The Gluten-Free Diet: Recognizing Fact, Fiction, and Fad

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The gluten-free diet (GFD) is a critical medical treatment for the millions of individuals worldwide with celiac disease (CD), an autoimmune condition for which no other therapy is currently available. The prevalence of CD is increasing,[1] reflected by escalating awareness of CD in the scientific community. This increase in disease prevalence and awareness of CD, however, does not account for the disproportionate increase in growth of the gluten-free food industry (**Figure**). According to market research, consumers without CD purchase the vast bulk of gluten-free products.[2]

In reality, remarkably little is known about the motives of most individuals who adopt a gluten-free lifestyle. According to a 2015 survey of more than 1500 American adults, "no reason" (35%) was the most common explanation for selecting gluten-free foods, followed by "healthier option" (26%), and "digestive health" (19%).[3] "Someone in my family has a gluten sensitivity" (10%) was more common than those reporting, "I have a gluten sensitivity," which was the least common rationale cited (8%).[3]

The increasing popularity of the GFD has important implications for children. Parents sometimes place their children on a GFD in the belief that it relieves symptoms, can prevent CD, or is a healthy alternative without previous testing for CD or consultation with a dietitian. Although some children experience relief of symptoms, signifying that CD testing is warranted, many are asymptomatic from the start. The health and social consequences worthy of consideration in advance of starting a child on a GFD are not described adequately online or in books promoting an empiric GFD trial.

This Commentary will provide an update on the current GFD fad and will disentangle facts from commonly held beliefs regarding the GFD, its known benefits, and disadvantages, specifically addressing several issues related to children.

The Gluten-Free Trend in the US and Worldwide

An estimated 0.5% of individuals living in the US adhere strictly to a GFD,[4] although a far greater proportion of the population gravitates towards gluten-free foods to more variable degrees. A 2015 Nielsen survey of 30 000 adults in 60 countries worldwide (reported margin of error ± 0.6%) found that 21% of individuals surveyed rated gluten-free as a "very important" attribute when making food purchasing decisions.[5] The widest appeal was seen in Latin America (32%) and the Middle East/Africa (28%),[5] with 15%-21% of Americans seeking gluten-free products.[5,6] Of 1000 Americans surveyed in 2015, the purchase of gluten-free foods was more common among women (23% vs 19% of men), nonwhites (31% vs 17% white respondents), those with a high school diploma or less (26% vs 17% with some college education), and those with a household income below $30 000 (24% vs 15% of those whose household income was $75 000 or greater).[6] Older generations appear to be less susceptible to the draw of the gluten-free industry[6] despite reports of greater prevalence of nonceliac gluten sensitivity (NCGS) among older adults.[7] According to Nielsen, 37% of respondents age 20 years and younger and 31% of those age 21-34 years were willing to pay the often substantially greater prices for gluten-free products, and only 22% of respondents age 50-64 years and 12% of those age 65 years or greater were willing to do so.[5]

Yet market research by the Mintel Group shows that, despite the increasing belief held by Americans that the GFD is a fad (31% in 2013 to 47% in 2015), in 2015 25% of American consumers reported consuming gluten-free foods.[8] The gluten-free industry enjoyed a growth of 136% from 2013 to 2015, reaching estimated sales of $11.6 billion in 2015[8], far outpacing CD awareness and increases in prevalence.

Fact or Fiction?

Available data regarding the GFD warrant clarification and emphasis, given considerable and systematic circulation of misinformation regarding the diet's potential for harm as well as good. This segment will provide an evidence-based approach to address several of the most common inaccuracies regarding the GFD.

Fiction: The GFD is a healthy lifestyle choice with no disadvantages.

Fact: For individuals who do not have CD, wheat allergy, or NCGS, the latter which has been described in adults but for which there is little evidence in children, there are no data supporting the presumed health benefits of a GFD. In fact, the opposite may be true in certain cases, particularly when the diet is followed without the guidance of an experienced registered dietitian or physician.

