Health Benefits and Adverse Effects of a Gluten-Free Diet in Non–Celiac Disease Patients

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Keywords
Celiac disease, gluten, gluten-free diet, nonceliac gluten sensitivity

Abstract: Gluten-related diseases such as celiac disease and gluten ataxia are rare conditions, affecting less than 1% of the population in the United States. Despite the rarity of these diseases, there have been significant increases in the adoption of a gluten-free lifestyle and the consumption of gluten-free foods in the United States over the last 3 decades. More than $15.5 billion were spent on retail sales of gluten-free foods in 2016. The gluten-free diet is driven by multiple factors, including social and traditional media coverage, aggressive consumer-directed marketing by manufacturers and retail outlets, and reports in the medical literature and mainstream press of the clinical benefits of gluten avoidance. Individuals may restrict gluten from their diets for a variety of reasons, such as improvement of gastrointestinal and nongastrointestinal symptoms, as well as a perception that gluten is potentially harmful and, thus, restriction represents a healthy lifestyle. Emerging evidence shows that gluten avoidance may be beneficial for some patients with gastrointestinal symptoms, such as those commonly encountered with irritable bowel syndrome. However, high-quality evidence supporting gluten avoidance for physical symptoms or diseases other than those specifically known to be caused by immune-mediated responses to gluten is neither robust nor convincing. In fact, gluten avoidance may be associated with adverse effects in patients without proven gluten-related diseases. This article provides insight regarding gluten avoidance patterns and effects on patients without gluten-related diseases, and highlights concerns surrounding gluten avoidance in the absence of a gluten-mediated immunologic disease.

Epidemiology and Economics of a Gluten-Free Diet

The consumption of gluten-free foods has significantly increased over the last 30 years. More than $15.5 billion were spent on retail sales of gluten-free foods in 2016, which is more than double the amount spent in 2011.[1] The rapid rise in the popularity of a gluten-free diet (GFD) and gluten-free foods has been driven by multiple factors,

including social and traditional media coverage, aggressive consumer-directed marketing by manufacturers and retail outlets, and reports in the medical literature and mainstream press of the clinical benefits related to gluten avoidance. A lifelong GFD is well recognized as the standard of care for patients with gluten-related diseases such as celiac disease and gluten ataxia, in which immune-mediated inflammatory responses to gluten proteins are directed primarily against the small intestinal mucosa and cerebellar Purkinje fibers, respectively.[2] Immunoglobulin (Ig) E–mediated wheat allergy is another relatively rare gluten-related disease that requires restriction of wheat from the diet. However, people without these well-defined clinical entities have embraced a GFD due to perceived health benefits or because of a belief that gluten ingestion leads to harmful or bothersome effects.

Accumulating translational and clinical trial evidence supports a putative role of diet in the generation of irritable bowel syndrome (IBS) symptoms, as the majority of patients seeking care for symptoms of IBS link their gastrointestinal symptoms to their diet. Specific diets that are low in fats; carbohydrates; gluten; or fermented oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) have all been shown to improve IBS symptoms.[3,4] It is widely accepted that ingestion of grains such as wheat, rye, and barley by patients in whom celiac disease has been definitively excluded can be associated with typical IBS-like symptoms, including abdominal pain, bloating, and bowel habit disturbances, as well as extraintestinal manifestations such as fatigue. As a result, the entity known as nonceliac gluten sensitivity (NCGS) has emerged as a diagnosis for patients who do not have celiac disease or a wheat allergy, who exhibit IBS-like gastrointestinal symptoms after ingesting gluten-containing food, and who have improvement in these symptoms on a GFD. Nonceliac wheat sensitivity has been proposed as a more collective term for components of wheat other than gluten that contribute to symptoms in these patients.

