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# Celiac Disease, Wheat Allergy, and Gluten Sensitivity: When Gluten Free Is Not a Fad

Michelle Pietzak, MD

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As the gluten-free diet (GFD) gains in popularity with the general public, health practitioners are beginning to question its real health benefits. For those patients with celiac disease (CD), the GFD is considered medical nutrition therapy, as well as the only proven treatment that results in improvements in symptomatology and small bowel histology. Those with wheat allergy also benefit from the GFD, although these patients often do not need to restrict rye, barley, and oats from their diet. Gluten sensitivity is a controversial subject, where patients who have neither CD nor wheat allergy have varying degrees of symptomatic improvement on the GFD. Conditions in this category include dermatitis herpetiformis (DH), irritable bowel syndrome (IBS), and neurologic diseases such as gluten-sensitive ataxia and autism. It is important for patients and healthcare practitioners to understand the differences between these conditions, even though they may all respond to a GFD. Patients with CD can experience comorbid nutrition deficiencies and are at higher risk for the development of cancers and other autoimmune conditions. Those with wheat allergy and gluten sensitivity are thought not to be at higher risk for these complications. Defining the symptoms and biochemical markers for gluten-sensitive conditions is an important area for future investigations, and high-quality, large-scale randomized trials are needed to prove the true benefits of the GFD in this evolving field. (*JPEN J Parenter Enteral Nutr.* 2012;36:68S-75S)

**Keywords:** gluten; gluten-free diet; celiac disease; wheat allergy; gluten sensitivity; dermatitis herpetiformis; ataxia; autism; irritable bowel syndrome

In recent years, the gluten-free diet (GFD) has gone mainstream and is no longer restricted to specialty food stores and small Internet distributors. As of 2009, products labeled as "gluten free" have exploded into an almost $1 billion business, with sales increasing at an exponential rate.[1] In contrast to just a decade ago, when "gluten free" was associated with rice cakes that tasted like Styrofoam and dry, crumbling bread products, today's GFD is perceived as "healthy" and "tasty." However, the general public's recent embrace of the GFD lifestyle is also associated with the perception by many in the medical field that the GFD is a "fad diet." In fact, the GFD is considered medical nutrition therapy for several conditions, such as celiac disease (CD), the skin rash dermatitis herpetiformis (DH), and neurologic conditions such as gluten-sensitive ataxia. But does the GFD work for other conditions with gastrointestinal and neurologic symptoms, such as irritable bowel syndrome (IBS) and autism? Is a GFD healthier for everyone?

This review differentiates between those diseases that have decades of studies showing the benefits of the GFD and those that have proposed benefits based on hypotheses, case studies, and recent reports on selected populations. The importance of CD as the prototype for an autoimmune disorder that responds to the GFD is highlighted, with its documented complications of nutrition deficiencies, comorbid autoimmune conditions, and increased risk for a variety of malignancies. Wheat allergy also is discussed, as well as how its symptoms and diet may differ from that of those patients with CD. The concept of gluten sensitivity is elaborated, with emphasis on the conditions known to respond to a GFD and those that still require further definition and examination.

Although one could argue that humans have not evolved to digest gluten, and perhaps it should not be in our diet, the GFD is a challenging one and should not be taken lightly just because it is nutrition therapy and not a pharmacologic agent. This review further considers why patients and their healthcare practitioners need to be

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aware of the differences between CD, wheat allergy, and gluten sensitivity. Labeling in the United States presents many obstacles,[2,3] and unnecessary gluten restriction may affect a patient's ability to socialize, travel, and dine in restaurants.[3] Ultimately, additional studies on gluten-sensitive conditions are needed using more rigorous scientific methods to further define the benefits of the GFD in those without true documented CD or wheat allergy.

