JGH Open Open Access An open access journal of gastroenterology and hepatology

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.13063

REVIEW ARTICLE

Can diet change the natural history of gastrointestinal diseases?

Eamonn M M Quigley

Lynda K and David M Underwood Center for Digestive Disorders, Houston Methodist Hospital and Weill Cornell Medical College, Houston, Texas, USA

Key words
celiac disease, constipation, diet, diverticular disease, eosinophilic esophagitis, food allergy, food intolerance, natural history, non-celiac wheat intolerance, post-infection irritable bowel syndrome.

Accepted for publication 27 March 2024.

Correspondence
Eamonn M M Quigley, Houston Methodist Gastroenterology Associates, 6550 Fannin St, SM 1201, Houston Methodist Hospital, Houston, TX 77030, USA. Email: equigley@houstonmethodist.org

Declaration of conflict of interest: Research support from Biomerica.

Abstract

Belatedly, gastroenterologists have begun to pay attention to the role of diet in the exacerbation of gastrointestinal symptoms in many digestive disorders—a recognition that has spurred both high-quality clinical trials and translational research into this area. It has become clear that multiple mechanisms acting either in isolation or together can induce gut symptoms and that appropriate interventions can lead to significant relief. What this review will explore is not the role of diet in the production of certain symptoms or symptom clusters, but rather whether a dietary intervention can beneficially alter the natural history of a gastrointestinal disease—a much more demanding expectation. Yet there are examples of where a diet, if sustained, can have a long-term impact on at least some of those affected by conditions such as eosinophilic esophagitis, celiac disease, food allergy, and constipation.

Introduction

Before we embark on a consideration of the impact of diet on any gastrointestinal (GI) disease or disorder, let us take a step back and consider the challenge that a dietary intervention faces—to alter the natural history of a disease. How, you may ask, is the natural history of a disease defined? This term refers to the progress of a disease in an individual over time, in the absence of intervention. The process begins with exposure to, or accumulation of, factors capable of causing disease and without medical intervention, the process ends with recovery, disability, or death.[1] Two very important issues relevant to many GI disorders emanate from this. First, recovery may be spontaneous and permanent, or, to add some confusion, may be temporary. The latter is illustrated by the tendency of so many GI ailments to wax and wane and feature periods of remission interspersed between episodes of symptomatic flares. Second, for many common GI conditions, mortality rates are very low, so "disability" becomes the issue. How does this term translate for a GI condition: return of normal GI function, restoration of quality of life to population norms? We will, therefore, be careful to avoid these nuances and focus on instances where a dietary change or intervention results in sustained recovery—clinical, endoscopic, and/or pathological. It is important to also define the scope of this exercise—it will be confined to dietary change and will not address the impact of supplements.

Food and GI symptoms

Not a day goes by where I am not told by a patient that "I have a food allergy doctor" and my task is to identify the allergen and provide permanent cure. Before launching into detailed studies to prove an allergy to a given component of the diet, it is imperative that we consider the many ways that food ingestion can provoke symptoms:[2–4]

1. Physiological: It is critical to remember that all physiological processes in the gut, including motility, secretion, and blood flow respond to food intake, or the anticipation thereof in order to optimize digestion and absorption.[3] No wonder then that the post-prandial exacerbation of symptoms is so prevalent across GI diseases from GERD to peptic ulcer disease, cholelithiasis to Crohn's disease, and irritable bowel syndrome (IBS) to inflammatory bowel disease (IBD), for example. In IBS, for instance, an exaggerated gastro-colonic reflex resulting in augmented colonic motor activity is a long-recognized hallmark of the condition.[5]
2. Classical IgE-mediated food allergy.
3. Other immune-mediated disorders: Celiac disease and eosinophilic gastroenteropathies.
4. Food intolerance: Intolerance to lactose, sucrose, fructose, sorbitol and other fermentable, oligosaccharides, disaccharides, monosaccharaides, and polyols (FODMAPs).
5. Microbiome–food interaction: This is a growing topic.[6] The role of bacteria in fermenting undigested carbohydrates is fundamental to the genesis of symptoms in lactose intolerance,