The avoidance of gluten has extended to the population of healthy individuals who believe that adhering to a GFD may have immediate health benefits or may prevent the development of future diseases. These individuals have been described broadly as people who avoid gluten (PWAG) and comprise the majority of people who are partaking of a GFD. Such people may seek to cut back or eliminate gluten due to symptoms that have not been proven to arise as a result of gluten ingestion, or they may be asymptomatic. People thought to have gluten-specific symptoms or NCGS are also occasionally included under the PWAG umbrella. US data from the National Health and Nutrition Examination Survey (NHANES) from 2009 to 2014 showed that although the prevalence of celiac disease remained stable and the prevalence of undiagnosed celiac disease decreased by 50% during this time period, the prevalence of PWAG more than tripled.[5] Seventy-two percent of people who adhered to a GFD in 2014 would be considered PWAG vs 44% in 2009.[5] It should be noted that the NHANES defined PWAG as people without celiac disease who avoided gluten, which likely included individuals with NCGS or wheat sensitivity.

A population questionnaire[6] in the United Kingdom showed that 3.7% of the population claimed to be on a GFD, and a survey reported on National Public Radio[7] found that almost one-third of adult Americans would prefer to reduce or avoid gluten consumption altogether. In certain populations, such as athletes, as many as 50% report variable adherence to a GFD.[8] However, less than 1% of the US population has celiac disease, gluten ataxia, or wheat allergy.[2] NCGS has been estimated to have a prevalence of 0.6% to 13.0%[9]; in patients with reported NCGS who undergo blinded, placebo-controlled, crossover studies, however, the diagnosis is confirmed in only approximately 16% to 30%.[10,11] Thus, the majority of PWAG do so without a confirmed medical diagnosis necessitating a proven need. Moreover, substantially reducing or eliminating gluten-containing foods from the diet could have negative health and economic effects. Despite the recent publicity and interest surrounding a GFD in popular culture, the medical literature pertaining to the topic has lagged behind. This article provides insight regarding gluten avoidance patterns and effects on patients without gluten-related diseases, and highlights concerns surrounding gluten avoidance in the absence of a gluten-mediated immunologic disease (Table).

Gluten and Immunogenicity

Gluten refers to a family of proteins known as prolamins (primarily glutenin and gliadin) that constitute the storage protein in the starchy endosperm of many cereal grains such as wheat, barley, and rye. Each type of cereal grain contains differing amounts of gluten as well as other proteins. One beneficial characteristic of gluten proteins is their viscoelasticity, which lends itself to the production of palatable doughs and bread products. Gluten-containing grains such as wheat make up a large portion of the modern Western diet. This is, in part, due to their palatability, ease of cultivation and procession into a wide variety of foods, large-scale production ability, and high nutritional content by weight.

Although the genetics and characteristics of plants such as wheat can be rapidly modified, the human body is not as malleable. The various prolamins (eg, glutenin, gliadin) that comprise gluten must be digested within the small intestinal lumen after consumption; however, they

Table. Potential Benefits and Harms of a GFD in Non–Celiac Disease Patients

Conditions With Potential Benefits From a GFD	Potential Harms of a GFD
Gluten-sensitive irritable bowel syndrome	Deficiencies of micronutrients and fiber
Nonceliac gluten sensitivity	Increases in fat content of foods
Schizophrenia or other mental health conditions	Hyperlipidemia
Atopy	Hyperglycemia
Fibromyalgia	Coronary artery disease
Endometriosis	Increased financial costs
Obesity	Social impairment or restrictions
Athletic performance	

GFD, gluten-free diet.

are long peptide molecules rich in proline and glutamine that are difficult for humans to digest. Both glutenin and gliadin are composed of similar, repetitive amino acid sequences. As many as 45 different gliadins can be present in a single wheat variety. These gliadins are further divided by their electrophoretic motility into α, γ, and ω subfractions. Individual gliadin peptides exhibit different biological properties, all of which have potential involvement in the pathogenesis of gluten-related diseases.

In addition, certain human leukocyte antigen (HLA)-DQ2 T-cell haplotypes have been identified in proline-rich sequences of gliadin. One particular gliadin peptide of 33 residues, α2-gliadin 57–89, has been implicated as a cause of gluten-mediated immunogenicity. It is produced by normal gastrointestinal proteolysis and contains 6 partly overlapping copies of 3 T-cell epitopes. After degradation by intestinal tissue transglutaminase, α2-gliadin 57–89 has been shown to be a strong stimulator of T lymphocytes. Other sequences of α-gliadin have been shown to activate innate immunity mechanisms or interact with CD8+ cytotoxic T cells.[12] It is plausible that numerous different amino acid sequences among the multitude of gluten peptides may lead to the activation of immune responses involved in the pathogenesis of gluten-related diseases.