Gluten-free packaged foods frequently contain a greater density of fat and sugar than their gluten-containing

CD	Celiac disease
GFD	Gluten-free diet
NCGS	Nonceliac gluten sensitivity

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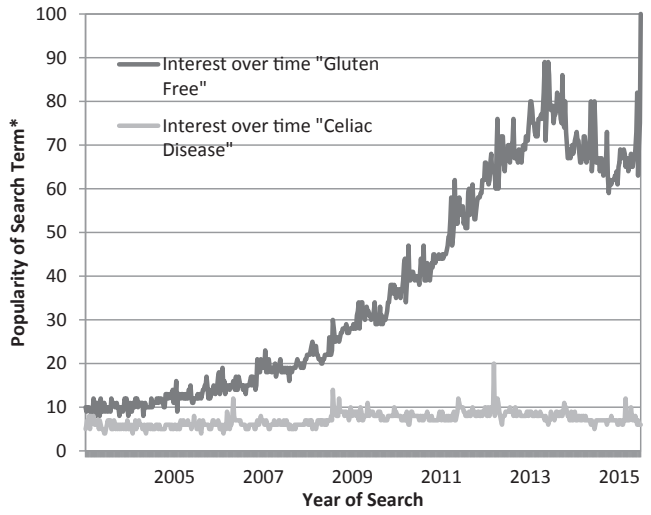

Figure. Google Trends plot of search histories related using the terms "gluten free" and "celiac disease" (2004-2015). Source: Google Trends (www.google.com/trends). Accessed December 23, 2015. *Y-axis values reflect total searches for a term relative to the total number of searches done on Google over time.

counterparts.[9] Increased fat and calorie intake have been identified in individuals after a GFD.[10,11] Obesity, overweight, and new-onset insulin resistance and metabolic syndrome have been identified after initiation of a GFD.[12-14] A GFD also may lead to deficiencies in B vitamins, folate, and iron,[15,16] given a lack of nutrient fortification of many gluten-free products.

There is emerging evidence that those consuming gluten-free products without sufficient diversity may be at greater risk of exposure to certain toxins than those on an unrestricted diet. Arsenic is frequently present in inorganic form in rice, a concern for those on a GFD given that rice is a common ingredient in gluten-free processed foods.[17] Serum mercury levels were 4-fold greater among adults with CD consuming a GFD than controls not restricting gluten.[18] The source of mercury and other toxins is not known nor have the health implications of these findings been fully delineated. Although the discourse regarding arsenic in rice is relatively recent, the reality is not new—arsenic has long been a natural, as well as human-added, component of soil. Rice is particularly efficient in its uptake of inorganic arsenic. Individuals on a GFD followed by a registered dietitian may be better positioned to be selective with processed starches to improve intake diversity, increase the relative quantity and variety of unprocessed foods, and implement methods of cooking rice to limit exposure to inorganic arsenic.[19]

There also are noteworthy non-nutritional implications of a GFD. Worldwide, those purchasing gluten-free products will encounter far greater food costs than gluten containing competitors.[20,21] Social isolation and inconvenience have been reported by children with CD requiring a GFD,[22] and some with CD report a deterioration in their quality of life while on a GFD,[21,23,24] linked in many cases to the diet itself.

Routine initiation of a GFD may obscure a diagnosis of CD for adults and children. Those with relief of symptoms after gluten exclusion may be unwilling or unable to resume a gluten-containing diet to allow for diagnostic testing. In this regard, wider adoption of a GFD may have implications for CD detection rates at a population level.

Fiction: Gluten is toxic.

Fact: There are no data to support the theory of an intrinsically toxic property of gluten for otherwise-healthy and asymptomatic adults and children, and certain studies have specifically demonstrated a lack of toxic effect.[25,26] Gluten, comprising gliadins and glutenins, is one of the many protein components of wheat and for the majority of people, gluten proteins pass through the gastrointestinal tract without leading to disease. Gluten contributes to the elasticity of breads and vital gluten, an additive containing nearly all gluten protein and very little carbohydrate, is widely added to bread mixtures to enhance this property. Although several dozen T-cell stimulatory epitopes have been identified among gluten proteins, a distinct 33-mer α-gliadin peptide appears to be among the most immunogenic.[27] Further, gluten epitopes generally contain multiple glutamine and proline residues, making them resistant to enzymatic degradation in the gastrointestinal tract,[28] which may otherwise reduce their immunogenicity. In those with CD, during times of increased intestinal permeability, immunogenic gliadin fragments are deamidated by activated tissue transgluaminase and interact with major histocompatibility complex class II receptors. Aspects of the innate and adaptive immune system are then triggered as well as cytokine release and mucosal damage. This process does not occur in all individuals who carry CD risk genes (HLA DQ2 and/or DQ8), and the precise factors that lead to disease pathogenesis for those who do develop CD are not understood completely.