## Celiac Disease

CD is an immune-mediated reaction to gluten, which occurs in genetically predisposed individuals. The prevalence of CD is estimated to be 0.5%–1% of the general population where there is genetic risk,[4,5] and the incidence of CD has been thought to be increasing over the past several decades.[6] Patients with CD react to dietary proteins, called prolamins, in certain grains. Although all grain products, including rice, contain prolamins, the specific prolamins found in wheat (gliadin), rye (secalin), and barley (horedin) are the ones implicated to cause an immunologic reaction in those who have CD.[7] A small proportion of patients with CD also have an independent immune reaction to oats, which contain avenin.[8] In North America, most oats are crop rotated and milled with wheat and are therefore considered to have levels of contamination, with wheat gluten high enough to make them not acceptable for the routine GFD.[9] It is possible that pure and uncontaminated oats, made into products that contain less than 20 mg of gluten per kg of oats product, may be incorporated safely into the diet of well-controlled adult patients with CD.[10,11]

Two main conditions must be necessary for the development of CD: the ingestion of gluten and a genetic predisposition to CD. Infants, who have not yet been exposed to gluten in the diet, will not manifest the symptoms of CD. Likewise, if patients do not have the human leukocyte antigens (HLA) found commonly in CD, HLA DQ2 or HLA DQ8, they are at very low risk of developing CD. Although a significant proportion of the population has these HLA alleles, most do not develop CD. Modifying factors that may contribute to CD development in genetically at-risk individuals include method of infant feeding (formula vs duration of breastfeeding),[12] method of birth (vaginal vs caesarean section),[13] timing of the introduction of gluten into the diet,[12] season of birth,[14,15] infections during early childhood,[16] and several recently described non-HLA genes.[17] The presence of autoimmune diseases in the patient or family (such as type I diabetes, autoimmune thyroid disease, rheumatoid arthritis, and autoimmune liver disease) also put the patient at higher risk for CD. Patients with Down syndrome, Williams syndrome, Turner syndrome, and cystic fibrosis, for unclear reasons, are also at increased risk for CD over that of the general population.[7,18,19] It is important to note, however, that elevated antigliadin antibodies (AGA) can be seen in Down syndrome and cystic fibrosis patients, perhaps because of the increased intestinal permeability to these proteins.

The "classic" presentation of CD is that of a toddler who has been ingesting gluten for several months to years, who subsequently develops diarrhea, weight loss, anorexia, abdominal distension, and perhaps even vomiting or constipation. These children are acutely ill with protein-calorie malnutrition and often seek and receive prompt medical attention for the diagnosis. Unfortunately, this "classic" presentation is a misnomer, as most patients are now presenting in older age groups with a variety of symptoms. These older patients are often labeled as having IBS, lactose malabsorption, inflammatory bowel disease, or even hypochondria.

Extraintestinal manifestations of CD can include virtually every organ system. In the musculoskeletal system, arthritis, muscle pain, dental enamel defects, and osteopenia/osteoporosis are common presentations. Both males and females may experience short stature, delayed onset of puberty, and even idiopathic infertility. Women with undiagnosed or untreated CD have higher rates of infertility, spontaneous abortions, fetal neural tube defects, and low birth weight infants.[20,21] Nutrition deficiencies can include iron deficiency anemia, protein-calorie malnutrition, and a variety of mineral and fat-soluble vitamin deficiencies (such as zinc, folic acid, selenium, and vitamins $B_6$, $B_{12}$, D, E, and K).[3,22] Patients with CD may manifest a variety of neurologic symptoms, including headaches, seizures, anxiety, depression, schizophrenia, and peripheral neuropathy.[23,24] Although some of these manifestations are due to comorbid nutrition deficiencies, improvement of longstanding symptoms with supplements and the GFD can be variable.[25]

Screening for CD can be done by serologic antibody tests: AGA IgG and IgA, antiendomysial IgA (EMA), and antitissue transglutaminase (tTG) IgG and IgA. These antibodies vary highly in their sensitivity and specificity in different populations and may be less reliable in young children. AGA IgG and IgA, because of their low sensitivity and specificity, are no longer routinely recommended as a first-line screen for CD in otherwise healthy adult patients. However, recently developed IgG and IgA antibodies to deamidated gliadin peptide (DGP, a synthetic peptide derived from γ-gliadin of wheat) show improved sensitivity and specificity compared to AGA and closely parallel the development of TTG IgA in developing CD.[26,27] As IgA deficiency is more common in CD and may yield falsely low AGA IgA, DGP IgA, EMA IgA, and tTG IgA titers, a total IgA level should also be measured. A tTG IgG can also be performed.[18]