Furthermore, as new gluten peptides emerge via genetic modification resulting from modern agriculture practices, more immune-activating gluten peptides may be seen in food. Gluten-derived peptides, such as gliadin and glutenin in wheat, secalin in rye, and hordein in barley, have been identified as important antigen-producing proteins in patients with celiac disease.[13] In a minority of patients with celiac disease, avenin in oats has also been shown to elicit an immune reaction.[14] One theory regarding the ability of gluten and its related proteins to cause gastrointestinal symptoms in the absence of an overt gluten-related disease states that human intestinal tracts have not yet fully evolved to deal with modern grain proteins, especially to the degree of exposure that is inherent in contemporary diets.[9] It is also possible that in individuals with NCGS, gluten proteins may elicit adverse pathophysiologic responses that are different from the well-characterized mechanisms observed in patients with gluten-related diseases.

Gluten and Irritable Bowel Syndrome

Diet has been shown to play an important role in some patients with IBS,[15] and multiple studies have evaluated both gluten exposure and the clinical benefits of the implementation of a GFD in patients with IBS. In one of the earliest studies of a GFD for IBS, Wahnschaffe and colleagues described a group of IBS patients with negative serum celiac disease antibodies and positive intestinal celiac disease antibodies detected on duodenal aspirate who had both improvement in their IBS symptoms and a reduction in intestinal antibody levels when placed on a GFD for 6 months.[16] It could be argued that these biomarkers and the response to the GFD are consistent with latent or potential celiac disease; however, these patients would likely be labeled as having NCGS in clinical practice where intestinal antibodies are not routinely obtained. In another study from the same investigators, patients with diarrhea-predominant IBS (IBS-D) who were HLA-DQ2/8–positive and who had elevated levels of IgG celiac disease–associated serum antibodies had greater reductions in IBS symptom scores after 6 months on a GFD than patients who were HLA-DQ2/8–negative and IgG celiac disease–antibody negative (60% vs 12% reduction, respectively).[17]

Despite multiple studies that have suggested a higher prevalence of celiac disease markers in patients with IBS compared to the general population,[18-21] current evidence has not proven that these laboratory values can be used with confidence to predict response to a GFD. In a commonly cited report, Biesiekierski and colleagues demonstrated that gluten ingestion was associated with both gastrointestinal and nongastrointestinal symptoms in 34 patients with IBS who did not have celiac disease.[22] Patients were randomized to receive either gluten or placebo for 6 weeks, and symptoms, markers of intestinal inflammation and injury, and immune activation were monitored. Sixty-eight percent of patients in the gluten-ingesting group reported inadequate IBS symptom

control vs 40% in the placebo group (P=.0001). In addition, gluten-ingesting patients were significantly worse for overall symptoms, pain, bloating, satisfaction with stool consistency, and tiredness within 1 week. Antigliadin antibodies were not identified in these patients, and there were no significant changes in fecal lactoferrin, levels of celiac antibodies, C-reactive protein, or intestinal permeability, nor were any differences noted in any endpoint based on HLA-DQ2/8 status.

Vazquez-Roque and colleagues reported the effects of a randomized, 4-week trial of a GFD (23 patients) compared to a gluten-containing diet (GCD; 22 patients) on daily bowel function, bowel transit, mucosal permeability, and cytokine production in patients with IBS-D diagnosed by Rome II criteria in whom celiac disease had been excluded.[23] Patients on a GCD had more bowel movements per day, greater intestinal permeability, and greater inflammatory cytokine levels compared to patients on a GFD. There was no effect on colonic permeability, intestinal transit, or histology. However, the adverse effects of gluten were higher in patients who were HLA-DQ2/8–positive, suggesting an adaptive immune response to gluten exposure with alterations in gut permeability and inflammation that might reverse with gluten restriction. Aziz and colleagues reported the results of a study of 41 patients with IBS-D who were treated with a dietitian-led GFD for 6 weeks.[24] Twenty patients were HLA-DQ2/8–positive and 21 were HLA-DQ2/8–negative. At the end of the study period, 71% of patients on the GFD reported improvement based on a decrease in the IBS Symptom Severity Score of at least 50 points, with reductions in the mean score from 286 at baseline to 131 at the end of 6 weeks. Although this reduction was similar between both HLA-DQ groups, IBS patients who were HLA-DQ2/8–negative had a greater reduction in abdominal distension, and HLA-DQ2/8–positive subjects had a greater reduction in depression scores and increase in vitality scores. Seventy-two percent of patients with a clinical response remained on a GFD 18 months after the study was completed.