etc. Several other diet–microbiome interactions have been identified but are beyond the scope of this review.
6. Food-borne infections: Despite advances in sanitation in many parts of the world, enteric infections continue to "top the charts" of GI diseases around the world and are especially concentrated in developing countries and socio-economically deprived areas.[7] GI impacts of enteric infections are not confined to the immediate consequences of the infection but can involve the de novo development of much longer-lasting syndromes such as IBS and functional dyspepsia.[8]
7. Symptoms generated by other food components: Examples include food additives or chemicals, or the direct irritant effects of spicy foods.[4]

Where among all these mechanisms is there scope for an alteration in natural history? Availability of clean water, adequate sanitation, and adherence to standards for food production and preparation could go a long way toward reducing the prevalence of food-borne enteric infections, but such public health measures are beyond the scope of this review. We will concentrate instead on how a modification in one's diet can alter the natural history of a disease process.

The many manifestations of food allergy

Food allergy can be defined as an immune-mediated reaction to protein-containing food[9] and represents an obvious example of how a dietary intervention, in this case the removal of the allergen, can dramatically influence natural history. It has been suggested that the prevalence of the many manifestations of food allergy is underestimated worldwide and may, indeed, be on the increase.[10] One review provided quite high estimates of rates of "convincing food allergy" at approximately 8% for children and 11% for adults in the United States.[11] Noteworthy were the high rates across adulthood—contrary to the traditional view of food allergy as a childhood disorder.

Classical, IgE-mediated food allergy. The classical and best-known form of food allergy refers to IgE-mediated responses and features the rapid onset of urticaria, angioedema, bronchospasm, and may progress to full-blown anaphylaxis. GI symptoms such as abdominal pain and diarrhea may be a feature. The incidence and prevalence of food allergy is very dependent on the criteria used to define it; ranging, in one meta-analysis, from as high as 10% for self-reported allergy to as low as 1% when IgE sensitization and symptoms were required.[12] When the ultimate test is invoked, namely, a food challenge, rates fall to just 0.3% for cows' milk and 0.02% for fish.[12] Ninety percent of all instances of food allergy are attributed to just eight foods—milk, eggs, wheat, tree nuts, peanuts, soy, fish, and shellfish. Some allergies such as that to cows' milk protein, as well as allergies to eggs, wheat, and soy are more common in children and may resolve when they grow older.

The double-blind oral food challenge test remains the gold standard for the diagnosis of food allergy, but is logistically challenging and includes a risk of inducing a severe allergic reaction. Skin prick tests are more commonly performed and have a high negative predictive value but suffer from a low positive predictive value related to low specificity. Other tests that may be useful are assays of allergen-specific IgE and patch testing, but one needs to be aware of the sensitivity and specificity of each test.[4]

Alpha-Gal syndrome. This condition is seen in areas where the Lone Star tick is endemic. Alpha-gal (galactose-α-1,3-galactose) contained in tick saliva is injected sub dermally by a tick bite and leads to the formation of antibodies. Subsequently, when various meats and animal products are ingested, an IgG- and IgE-mediated allergic response develops due to cross-reactivity with the alpha galactose epitope present on many mammalian tissues. What differentiates this food allergy from the classical variety described above is its delayed onset—typically 3–8 h after meat ingestion. Symptoms can range from urticaria to full-blown anaphylaxis.[13,14]

Food-dependent, exercise-induced anaphylaxis. This is another somewhat unique manifestation of an IgE-mediated allergy.[15,16] The implicated food is ingested before exercise and the allergic manifestations (urticaria, wheezing, angioedema, GI symptoms such as diarrhea and hypotension) develop during or within 30 min after exercise. Though many foods have been reported to be involved in this syndrome, wheat has been the most invoked cofactor. Roles for non-steroidal anti-inflammatory drugs (NSAIDs) and alcohol have been also proposed. While the pathophysiology of this unique syndrome has not been clearly defined, one hypothesis proposes an IgE-mediated response to ω5-gliadins in gluten.

