recurrent abdominal pain, growth issues, anemia, arthritis, neurologic symptoms, or no symptoms. In adults, symptoms at presentation vary widely and may include iron deficiency anemia, vitamin B₁₂ deficiency, vitamin D deficiency, osteoporosis, bloating, heartburn, chronic fatigue, skin lesions, various neurologic and musculoskeletal presentations, and in some cases elevated liver enzymes and infertility (Box 1).

CELIAC DISEASE: ASSOCIATED CONDITIONS

CD is often associated with other autoimmune conditions. Commonly associated conditions include but are not limited to autoimmune thyroid disease, dermatitis herpetiformis, recurrent oral aphthae, autoimmune liver and/or biliary disease, type 1 diabetes, pernicious anemia, alopecia areata, juvenile rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and psoriasis.
diabetes mellitus, Sjögren syndrome, Turner syndrome, Down syndrome, and Williams syndrome (Box 2).19

CELIAC DISEASE: SCREENING PRACTICES

CD for many years was believed a predominately pediatric disease characterized by diarrhea and malabsorption. Starting in the 1950s, major advancements were made in understanding the pathogenesis, diagnosis, and treatment of CD, including serologic testing and small bowel biopsy techniques. It is now clear that the disease spans all demographics and has a widely variable presentation.20 Historically, individuals were only tested for CD when they presented with diarrhea and evidence of malabsorption; however, it seems that presenting symptoms vary and may depend on the region in which the patient resides. Advances in screening modalities in high-risk populations have increased diagnosis and identified a significant number of asymptomatic patients who previously would not have been screened.21–25 Epidemiologic studies suggest that there are still large numbers of undiagnosed patients and also suggest the prevalence of CD is increasing for unclear reasons.26–29

CELIAC DISEASE: WHO TO SCREEN

The World Health Organization recommends mass screening for diseases that fulfill the following criteria: early clinical detection is difficult (diseases that have variable

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signs/symptoms or are asymptomatic); the condition affects at least 1% of the population; and available screening tests are highly sensitive and specific and effective treatments are available, whereas untreated disease can lead to complications. Some researchers argue that providers should perform universal screening because it is cost effective and can significantly increase a timely diagnosis, particularly given the myriad clinical manifestations and excessive health care utilization prior to diagnosis. As such, there is a large volume of literature supporting more aggressive screening practices that may lead to a 40% increase in diagnosis.

In traditional practice, screening for CD has been triggered by gastrointestinal symptoms of diarrhea or malabsorption. Increased knowledge of CD and heightened awareness of associated conditions have led to wider screening recommendations and include screening relatives and those with associated disorders (see Box 2).

American College of Gastroenterology guidelines recommend screening individuals with signs or symptoms of malabsorption, laboratory evidence for CD, a first-degree relative with a diagnosis of CD even if the individual being tested is asymptomatic, elevated liver enzymes with no other clear etiology, and type 1 diabetes mellitus with signs/symptoms or laboratory evidence suggestive of CD.

**CELIAC DISEASE: DIAGNOSIS**

A diagnosis of CD should be made based on blood tests and small intestinal biopsies. With the advent of serologic testing, TTG-IgA has a sensitivity and specificity of 95% with a greater likelihood of being a true positive result as the titer increases. Given increased IgA deficiency in the celiac population, a normal IgA level should be confirmed. There is also a role for secondary serologies in some testing scenarios. Endomysial antibody is more costly, more subjective to interpretation, and less widely available, although highly sensitive, and can be useful in equivocal TTG testing scenarios. IgG deamidated gliadin can be useful in some scenarios, particularly in those patients who are IgA deficient.

Testing must be done on a gluten-containing diet, which has traditionally been a minimum of 10 g/d (approximately 4 slices of bread) for a period of 6 weeks, but more recent data suggest that possibly a smaller amount and a shorter interval are adequate in many cases. Greater than 3 g/d of gluten for 2 weeks has been
demonstrated to produce histologic changes in 68% of patients.\textsuperscript{36} Endoscopic biopsy remains the gold standard for confirmation of diagnosis.

A major limitation of the current diagnostic studies is that serologic testing and small bowel biopsies are only useful when an individual has current exposure to gluten. There is a high false-negative rate if testing is done while on a GFD, which reiterates the importance of early screening in high-risk or symptomatic individuals before they adopt a GFD. If individuals are already on a GFD, then they should be advised to reintroduce gluten prior to testing, if able. In practice, a large percentage of individuals are not willing to reintroduce gluten because of feeling poorly after re-exposure. In this circumstance, obtaining HLA-DQ2 and HLA-DQ8 can be helpful for ruling out a large proportion of individuals without CD if they do not have these alleles. Newer literature also suggests that an HLA-DQ gluten tetramer test might accurately identify or rule out patients with CD in the absence of gluten intake, although this is not yet widely accepted or available.\textsuperscript{37}