Patients with symptoms and positive screens should have an endoscopic intestinal biopsy to confirm enteropathy prior to the initiation of a GFD.[18]

How does gluten interact with the immune system in CD? Some studies indicate that gluten is incompletely digested in the human gastrointestinal tract. "Toxic fragments," which stimulate an immune response, survive digestion and are absorbed (via a yet undiscovered mechanism) through the mucosal layer of the small intestines. In CD, tTG changes the shape of these gluten fragments into a conformation that has a strong affinity for HLA DQ2 on antigen-presenting cells. These cells "present" the gluten to the immune system as a foreign entity, stimulating the T helper 1 response, which leads to the intestinal damage.[28]

## Wheat Allergy

The top 8 food allergens in the United States are milk, eggs, fish, crustacean shellfish, peanuts, tree nuts, soybeans, and wheat. Although roughly 5% of individuals in Westernized nations may have a true food allergy, only about 0.1% has a documented wheat allergy. Similar to CD, wheat allergy is an immune-mediated reaction to the proteins found in wheat products. As opposed to CD, wheat allergy is an IgE-mediated reaction to the water- and salt-insoluble gliadins, particularly ω-5 gliadin.[29] This gliadin is a major allergen of wheat-dependent exercised-induced anaphylaxis ("Baker's asthma"). However, patients with wheat allergy usually do not need to restrict other prolamin-containing grains, such as rye, barley, and oats, from their diet. Therefore, a wheat-free diet can be more liberal than a strict GFD. The symptoms of wheat allergy usually occur in the mouth, nose, eyes, and throat (swelling, itching, and irritation); the skin (rash, hives, swelling); respiratory tract (wheezing, difficulty breathing, anaphylaxis); and gastrointestinal tract (cramps, nausea, emesis, gas, bloating, diarrhea, and abdominal pain). The gastrointestinal manifestations of wheat allergy and CD can be indistinguishable from each other. Unlike CD, wheat allergy does not cause permanent gastrointestinal or other organ damage once the acute reaction has resolved.

Wheat allergy usually develops during the early infancy or toddler years and is less common in adolescents and adults. Most children with wheat allergy also have other food allergies. One of the main reasons to distinguish between CD and wheat allergy is that the latter is usually outgrown between the ages of 3 and 5 years (whereas CD is lifelong). It is hypothesized that the allergenicity of wheat is strengthened by activated tTG and that there is increased absorption of allergens through the gastrointestinal tract in these patients.[29] As with CD, this symptomatology improves with elimination of wheat and wheat products from the diet. Symptoms can be prevented with strict wheat avoidance and treated with antihistamines and corticosteroids. Affected individuals may need to have epinephrine readily available in case of an anaphylactic reaction, which can be potentially life threatening. Although the immunologic reactions in CD can be severe, they do not cause life-threatening anaphylaxis.

## Gluten Sensitivity

Gluten sensitivity is thought to exist in a patient when removal of gluten from the diet results in symptomatic improvement. By definition, these patients have neither CD nor wheat allergy, and both of these conditions must be ruled out before labeling a patient as "gluten sensitive." At present, this is a clinical diagnosis based on response to the GFD, as there are no specific blood tests for this condition. In contrast to CD and wheat allergy, gluten sensitivity has traditionally been thought *not* to be immune mediated. The gastrointestinal complaints can be difficult to distinguish between these 3 conditions, as gluten sensitivity may also present with gas, nausea, emesis, bloating, abdominal pain, and overt diarrhea. However, as opposed to CD, the manifestations of the gastrointestinal sensitivity are thought not to cause permanent damage or result in nutrition deficiencies or higher rates of malignancies.