Nonceliac Gluten Sensitivity

NCGS is an umbrella term that has been associated with a wide range of both gastrointestinal and nongastrointestinal symptoms that respond to gluten restriction and recur with gluten ingestion. These symptoms may include bloating, abdominal discomfort and pain, altered bowel habits, flatulence, rash, fatigue, headaches, mental disturbances, irritability, depression, bone and joint pain, and even attention deficit disorder. There is abundant overlap between IBS, other functional gastrointestinal disorders, and NCGS. In fact, all celiac disease–excluded patients with IBS-like gastrointestinal symptoms that respond to a GFD and whose symptoms return with ingestion of gluten could be classified as having NCGS. Because of the overlap of disorders, the medical literature has not always clearly differentiated between these groups when evaluating the effects of a GFD or other dietary manipulations.[25] In contrast to celiac disease, NCGS patients, by definition, must not have detectable celiac disease–associated antibodies and may be HLA-DQ2/8–negative. They also should not have histologic abnormalities of the small intestine. Whereas celiac disease leads to increased small intestinal permeability and activation of the adaptive immune response, most studies have shown that patients with NCGS have normal intestinal permeability and activation of the innate immune response without activation of the adaptive immune response.[26-30] However, some disagreement exists in these areas of research.

Researchers have proposed that other components in wheat, in addition to gluten proteins, contribute to the activation of the innate immune response and elicit symptoms in patients with NCGS. Many studies evaluating the effects of dietary gluten use wheat as their source of gluten, which raises the issue of collinearity in studies assessing gluten and its effects. Amylase-trypsin inhibitors are proteins found in wheat and commercial gluten that have been shown to activate the innate immune response.[31] Wheat germ agglutinin has also been shown to exert immune-mediated effects, which potentially lead to gastrointestinal symptoms.[32,33] Some investigators have proposed that a more appropriate term for NCGS might be nonceliac wheat sensitivity,[34] as it is a more inclusive term that might account for other components in wheat besides gluten that could contribute to symptoms.[35,36] In addition, a low-FODMAP diet has been shown to improve gastrointestinal symptoms in patients with functional bowel disorders.[3,4] Some patients who have improvement with restriction of wheat or gluten may actually be responding to a concomitant restriction of FODMAPs. In a double-blind, placebo-controlled, crossover, rechallenge study, Biesiekierski and colleagues showed that following restriction of FODMAPs, only 8% of 22 patients with self-reported NCGS and Rome III criteria for IBS had gluten-specific symptoms.[25] A recent study evaluated fructans alone vs gluten vs placebo in patients with self-reported NCGS.[37] Skodje and colleagues conducted a randomized, double-blind, placebo-controlled, crossover study and found that both IBS symptoms (rated on a gastrointestinal symptom rating scale) and bloating were significantly worse after fructan ingestion compared to gluten.[37] However, there was no significant difference between fructan and placebo or gluten and placebo.

Elli and colleagues aimed to identify NCGS patients among those with functional gastrointestinal symptoms