Food protein-induced allergic proctocolitis. Food protein-induced allergic proctocolitis occurs in infants and presents with the passage of blood mixed with mucus in the stool. Typically resolves within the first year of life and is accompanied by an eosinophilic infiltration in the rectal mucosa.[17]

Food protein-induced enterocolitis. Food protein-induced enterocolitis occurs in infants who develop lethargy, vomiting, and diarrhea within 1–4 h of exposure to trigger foods such as milk, soy, oats, rice, and fish.[18] In the most severe cases, hypothermia, hypotension, and acidosis may ensue. This allergic syndrome is not IgE-mediated but rather may involve antigen-specific T-cells.

Pollen-food allergy/oral food allergy syndrome. This syndrome develops when an individual who is allergic to pollen eats raw fruits or vegetables (allergens are denatured by heat) that contain cross-reacting proteins.[19] The reaction may be local and confined to the oro-pharynx or systemic. Prevalence varies by age (more common in adults) and environmental pollen counts but among those with pollen-related allergies may be as high as 25%.[19–21]

Other immunologically mediated responses to food

Eosinophilic esophagitis. Eosinophilic esophagitis (EoE) is a relatively recently described entity[22] that usually presents in isolation but on occasion represents a component of a more generalized eosinophilic disorder, eosinophilic

gastroenteropathy.[23] EoE is defined by symptoms of esophageal dysfunction in a patient with esophageal biopsies demonstrating at least 15 eosinophils per high-power field in the absence of other conditions associated with esophageal eosinophilia and, most notably, gastroesophageal reflux disease.[22] There seems to be a real increase in incidence in EoE and, though it can occur at any age, seems to be most common among White males aged between 20 and 40, and is especially common among those with a personal and/or family history of other allergic manifestations.[24] While the pathophysiology of EoE is multifactorial, a response to allergens, including food allergens, clearly plays a role; thus, the interest in food elimination diets in the management of this disorder. Various approaches to dietary management have been taken. In a recent meta-analysis, the six-food elimination diet (eliminating milk, wheat, soy, eggs, tree nuts/peanuts and fish/shellfish) proved most effective with an overall efficacy of 61%; in contrast to other food allergies, an elimination strategy based on the results of allergy testing was less successful and has led to a lack of enthusiasm for food allergy testing in EoE.[25] However, a recent study demonstrated a modest efficacy for food-specific IgG4 antibodies in guiding success in response to an elimination diet in EoE.[26] When undertaken, the most usual elimination diet protocol involves beginning with the six-food protocol and assessing histological response. If the individual responds, individual foods are progressively introduced until a regimen that retains remission is achieved, a process that may involve multiple endoscopic studies and pathological examinations. The logistical hurdles involved in this approach together with the availability of other therapies have limited its application in clinical practice.[27] It can work, however; in one study of 213 adults with EoE who completed a six-food elimination diet and were followed for up to 6 years, 77% experienced symptomatic and 54% histological improvement, and in 69% of those who completed the reintroduction protocol, a single food trigger was identified, suggesting that, in some with EoE, an elimination diet may change the natural history of the disorder.[28] In an interesting twist to the EoE story that is reminiscent of the pollen-food allergy syndrome, Visaggi and colleagues noted an interaction between allergy to pollen and response to the six-food elimination diet in EoE. They noted that the histologic response to the diet was significantly greater during compared with outside pollen season among those who had a skin prick test positive for pollen.[29]