A recent provocative study by Sapone et al[30] is one of the first to try to elucidate the pathophysiologic mechanisms underlying gluten sensitivity. Patients with biopsy-proven CD, those with gluten sensitivity, and healthy controls who had endoscopy for dyspepsia underwent a supervised 4-month gluten challenge. The main gastrointestinal symptoms of the gluten-sensitive individuals were gas, diarrhea, weight loss, and abdominal pain. Of note, they also exhibited the extraintestinal symptoms of glossitis, muscle cramps, leg numbness, bone or joint pain, osteoporosis, and unexplained anemia. All of the gluten-sensitive individuals were EMA IgA and tTG IgA negative, but about half had positive AGA IgG and/or IgA and HLA DQ2 and/or DQ8. Those who were tested for wheat IgE were negative for this marker for wheat allergy. As opposed to those with CD, the gluten-sensitive individuals did not demonstrate elevations in interleukin-6 or interleukin-21 and had only a mild increase in intraepithelial lymphocytes on intestinal biopsy, indicating a more limited involvement for the adaptive immune system in this process. Biopsies from those gluten sensitive also showed reduced expression of the T regulatory cell molecules FOXP3 (forkhead box P3) and TGFB1 (transforming growth factor $\beta_1$), signifying that there may be a decreased recruitment of T regulatory cells to the small bowel in those gluten sensitive compared with individuals who are gluten tolerant. Interestingly, the gluten-sensitive group did show decreased intestinal permeability (as measured by urinary lactulose/mannitol) along with increased expression of the gene

*CLDN4* (claudin 4, a tight junctional protein). This suggests marked differences between gluten sensitivity and CD with regard to mucosal barrier function at the level of the intestinal epithelial cell tight junctions. Gluten-sensitive individuals also had higher expressions of toll-like receptors 1, 2, and 4 in intestinal biopsies as compared to healthy controls, inferring a more major role for the innate immune system in this condition.[30]

Two conditions often placed within the category of gluten sensitivity are DH and gluten-sensitive ataxia. However, some investigators now consider these 2 conditions to be part of the CD spectrum and not in the "sensitivity" category. Several other neurologic disorders, as well as autism and IBS, have also been reported to show improvements on the GFD.

## Dermatitis Herpetiformis

Many CD experts consider the DH skin rash (also known as Duhring disease, named after the individual who first described it in 1884) to be pathognomonic for CD. The rash can be difficult to diagnose, as its appearance can evolve over time. DH particularly involves the extensor surfaces of the face, elbows, knees, and buttocks. It begins as an erythematous macule (red and flat), progresses to an urticarial papule (itchy and raised), and eventually manifests as tense vesicles (fluid-filled hives) resembling the shingles seen with herpes zoster. Patients with DH will often unroof and scratch the vesicles to the point where the chronic skin changes may mimic eczema or psoriasis. Two differentiating hallmarks of DH are that of severe pruritus and symmetrical distribution (ie, both sides of face, both buttocks, both knees). Most patients with DH do not complain of frank gastrointestinal symptoms; however, 75% will demonstrate villous atrophy on small bowel biopsy. Diagnosis of DH is made with skin biopsy, sent frozen for special granular IgA stains in the dermal papillae. If DH is confirmed via skin biopsy, the patient does not require endoscopy for small bowel biopsy but does require a GFD. Dapsone, an anti-inflammatory antibiotic, is the drug of choice to alleviate the acute pruritus, although other medications are available. Strict adherence to a GFD is currently recommended to prevent flares and complications, such as vitiligo, alopecia areata, sarcoidosis, autoimmune thyroid disease, type I diabetes, and systemic lupus erythematosis. Some patients are also sensitive to products containing latex and iodine.[31,32]

## Ataxia and Other Neurologic Manifestations

The term *gluten ataxia* was first proposed by Hadjivassiliou et al[33] in 1998 in patients with progressive, idiopathic ataxia (a lack of coordination of muscle movements) and elevated AGAs. All of these patients in this initial description had gait ataxia, some had limb ataxia, and more than half had peripheral neuropathy. Roughly a third had distal duodenal biopsies consistent with CD. About 20% had evidence of cerebellar atrophy on magnetic resonance imaging (MRI), and 2 individuals demonstrated immunologic damage (lymphocytic infiltration) of the cerebellum, peripheral nerves, and posterior columns of the spinal cord on autopsy. Since that time, several studies have examined the higher prevalence of AGAs in patients with both sporadic and familial ataxia.[25] In a review of 147 patients with gluten ataxia followed over 12 years in one center, the male to female ratio was equal, and the mean age of onset of ataxia was 53 years. All were AGA+, 22% were EMA+, 56% were tTG IgA+, 70% were HLA DQ2+, 28% had enteropathy on biopsy, and up to 60% had MRI evidence of cerebellar atrophy.[25]