**CELIAC DISEASE TREATMENT**

Treatment of those with CD is multidisciplinary and involves strict compliance with a GFD, education by a registered dietician, support groups to help with compliance, evaluation of bone health, and testing for/treating common micronutrient deficiencies.\textsuperscript{19} To date, a strict GFD is the only accepted therapy for CD. Numerous alternate treatment modalities are under investigation, including enzyme therapies to digest gluten, polymers to bind gluten, probiotics, and therapies to alter permeability or tight junctions or to alter the immune or inflammatory response, including the use of vaccines to induce tolerance. Although studies are in progress, there are no new therapies approved to this point.\textsuperscript{38}

Following a strict GFD has many challenges, although it has become easier over the past several decades because of increased availability and variety of GF foods. One of the major challenges for those who need to be strictly GF includes inadvertent gluten exposure from cross-contamination. Cross-contamination may occur when gluten-containing products are prepared in the same area as GF foods (cutting board, utensils, cookware, toaster, and storage containers) and from spreadable foods when utensils are used after contact with gluten-containing items. Practical tips for eating out include researching restaurants for GF items and/or calling ahead during off hours to talk to the chef directly about meal preparation.

Going GF does have some benefits. As discussed previously, following a GFD is necessary in those with IgE-mediated WA and CD, and, in CD, compliance improves intestinal healing and absorption of essential nutrients. Additional potential benefits of following a GFD that are inherent in following any strict nutrition plan include taking the time to read nutrition labels carefully, which may lead to decreased ingestion of many processed foods and refined sugars. Additionally, as the GFD trend grows in popularity, the availability and selection of GF foods have expanded and now include more palatable options and decreased risk of nutritional deficiencies, because more are being enriched with key vitamins and minerals, which they were previously devoid of.

**DEBUNKING GLUTEN-FREE DIET MYTHS**

The belief that GF products are “healthier” compared with similar gluten-containing products is not based on any sound evidence and in many cases is incorrect. GF products are commonly lower in fiber, iron, B vitamins, calcium, vitamin D, phosphorus, and zinc. Thompson and colleagues\textsuperscript{39} illustrated that only 31% of women and 63%
of men who followed a GFD consumed recommended amounts of fiber, iron, and calcium. A 7-day prospective study comparing dietary intake patterns between 55 patients with CD on a GFD for greater than 2 years to 50 patients with newly diagnosed CD showed that more than 1 in 10 newly diagnosed and GFD-experienced women had inadequate intake of thiamine, folate, vitamin A, magnesium, calcium, and iron whereas more than 1 in 10 newly diagnosed men had inadequate thiamine, folate, magnesium, calcium, and zinc intake. Furthermore, GF products commonly also contain more calories from fat and carbohydrates to improve palatability and texture because of the absence of gluten. Zuccotti and colleagues compared macronutrient intake in 18 children with CD to 19 children without CD. The median energy intake in children with CD was significantly higher in calories, higher in carbohydrate intake, and lower in fat compared with healthy controls.

NONCELLIAC GLUTEN SENSITIVITY

A large proportion of those individuals following a GFD are suggested to have NCGS. Although not well understood, NCGS does have a set of diagnostic criteria to help separate it from other gluten-related disorders based on a consensus meeting in 2015, called the Salerno criteria. NCGS is a clinical syndrome in which an individual describes intraintestinal and extraintestinal symptoms in response to ingestion of gluten and which improve in response to gluten avoidance, with CD and WA appropriately ruled out (including celiac serologies, small bowel biopsy as indicated, and wheat-specific IgE and skin prick test). The criteria suggest that optimally a double-blind, placebo-controlled gluten diet challenge containing 8 g/d of gluten without FODMAPs should be performed for confirmation but recognizes that this is not practical and, in most cases, not acceptable to patients. Although there have been reports that an older serology with low specificity for CD, IgG AGA, might be positive in some NCGS cases, there are no accepted serologies for diagnosis and no established genetic markers for diagnosis. Compared with CD, with a prevalence of 1% and WA with a prevalence of 0.4%, NCGS is estimated to have a prevalence of between 0.63% and 6%. Given the wide range of symptoms that cross over between other disorders, it is not clear if this prevalence truly represents NCGS or a range of disorders. The University of Maryland Center for Celiac Research performed a study between 2004 and 2010 of gluten-sensitive patients and reported the most common gluten-triggered symptoms included abdominal pain, eczema/rash, headache, difficulty focusing or foggy mind, fatigue, diarrhea, depression, anemia, numbness in the extremities, and joint pain.

Studies of this patient population have suggested variable triggers, including gluten, FODMAP, wheat α-amylase/trypsin inhibitors, and perhaps even changes in the microbiome and dysbiosis. The studies suggesting other sources of dietary trigger, such as FODMAPs, do not explain the extraintestinal symptoms that are common with this disorder. Further investigations are ongoing but this is currently accepted as a separate and unique gluten-related disorder.

SUMMARY

Unfortunately, awareness does not equal knowledge or understanding. Although there are clear medical indications for a GFD and clinical scenarios in which patients seem to symptomatically benefit from a GFD, there are also scenarios in which the risks of a GFD may outweigh benefit. Awareness of these differences facilitates appropriate diagnosis and counseling of patients and improves long-term management. With numerous ongoing studies of possible alternate CD treatments and investigations
into the pathophysiology and diagnosis of NCGS, this is anticipated to be a continuously changing and robust field of study.

REFERENCES