and conducted a multicenter, double-blind, placebo-controlled trial in which patients were given a GFD for 3 weeks, then randomized to either gluten or placebo for 7 days, followed by crossover.[38] Among the 98 patients who completed the gluten challenge, 28 (28.6%) reported symptomatic relapse and decreased quality of life attributable to gluten reintroduction. Overall, 14% of patients had symptomatic relapse and were defined as having NCGS. Di Sabatino and colleagues performed a similar double-blind, placebo-controlled, crossover trial evaluating the effects of gluten on patients with suspected NCGS.[39] Patients received either gluten or placebo for 1 week followed by a 1-week crossover. The authors found a gluten response in 20% of the patients, with abdominal bloating, abdominal pain, foggy mind, depression, and aphthous stomatitis being the most significant symptoms when patients received gluten rather than placebo. A systematic review and meta-analysis of rechallenge studies in NCGS reviewed 11 studies and found that only 30% of patients with diagnosed NCGS relapsed after a gluten challenge, with a broad observed range of 7% to 77%.[10] The meta-analysis was characterized by considerable study heterogeneity related to different sample sizes, patient populations, amounts of gluten administered, durations of the gluten challenge, and types of placebo. A recent systematic review by Molina-Infante and Carroccio evaluated 10 double-blind, placebo-controlled, gluten challenge trials in patients with NCGS.[11] Most studies showed a significant increase in symptom scores with a gluten challenge; however, only 16% of NCGS patients showed gluten-specific symptoms. In addition, 40% of patients were judged to have had a nocebo response.[11]

Francavilla and colleagues evaluated 1114 pediatric patients with chronic gastrointestinal symptoms who did not have celiac disease or wheat allergy.[40] Patients exhibiting a positive correlation between symptoms and gluten ingestion were then included in a double-blind, placebo-controlled, crossover gluten challenge. Only 36 children were eligible (96.7% of patients did not exhibit any correlation to gluten ingestion). A minimum 30% decrease in global symptoms between gluten and placebo was considered to be a positive response, and only 39% of patients with a positive correlation of symptoms to gluten ingestion (11/36) met this threshold. Peters and colleagues evaluated the effects of gluten on individuals' mental states.[41] Patients with self-reported NCGS were recruited from the trial by Biesiekierski and colleagues discussed earlier,[25] and were included in the study if they met Rome III criteria for IBS and had improvement in symptoms with adherence to a GFD for at least 6 weeks. Celiac disease was excluded. Patients were entered into a double-blind, placebo-controlled, 3-day challenge trial of wheat gluten, whey protein, and placebo, with a minimum 3-day washout period between each group.[41] Gluten ingestion was associated with higher depression scores compared to placebo but not to whey protein, based on a validated 80-question survey (State-Trait Personality Inventory). No differences were found between the groups for anxiety, anger, or curiosity. Thus, although these studies support the existence of NCGS, it appears that such individuals represent a relatively small portion of patients with IBS-like symptoms.

Other Patient Populations

Patients With Schizophrenia

It has been suggested that patients with schizophrenia have higher levels of antigliadin autoantibodies (but not celiac disease) than the general population, and have hypothesized a linkage between these antibodies and psychiatric diseases.[42] Two studies by Dohan and colleagues reported that individuals had a reduction in schizophrenia symptoms when gluten was excluded from their diets.[43,44] However, subsequent studies have produced mixed or negative results,[45-50] and recent reviews concluded that there are no consistent results among studies that have investigated possible relationships between schizophrenia, celiac disease, antigliadin antibodies, and the effect of gluten restriction on symptoms.[51,52]

Patients With Atopy

Patients with NGCS and IBS symptoms have been reported to have a higher prevalence of atopic diseases as well as nongrain food allergies in childhood.[30] There is conflicting evidence whether these patients have non–IgE-mediated food sensitivity via basophilic activation and inflammation.[30,36] A study in a pediatric population showed that 30% of patients with IBS-like gastrointestinal symptoms and mucosal lesions with negative tissue transglutaminase antibodies or HLA-DQ2/8 had improvement in both atopic and gastrointestinal symptoms with a GFD.[53] However, IgE antibody testing to assess for wheat allergy was not documented in this study.

Patients With Fibromyalgia

A recent study by Slim and colleagues reported the results of the first study of a GFD for fibromyalgia.[54] In this trial, 75 patients with fibromyalgia who had at least 5 of 14 potential gastrointestinal or extraintestinal symptoms possibly related to gluten ingestion were randomized to receive a GFD or a hypocaloric (≤1500 kcal/day) diet for 24 weeks. The GFD and hypocaloric diet resulted in symptom improvement for both gluten-sensitive and fibromyalgia symptoms based on multiple scoring systems; however, there was no difference between the 2 diets for changes observed in either symptom group.

Importantly, the beneficial effects persisted over the 6-month study period, making an association with placebo effect less likely.