Celiac disease. Celiac disease is another disorder that is increasing in prevalence[30] and is based on a complex immunological response to a food antigen that, like EoE, develops over time. Celiac disease reflects the confluence of genetic, environmental, and dietary factors as evidenced by its development in genetically susceptible individuals who, in response to unknown environmental factors, mount an immune response that is subsequently triggered by the ingestion of gluten against the mucosa of the small intestine.[31] Celiac disease needs to be carefully distinguished: first, from wheat allergy which behaves in a manner similar to that of other IgE-mediated food allergies and also plays a prominent role in the syndrome of food-dependent, exercise-induced anaphylaxis (*vide supra*), and, second, from the poorly understood entity non-celiac gluten (or wheat) sensitivity (NCGS) (*vide infra*).[32] In genetically susceptible and wheat-ingesting populations, the prevalence of celiac disease is in the region of 1% and significant shifts in age at diagnosis (older) and clinical presentation (less classical malabsorption and more atypical features) have been noted in recent decades.[33–35] Indeed, it is likely that many cases remain undiagnosed, and while such individuals may not suffer any related decrease in life expectancy,[36] they may be at greater risk for the development of chronic fatigue, osteoporosis, dermatitis herpetiformis, as well as autoimmune thyroid disease.[36,37] On long-term follow-up, 20% of those with positive serology were ultimately diagnosed with celiac disease.[38] Taken together, these findings support screening for celiac disease in at-risk populations.[39]

There is no doubt that a gluten-free diet, if strictly adhered to, will alter the natural history of celiac disease. Over time, symptoms should resolve and small intestinal morphology normalizes. While this is to be expected in children, the outcome among those diagnosed in adulthood is less clear. In one series which followed patients for up to 5 years on a gluten-free diet, 81% experienced a clinical response, but only 32% had experienced mucosal recovery at 2 years, with that percentage increasing to 66% at 5 years. Mucosal nonrecovery was associated, not surprisingly, with noncompliance with the diet, severe disease, and the presence of total villous atrophy at presentation.[40] Noncompliance may be inadvertent—in one study, most patients on a gluten-free diet were being exposed to measurable amounts of gluten.[41] All of these findings underline the importance of the role of the dietitian in the initial management and follow-up of patients with celiac disease.

One small subgroup of celiac patients whose natural history may not be impacted by a gluten-free diet are those with refractory or complicated celiac disease, terms which encompass the two subtypes of refractory celiac disease, ulcerative jejunoileitis, enteropathy-associated T-cell lymphoma, abdominal B-cell lymphoma, small bowel adenocarcinoma, and collagenous sprue. The overall mortality for this group is around 40% and is significantly influenced by immunophenotype, being much worse for those whose T-cells exhibit an abnormal phenotype.[42,43]

Food intolerance

In most instances where an individual reports the development of symptoms in relation to a particular food, the issue is intolerance, not allergy. Intolerance may reflect a limited capacity to metabolize a nutrient due to an absolute or relative deficiency in the relevant enzyme(s), such as lactase, sucrase-isomaltase, or aldolase b, resulting in intolerance to lactose, sucrose, and fructose, respectively. Given the sensitivity of these brush border enzymes to epithelial injury deficiency may also be temporary such as in the aftermath of gastroenteritis in children. The accumulation of data attesting to the impact of a diet low in fermentable oligosaccharides, disaccharides, monosaccharaides, and polyols (FODMAPs) in IBS illustrates how an individual with visceral hypersensitivity, such as IBS, may be intolerant of what would be relatively normal loads of these nutrients.[44] While the long-term impact of the low-FODMAP diet continues to be evaluated, there is no doubt that the avoidance of food to which one is intolerant can be life-altering.

Non-celiac gluten sensitivity/non-celiac wheat sensitivity. The recognition of this controversial entity arose from patient reports of an improvement in their symptoms and of IBS-type symptoms, in particular, when they self-imposed a gluten-free diet. This observation was supported by clinical trials, such as that reported over 15 years ago by Wahnschaffe and colleagues who reported that 60% of their patients with IBS with diarrhea responded to a 6-month trial of a gluten-free diet, and that this response was predicted by possessing the HLA-DQ2 haplotype and being positive for IgG antibodies to gliadin and tissue transglutaminase.[45] Studies since then have provided conflicting evidence for a benefit for a gluten-free diet in IBS to the extent that one recent meta-analysis concluded that there was "insufficient evidence to recommend a gluten-free diet to reduce IBS symptoms."[46] This issue has been complicated by the realization that other components of wheat, such as fructans (a FODMAP), wheat-germ agglutinin, and amylase trypsin inhibitors, could be responsible for dietary intolerance to wheat, thus leading to the term which may preferable for this entity—non-celiac wheat sensitivity (NCWS).[47] Indeed, when it comes to the role of wheat sensitivity in IBS, some evidence suggests that it is the fructan component of wheat and not its gluten content that it is the culprit[48] while others provide data to support an immunological response to gliadin.[49]