The mechanisms by which gluten interacts with the nervous system have yet to be fully elucidated in detail. In human and rat cerebellum, there appears to be antibody cross-reactivity between gluten peptides and the Purkinje cells in the cerebellar cortex.[34] In addition, in the sera of patients with gluten ataxia, there is evidence for antibodies targeting Purkinje cell epitopes.[34] TTG IgA deposits have been reported in both jejunal tissue and around the blood vessels of the brain (cerebellum, pons, and medulla) of gluten-sensitive patients.[35-37]

GFD is the mainstay of treatment for gluten ataxia, although 1 uncontrolled trial reported improvement in 4 patients after intravenous immunoglobulin.[38]

Other reported neurologic manifestations of gluten sensitivity include inflammatory myopathy (which may improve with a GFD ± immunosuppression)[39] and sensory ganglioneuropathy (which may also respond to a GFD).[40] It is controversial whether multiple sclerosis, although reported to be associated with elevated AGAs, it truly part of the gluten sensitivity spectrum.[41,42] In addition, biopsy-proven CD reportedly has been associated with childhood partial epilepsy with occipital paroxysms.[43] Kieslich et al[44] reported the following neurologic findings in 75 pediatric patients with biopsy-proven CD on a GFD: ataxia, febrile seizures, single generalized seizures, muscular hypotonia with retarded motor development, and T2 hyperintensive white matter lesions on MRI (hypothesized to be from vasculitis or inflammatory demyelination). Addolorato et al[45] likewise published in 2004 that 75% of patients with untreated CD exhibited at least 1 hypoperfused brain region (as assessed by single photon emission computed tomography), significantly different from CD patients on a GFD and healthy controls. Interestingly, these perfusion defects, as seen in the superior and anterior areas of the frontal cortex and anterior cingulated cortex, have also been reported in psychiatric disorders, such as depression, anorexia nervosa, and anxious-neurotic behaviors.[46-48]

## Irritable Bowel Syndrome

Recent research suggests that some types of IBS may show symptomatic improvement on a GFD.[49] The symptoms of IBS are primarily that of pain, gas, bloating, and diarrhea with or without constipation. Many now believe that IBS is due to bacterial overgrowth in the small intestine.[50] In 1 study, after 6 months of a GFD, 60% of diarrhea-predominant IBS patients returned to normal stool frequency and gastrointestinal symptom score. Interestingly, the patients who responded to the GFD were more likely to have positive AGA IgG and TTG IgG than those who did not respond.[51] CD is often mislabeled as IBS by primary care practitioners. Many women with undiagnosed CD complain of IBS-like symptoms, such as gas, bloating, abdominal pain, and diarrhea alternating with constipation. Also, IBS and CD can coexist in the same patient![52] Most IBS experts and gastrointestinal societies agree that it is cost-effective to rule out CD before making the diagnosis of IBS.

Although IBS is thought to be due to intestinal bacterial overgrowth, some alternative practitioners are suggesting that gastrointestinal symptoms, headache, and poor memory may be attributed to intestinal overgrowth of *Candida albicans*. It is then recommended that these patients undergo a "*Candida* cleanse diet," which eliminates sugar, white flour, yeast, and cheese thought to promote candidal overgrowth. Although no clinical trials have documented the efficacy of this diet for treating any recognized medical condition, many patients note improvement in symptoms. This may be due to replacing processed foods with fresh ones and white flour with whole grains. Conversely, one may ask, "Do these patients have another type of gluten-sensitive condition?"[53]