Patients With Endometriosis and Chronic Pelvic Pain

Two studies have evaluated the effects of a GFD in patients with endometriosis and chronic pelvic pain.[55,56] Both studies claimed an improvement in pain scores after implementation of a GFD for 6 and 12 months, respectively.

People Who Avoid Gluten

As noted previously, the majority of PWAG do not have an established gluten-related disease or NCGS verified by a rechallenge test. This patient population either seeks to obtain benefit from symptoms without a confirmed diagnosis of a gluten-specific disorder, or these patients may seek some other benefit from a GFD rather than improvement in any specific symptom. One impetus for the practice of gluten avoidance in this population may be the perception that a GFD is a nutritionally healthier option than a traditional Western diet. Another potential perceived benefit of a GFD is that it is associated with weight loss. Kim and colleagues evaluated a GFD and its effect on obesity, metabolic syndrome, and cardiovascular risk in non–celiac disease participants in the NHANES from 2009 to 2014, and found that a GFD was associated with a decrease in weight over 1 year, lower waist circumference, and higher high density lipoprotein levels compared to the general population.[57] There was no significant difference in metabolic syndrome or other cardiovascular risks (eg, smoking, hypertension, total cholesterol). Limitations of this study include its retrospective nature and its ability to make only potential associations without establishing causality. In addition, just 1.3% of non–celiac disease patients reported following a GFD. Lastly, most GFD followers were health-conscious, well-educated women who may have been predicted to have better cardiovascular profiles than the general population, as well as greater diligence in pursuing weight loss.[58]

Some athletes have advocated for a GFD to enhance performance and stamina. In a 2015 questionnaire-based study of 910 athletes without celiac disease, 41% reported following a GFD more than 50% of the time (50%-100%).[8] Of that group, only 13% did so for the treatment of reported medical conditions, and 57% reported self-diagnosed gluten sensitivity. This group was made up of predominantly endurance sport athletes who reported gastrointestinal symptoms and fatigue that they believed were associated with gluten ingestion. Eighty-four percent of the patients following a GFD more than 50% of the time reported symptomatic improvement on the diet. Respondents indicated that their leading sources of information and guidance for a GFD were online (28.7%), their trainer or coach (26.2%), and other athletes (17.4%). A follow-up study of 13 cyclists without celiac disease was performed by the same investigators and consisted of a randomized, double-blind, crossover trial in which participants received either a GFD or GCD for 1 week, then crossed over after a 10-day washout period.[59] No significant differences were found between the diets when both gastrointestinal symptoms and athletic performance on timed trials were analyzed, suggesting that a nocebo effect played at least some role in results observed in the initial, larger trial.[8]

Potential Harms of a Gluten-Free Diet

Gluten-containing foods make up a large component of several diets, including the Western diet. These foods are relatively easy to cultivate and prepare, and represent readily available and cost-friendly options to meet the caloric demands of large populations. Gluten is also a common additive to prepared foods due to its physical properties and palatability. With the popularity of GFDs, it is important to understand the nutritional quality, potential costs, and availability of this diet as well as the effects that excluding gluten can have on the population and food industry.

Nutritional Quality of a Gluten-Free Diet

Several studies have evaluated the nutritional quality of GFD with direct comparison to GCD. However, there is a great deal of discordance among the results; some studies have evaluated the nutritional quality of a GFD in patients with celiac disease, which could be a confounder for nutrient deficiencies due to impaired absorption and chronic inflammation. However, these studies can also yield important information on the nutritional quality and adequacy of a GFD. A 2005 survey by Thompson and colleagues of 47 US adults with celiac disease who were adherent to a GFD showed that the recommended amount of calcium, iron, and fiber was consumed by 31%, 44%, and 46% of women and 63%, 100%, and 88% of men, respectively.[60] Two additional studies by the same lead author have shown that many gluten-free foods are not enriched and may be deficient in several nutrients, including dietary fiber, folate, iron, niacin, riboflavin, and thiamine.[61,62] Other studies evaluating the nutritional composition of processed gluten-free products have demonstrated higher levels of lipids, trans fat, protein, and salt compared to their gluten-containing counterparts.[63-66]