The precise nature and pathophysiology of sensitivities to wheat, gluten, and other compounds, which do not fulfill criteria for classical criteria for food allergy, remain unclear and contentious and the controversies rumble on.[49] New technologies may help clarify the issue. For example, detailed morphological studies have identified subtle mucosal changes in NCWS,[50] confocal laser endomicroscopy permits in vivo testing of mucosal responses to putative allergens,[51] and the role of IgG antibodies to various food components in predicting responses to elimination diets continues to be explored.[52–55]

Food-borne infections and toxins

Despite progress in sanitation and food safety, enteric infections still top the list of GI disorders worldwide, with the prevalence of these infections being disproportionately evident in the developing world.[7] Some of these will be food-borne; providing an obvious opportunity to change the natural history of a disorder for an entire population. The eradication of enteric infections could also eliminate one subset of disorders of gut-brain interaction (DGBI)—post-infection IBS and functional dyspepsia.[8,56,57] Indeed, a recent study demonstrated how an enteric infection could lead to loss of tolerance and sensitization to common foods.[58]

The complexity of how food may lead to GI symptoms is illustrated by the multiple mechanisms whereby fish, a common cause of classical IgE-mediated food allergy, may produce symptoms.[59] These include anisakiasis, which occurs when humans ingest fish infected with nematodes such as *Anisakis simplex* of *Pseudoterranova decipiens*, leading to a severe eosinophilic granulomatous response; scombroid poisoning due to the ingestion of poorly preserved fish (most frequently red meat fish such as mackerel, bonito, albacore, and tuna), in which bacterial proliferation leads to the conversion of histidine into histamine; toxic algae poisoning when fish or shell fish contaminated by toxic algae are consumed; ciguatera poisoning caused by ciguatoxin found in tropical fish; seafood intolerance caused by biogenic amines, which can develop in canned or pickled fish and food-borne infections carried by fish or shell fish, which is especially likely to occur on ingestion of fish farmed in, or harvested from, contaminated waters.[59]

Fiber, bran, and GI disease

Over 50 years ago, the Irish surgeon and missionary, Denis Burkitt, alerted the world to the relationships between diet and "Western diseases" based on his observations on disease prevalence in rural Africans.[60–62] He proposed that a low intake of dietary fiber from fruits, vegetables, and grains contributed to the Western epidemics of obesity, diabetes, diverticular disease, and colo-rectal cancer.[60,62] This fiber hypothesis has, for the most part, stood the test of time,[63–65] though actually demonstrating a protective effect for a high-fiber diet in Western populations has proven more difficult.[66–68] While increasing one's intake of dietary fiber or adding a fiber supplement has assumed a pivotal role in the management of constipation,[69] the evidence base to support its efficacy in diverticular disease is a little shaky. The seminal studies, which formed the basis for recommendations for fiber intake in the management of diverticular disease, were small in size and of less-than-optimal design,[69,70] and one more recent cross-sectional study failed to detect a relationship between fiber intake and constipation and diverticula in over 2000 individuals undergoing a screening colonoscopy.[71]

Conclusions

It is self-evident that diet, through many mechanisms, plays a critical role in gut function in health and disease and several GI disease processes where diet plays a pivotal role in its pathogenesis have been described, such as the many manifestations of food allergy, EoE, and celiac disease. In these disorders, dietary management can impact on natural history. In other disorders, diet is certainly a cofactor—its relative importance continues to be defined, but will undoubtedly vary between disorders and individual sufferers. The challenges presented by dietary intervention studies and, especially, those that attempt to define impact on natural history are formidable and, undoubtedly, have limited our ability to come to conclusions on diet in many common GI diseases. These studies require large study populations, long-term follow-up, and the ability to control for confounding variables—no easy task.

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