The pathogenesis of gluten-induced symptoms in those with NCGS is unclear, and there is also some debate regarding whether gluten is indeed the trigger for all individuals believed to have NCGS. Those with CD have shown greater degrees of intestinal permeability and greater markers of adaptive immunity than those with NCGS,[29] suggesting distinct mechanisms for symptoms in CD vs symptoms in individuals without CD.

Theories that the increasing prevalence of CD may be attributable to augmented quantities of gluten in wheat related to breeding are not supported by the literature.[30] Some have speculated that CD (and possibly NCGS as well) may be on the increase as the result of processing of foods[31] and increased per-capita gluten consumption such as through addition of vital gluten to foods.[30]

Fiction: CD is the only indication for a GFD.

Fact: There are multiple indications for dietary gluten exclusion.

CD: Diagnosis with CD is lifelong, and a well-defined indication for a strict GFD. Dermatitis herpetiformis, a cutaneous manifestation of CD, is uncommon in children, though likewise responds to a GFD.[32] CD is not rare in the US[33] or worldwide,[34] although detection rates of CD are poor in the US, where only 17% of those with CD are diagnosed.[33] No safe quantity of gluten intake has been established for patients with CD. Diverse complications of CD include osteopenia, nutritional deficiency, and malignancy such as lymphoma.[35-37] Individuals with CD carry identifiable HLA risk haplotypes, typically disease-specific autoantibodies, and mucosal lesions consistent with the condition.

Nonceliac gluten/wheat sensitivity: Gluten-containing foods may induce symptoms in certain individuals without CD.[38] NCGS is currently a poorly understood condition for which the clinical diagnostic criteria have only recently been clarified.[39,40] There is only nascent data describing the existence of NCGS in children.[41] Those with NCGS do not have CD or wheat allergy, yet experience gastrointestinal or extraintestinal symptoms induced specifically by gluten. The prevalence of NCGS ranges from about 0.5% to 6% according to recent reports.[4,40] Nonceliac wheat sensitivity[42] and people who avoid wheat and gluten[4,43] have been suggested as more fitting terms, given that NCGS is typically a self-diagnosis and it is not clear whether it is gluten to which individuals react. Recent evidence has supported the hypothesis that certain people with sensitivity to fermentable oligosaccharides, disaccharides, monosaccharides, and polyols may be misclassified as having NCGS.[44] Despite the nondescript nature of NCGS, there may be greater awareness of NCGS than CD.[45]

Empiric treatment for NCGS may interfere with a diagnosis of CD when other discernible causes of gluten sensitivity have not been excluded first. Although gliadin IgA antibody may be more prevalent in some with NCGS,[46] small bowel histology may be nonspecific and assays reliably distinguishing those with NCGS from the general population have not been developed to date, leaving an opportunity for self-diagnosis and overdiagnosis of NCGS. Only 6.6% of consecutive patients with presumed gluten sensitivity in an Italian study actually had NCGS—86% did not experience symptoms when gluten was reintroduced.[47] Other conditions such as irritable bowel syndrome, small bowel bacterial overgrowth, and fructose and lactose intolerance may be responsible for symptoms in those self-diagnosed with gluten sensitivity.[43]

Wheat allergy: A minority of those with gluten related symptoms are wheat allergic.[40] Symptoms in wheat allergic patients may be immediate (typically IgE mediated) or nonimmediate (typically T-cell mediated) and frequently are respiratory, cutaneous, or digestive in nature.[48] Diagnosis is achieved through a combination of clinical symptoms, possibly dietary challenge, in vitro assays for specific IgE antibodies, and prick testing. Wheat allergic individuals typically may safely consume other gluten-containing foods without issue following specific exclusion of wheat.

Fiction: A GFD is appropriate for first-degree relatives of an individual with CD or for infants at risk of developing CD.