Wu and colleagues performed a comprehensive comparison of gluten-free foods with matched gluten-containing foods in Australian supermarkets based on nutritional quality.[67] The Health Star Rating (HSR;

score 0-5), Australia's food-rating system, was the primary outcome of the analysis; secondary outcomes included individual nutrient contents. Among 3213 food products across 10 food categories evaluated, the average HSR of gluten-free foods was not superior to gluten-containing foods, and no nutritional advantage was found for gluten-free foods. Gluten-free foods consistently showed lower average protein content across core food groups, especially pasta and breads. Gluten-free dry pastas scored nearly 0.5 stars less than gluten-containing pastas. However, there is debate regarding the small portion of protein from grains that make up total dietary protein and, therefore, whether the amount of protein is a significant concern. The primary outcome (ie, the average HSR) was not different among other staple, grain-based food groups (eg, breads and breakfast cereals). Apart from protein content, all other nutritional measures in the secondary analysis, including total energy, fiber content, saturated fats, total sugar, and sodium content, had no clear patterns of differences between gluten-free and gluten-containing foods. A similar study in Austria systematically evaluated 7 categories of foods, comparing 63 gluten-free foods to 126 of their gluten-containing counterparts based on nutrient composition, nutritional information, and cost.[68] The authors found a greater-than-2-fold decrease in protein content of gluten-free products across more than 50% of all food categories. Lower sodium and fiber contents were found in the majority of gluten-free products. A 2013 nutrition survey performed in support of a thesis included 58 healthy adults on a GFD and showed that men on a GFD consumed significantly lower amounts of carbohydrates, fiber, niacin, folate, and calcium, but significantly higher amounts of fat and sodium, than men on a GCD.[69] Women on a GFD consumed significantly lower amounts of carbohydrates, fiber, folate, iron, and calcium, but significantly more fat, saturated fat, and cholesterol, than women on a GCD. Overall, adults adhering to a GFD did not consume enough nutrient-dense foods to meet all nutritional recommendations.

Clinical outcomes data related to the effects of a GFD are sparse and inconsistent. A study by Lebwohl and colleagues examined a large group of non–celiac disease men (n=45,303) and women (n=64,714) from the Health Professionals Follow-Up Study and the Nurses' Health Study, respectively, and assessed patients with low-, medium-, and high-gluten consumption based on food diaries.[70] The aim was to identify whether gluten consumption was associated with coronary heart disease. The authors found an inverse relationship between the outcomes of coronary artery disease and fatal and nonfatal myocardial infarctions with gluten intake. This observation prompted the hypothesis that avoidance of gluten may result in reduced consumption of beneficial whole grains, which has been linked to coronary artery disease. A recent systematic review evaluated cardiovascular disease risk factors and their possible association with a GFD in patients with celiac disease.[71] Although these investigators found consistent changes among 27 studies that include increases in total cholesterol, high-density lipoprotein, fasting glycemia, and body mass index, no demonstrable increase was found in the risk of cardiovascular events. It is important to note that most of the studies included in this review were of low methodologic quality and had multiple potential confounders and a lack of controls, which limit the conclusions of the analysis.

Financial Cost of a Gluten-Free Diet

Studies have shown that gluten-free alternatives are more expensive than their gluten-containing counterparts.[72-74] Stevens and Rashid performed a cost-comparison analysis of gluten-free and gluten-containing foods in 2 large-chain grocery stores.[74] All 56 gluten-free products were more expensive, with a mean unit price of $1.71 compared with $0.61 for gluten-containing products ($P<.001$). On average, gluten-free products were 242% more expensive than regular products. In the Austrian study mentioned previously,[68] gluten-free foods were also substantially higher in cost compared to their gluten-containing counterparts; cereals as well as bread and bakery products were upwards of 205% and 267% more expensive, respectively, compared to similar gluten-containing products.