## Autism and the Gluten-Free, Casein-Free Diet

The opioid hypothesis states that autism results from excessive brain opioid activity during the neonatal period. This leads to an inhibition of social motivation, yielding aloofness and autistic isolation. This hypothesis is supported by the arguments that animals exhibit similar behavior after injections of exogenous opioids (decreased vocalization and increased aloofness), direct biochemical evidence of abnormal peripheral endogenous opioids in autistic patients, and case reports of the therapeutic effects of naltrexone (a long-lasting opioid receptor blocking agent) in patients.[54,55] In 1991, Reichelt[56] theorized that gluten and casein peptides, which have similar chemical structures, play a role in the pathogenesis of autism. He assumed that "if a person has a sensitivity to either they will have sensitivities to both, although these sensitivities need not be of equal severity." He then put forward that the inability to adequately process gluten and casein is proposed to result in, or exacerbate, a variety of disorders, including autism, schizophrenia, and postpartum psychosis.

It is imagined that inadequately metabolized gluten and casein proteins break down into peptides that are absorbed across the gut barrier. These peptides, "gliadorphin" and "casomorphin," bind with endogenous opioid receptors, and high levels of peptides can be measured in the urine. A small proportion of these peptides cross the blood-brain barrier, causing "interference of signal transmission." Knivsberg et al[57] argued that these peptides have a negative pharmacological effect on attention, brain maturation, social interaction, and learning. Also, urine samples from autistic patients show an increased 24-hour low molecular weight peptide excretion and increased opioid levels in the cerebrospinal fluid in several studies.

There are high rates of using complementary and alternative medicine (CAM) by the parents of children with autism spectrum disorders, including dietary supplements and different restrictive diets. One of the main reasons that parents report CAM use is because of concerns about the safety and side effects of prescribed pharmacologic agents for autism. Likewise, there should be an equal concern to scrutinize the available evidence for the efficacy and effectiveness of restrictive diets that include the gluten-free, casein-free diet (GFCFD), as well as identify any associated risks. To further address these issues, 2 Cochrane Reviews were published in 2004 and 2008. The participants included children, adolescents, and adults clinically diagnosed with autism spectrum disorder per the fourth edition of the *Diagnostic and Statistical Manual of Medical Disorders* (*DSM-IV*) or the *International Classification of Diseases, Tenth Revision* (*ICD-10*). The types of interventions studied were GFD vs placebo/no treatment, casein-free diet vs placebo/no treatment, GFCFD vs placebo/no treatment, and GFD vs casein-free diet. The outcomes measured included urine peptide concentrations, standardized autistic behavioral assessments, communication/linguistic ability, cognitive functioning, motor ability, and "disbenefits" (harms, costs, and impact on quality of life).[58,59]

From 1965 to 2007, 61 studies were indentified, of which only 3 were considered to be of high enough quality to be included in the analysis.[57,60,61] The other 58 studies were thought to have either significant bias or were not randomized or blinded (mostly case reports). These 3 studies comprised 2 small trials: the first with 10 participants in each arm and the second with 15 participants total. In the first study, GFCFD was reported to reduce the autistic traits of "social isolation" and "bizarre behavior" at 12 months. In the second study, there was no significant difference in outcome measures between the diet group and the control group with regard to cognitive skills at 12 months, motor ability at 12 months, communication and language sampling at week 6, or Childhood

Autism Rating Scale at week 6. There were no reported adverse outcomes or potential disbenefits. These meta-analyses concluded that "this is an important area of investigation and large scale, good quality randomized control trials are needed."[58,59]

Is there a downside to using the GFCFD in autism? The GFCFD costs more than a standard diet and involves extra effort in providing the special meals for the child with autism and normal meals for the rest of the family. Many autistic children have well-established, particular dietary preferences that are difficult to change. Also, it is a challenge for parents to identify and source out food products that are guaranteed not to contain gluten or casein. The loss of the nutrients found in cow's milk products, such as calcium, protein, magnesium, potassium, and other vitamins and minerals, must be supplemented to the child in another way. There are also significant quality-of-life issues, in that the autistic patient is perceived as "different" and "special" and is already restricted in terms of lifestyle because of the disorder. Further social restrictions, in terms of diet, may place additional burdens on the family and patient.[59]

## Why Is It Important to Know the Difference Between CD, Wheat Allergy, and Gluten Sensitivity?

Even though CD, wheat allergy, and gluten sensitivity are treated similarly, with removal of wheat and/or gluten from the diet, it is important for patients and healthcare practitioners to be able to differentiate between these disorders for the following important reasons:

- *Nutrition deficiencies*: CD is an autoimmune condition, where the body's immune system starts attacking normal tissue, such as intestinal tissue, in response to eating gluten. People with CD are at risk for malabsorption of food in the gastrointestinal tract, causing nutrition deficiencies, particularly of protein, fat, iron, and the fat-soluble vitamins. This can lead to complications such as iron deficiency anemia and osteoporosis. Because a person with wheat allergy or gluten sensitivity usually does not have severe intestinal damage, he or she is not at risk for these nutrition deficiencies. Often, in wheat allergy and gluten sensitivity, only wheat or gluten restriction is needed, and dietary supplements and medical screens for nutrition deficiencies (ie, anemia, vitamin levels, bone density) are not warranted.
- *Development of other autoimmune conditions*: CD is an autoimmune condition, putting the patient at risk for other autoimmune conditions, such as thyroid disease, type I diabetes, joint diseases, and liver diseases. Because wheat allergy and gluten sensitivity are not autoimmune conditions, these patients are *not* at increased risk of developing additional autoimmune conditions over that of the general population.
- *Risk for malignancies*: CD involves the activation of a particular type of white blood cell, the T lymphocyte, as well as other parts of the immune system. Because of this, patients with CD are at increased risk to develop gastrointestinal cancers, particularly T cell enteropathy lymphoma.[62] Other gastrointestinal cancers, as well as skin cancer, have also been reported at higher rates in CD patients. Because food allergies and sensitivities do not involve this particular immune system pathway and do not cause severe gastrointestinal tract damage, these patients are not at increased risk for these cancers.
- *Increased mortality*: Because of the above nutrition complications, comorbid autoimmune conditions, and higher risk for malignancies, patients with CD have a 2- to 4-fold increased mortality rate, at every age, than that of the general population.[6,63] Patients with wheat allergy and gluten sensitivity do not have this increased risk of death due to these complications.
- *Familial risk*: First- and second-degree relatives of CD patients are at much higher risk than that of the general population to develop CD and also have other autoimmune disorders. Once an index case of CD is identified, screening for CD in first- and second-degree family members should be performed. Screening family members for wheat allergy or gluten sensitivity is not currently recommended.

Thus, although CD, wheat allergy, and gluten sensitivity may be treated with similar diets, they are not the same conditions. It is very important for a patient and his or her healthcare practitioner to know which condition the patient has, as the person with CD needs to be monitored for nutrition deficiencies, other autoimmune diseases, and gastrointestinal cancers.[3,18] In general, the symptoms from food allergies and intolerances resolve when the offending foods are removed from the diet and do not cause permanent organ damage.

## Conclusion

The GFD, although safe and effective, is currently only indicated for specific medical conditions:

1. Celiac disease? Yes, the GFD is the only validated treatment for this condition.
2. Wheat allergy? Yes, the GFD is indicated, but these patients usually do not need to restrict rye, barley, and oats unless they exhibit additional food allergies or sensitivities.
3. Gluten sensitivity? Yes, the GFD is indicated, particularly in the cases of DH and gluten ataxia. However, it is hard to define this condition, particularly if there are only vague gastrointestinal or neurologic symptoms present in the patient. More research is needed in this area.
4. IBS? Yes, the GFD may improve symptoms in diarrhea-predominant IBS. However, the healthcare practitioner must first rule out CD because the symptoms of IBS and CD are similar.
5. Autism? The GFD may or may not have benefits in subsets of patients with the autistic spectrum disorder. The GFD has the advantages of being proven safe and nontoxic without definitive nutrition deficiencies. However, the casein-free diet may require supplementation of protein, calcium, and other vitamins and minerals. In this population, one needs to account for patient preferences for foods and oral feeding aversions to certain textures and tastes, as well as quality-of-life issues. More research is needed in this area.
6. The general public? No, although the human race does not appear to be evolved to digest glutens well, and these proteins are highly immunologically reactive, no current data suggest that that general population should maintain a gluten-free lifestyle in the absence of the above conditions. More research is needed in this area as well.

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