Fact: Intentionally or out of convenience, many first-degree relatives may initiate a GFD after the diagnosis of a household member with CD. Pooled rates of CD among first-degree relatives in a recent meta-analysis were approximately 7.5%.[49] For children with greater-risk HLA haplotypes, such as those homozygous for HLA DQ2, 26% have evidence of CD autoimmunity by age 5 years.[50] Surveillance for CD is recommended for first-degree relatives of an identified individual with CD where carriage of a risk gene has not been excluded.[51,52] In cases in which gluten intake for such relatives is limited, a gluten challenge may be necessary in advance of CD screening. A GFD is not advisable for at-risk individuals under any circumstance without first testing for CD while the patient is consuming gluten in an unrestricted fashion.

The topic of gluten introduction in infants at risk for CD has been the subject of great scrutiny in recent years. Earlier literature suggested a diminished risk for CD among genetically susceptible infants introduced to gluten during 4-6 months of age.[53] Pinto-Sanchez et al[54] completed a meta-analysis of data subsequently amassed on the subject, exploring factors such as the timing, type, and quantity of gluten introduction, with variable results. The most current understanding based on long-term cohort studies in at-risk infants is that neither delaying gluten introduction from the recommended 6 months of age to 1 year,[55] nor introducing it at 4 months of age[56] alters long-term CD risk estimates, with the bulk of currently identified CD risk seeming to stem from the genetic haplotype of the individual rather than the timing of gluten introduction.[50,55,56]

Table. Summary of potential GFD outcomes

Advantages	Disadvantages	Risks
• Reversal of malabsorption, nutritional deficiencies, symptoms, and diminished comorbidities for those with CD and DH. • Relief of symptoms for those with NCGS and WA	• Expense • Inconvenience • Societal stigma associated with a GFD	• Nutrient deficits • Missed diagnosis of CD • Potential for toxicity • Quality of life impairment • Undesired weight gain • Constipation

DH, dermatitis herpetiformis; *WA*, wheat allergy.

Discussion

It is undeniable that many people perceive benefit from a GFD, often without a clear scientific explanation. Nevertheless, with the guidance of an experienced registered dietitian and provided that CD is excluded, for a minority of individuals the GFD may lead to better health and improved quality of life (Table).

There is no evidence that processed gluten-free foods are healthier than their gluten-containing counterparts, nor have there been proven health or nutritional benefits of a GFD, except as indicated previously in this commentary. Yet those who purchase gluten-free foods outside of a GFD and apart from treatment of disease comprise the bulk of gluten-free product consumers.[3]

Adults considering, or who have already implemented, a GFD because of physical symptoms should immediately involve a health care provider and request testing for CD. If a GFD is planned regardless of the results of CD testing, the guidance of a registered dietitian should be sought to safeguard against GFD-associated nutritional hazards. Despite ostensible similarities, there are important distinctions in management for those gluten-free by choice vs for treatment of CD, such as surveillance for autoimmune conditions, family members' health, and malignancy. An empiric GFD may come at considerable expense, and cost-benefit analyses are warranted to investigate routine CD screening for asymptomatic adults who opt to lead a completely gluten-free lifestyle.

There is arguably no role for a GFD for children outside of treatment of CD and wheat allergy. The likelihood of a diagnosis of NCGS in children is unclear, given the limited data available describing pediatric populations with NCGS.[41] Certainly there is no evidence to support a GFD for asymptomatic children without CD, or for delaying gluten introduction to infants to prevent CD. Given the substantial nutritional and quality of life risks, a GFD driven by factors apart from the treatment of specific disease or symptoms may carry more risk than benefit for children. The case of children with autism may pose an exception to this recommendation. Data supporting the use of this diet in children with autism spectrum disorders are scant[57] and have not been confirmed in double blinded studies.[58] Provided that children with autism are tested for CD and are monitored by a registered dietitian, however, there may be few drawbacks in those cases where no other treatment is available. Regardless of indication, appropriate CD testing for children is imperative if a GFD is planned in the absence of CD.

There are many unanswered questions regarding the GFD that are worthy of ongoing investigation. At this point, however, the GFD should be recommended judiciously and patients self-prescribing a GFD should be counseled as to the possible financial, social, and nutritional consequences of unnecessary implementation. Health care providers may not be able to end the GFD fad, but can certainly begin to play a larger role in educating patients, excluding CD, and preventing nutritional deficiencies in those choosing to stay gluten-free. ■

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