Social and Psychological Impact of a Gluten-Free Diet

In addition to the increased financial costs of a GFD, there are other costs that can be more difficult to quantify, such as sociopsychological impacts. The pleasurable and communal aspects of food are powerful, deep-rooted perceptions embedded in both individuals and society at large. A GFD requires persistent dedication to a restricted diet and lifestyle, possibly contributing to social isolation and negative psychosocial impacts. The difficulty in maintaining adherence to a GFD may also cause negative feelings and emotions in an individual, especially if he or she is noncompliant. Several studies have attempted to quantify this impact, many of which have included patients with celiac disease. Silvester and colleagues evaluated, by questionnaire, 260 community-dwelling adults on a GFD.[75] Reasons for gluten avoidance were assessed, and 90% of respondents reported a diagnosis of celiac disease. Among the 38 non–celiac disease participants, gluten avoidance was due to gluten sensitivity in 80% and a desire for a healthy lifestyle in 34% (multiple responses were allowed). Compared to participants with celiac disease, non–celiac disease participants were more likely to report rare gluten ingestion (odds ratio, 3.7).

Overall, strict adherence to a GFD in patients with celiac disease vs those without celiac disease was 56% and 42%, respectively. The non–celiac disease group also appeared to be less knowledgeable regarding many of the specifics of a GFD and was less likely to obtain advice from a health care professional. The Work and Social Adjustment Scale was used to evaluate the impacts of a GFD on the domains of work, home management, social leisure activities, private leisure activities, close relationships, and active lifestyle, including physical activity. Most participants reported minimal interference attributed to the GFD in daily functioning, relationships, and active lifestyle. However, 11% of respondents reported high levels of interference with social leisure activities. They reported spending more time, money, and energy on food and food preparation. There was a shift toward eating more meals at home vs out of the home, and eating was found to be less pleasurable. Emotional reactions regarding the GFD included feeling frustrated and misunderstood; however, participants also reported feeling accepted, empowered, and relieved. These positive emotions were more likely to be experienced than the negative emotions. The authors concluded that there is a measurable degree of social impairment related to the restrictions of a GFD; however, there can also be positive adaptation to meet its demands.

A 2006 survey of 2681 adult members of the Canadian Celiac Association found that 44% reported difficulties following a GFD.[76] Reasons included determining if foods were gluten-free (85%), finding gluten-free foods in stores (83%), avoiding restaurants (79%), and avoiding travel (38%). A separate survey conducted among the same population in 2013 reported that difficulties and negative emotions were experienced less frequently by patients on a GFD for more than 5 years, although food labeling and eating away from the home remained problematic.[77] A survey evaluating the adherence to a GFD in children and adolescents with celiac disease demonstrated that participants had better adherence at home and school compared to low adherence at social events.[72] Availability, cost, and food labeling were the main factors limiting adherence. Roma and colleagues questioned 73 children with celiac disease about the main causes of noncompliance; the most frequently reported reasons included poor palatability (32%), dining outside the home (17%), and poor availability of products (11%).[78]

Some patients who begin avoiding dietary gluten with the intention of improving their health and well-being may ultimately progress to develop pathologically obsessive behaviors regarding their diet. This condition, although not currently recognized in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*, is known as orthorexia nervosa. It differs from other eating disorders (eg, anorexia nervosa, bulimia nervosa) in that people obsess about healthy eating and not bodily appearance or weight loss while they pursue increasingly restrictive diets.

It should be mentioned that although small, a percentage of the US population on a GFD has undiagnosed celiac disease. The percentage has decreased in recent years, and was 0.3% in 2013 to 2014 based on data from the NHANES.[5] It is important to make the diagnosis of celiac disease in these patients due to the long-term prognostic implications. Therefore, it is worthy to note that many patients on a GFD due to perceived health benefits should have celiac disease ruled out by diagnostic evaluation.

Summary

The GFD continues to trend in popular culture and the media, and more people are restricting gluten from their diet. The medical community must seek to provide an evidence-based approach delineating both the benefits and potential harms of a GFD. Although convincing evidence is available to support the benefits of a GFD for certain patient populations without a gluten-related disease (especially patients with IBS and NCGS), the data are conflicting and not definitive. It appears that most individuals who participate in a GFD do not have a physiologic requirement for the diet and likely do not derive substantial benefit. Existing evidence for potential harms of a GFD include possible nutritional deficiencies, financial costs, and negative psychosocial implications. As with other dietary interventions, a GFD is a rapidly evolving topic, and additional insight is needed to guide a complete discussion between patients considering a GFD and their health care providers.

The authors have no relevant conflicts of interest to disclose.

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