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The Role of Food in the Functional Gastrointestinal Disorders: Introduction to a Manuscript Series

William D. Chey, MD, AGAF, FACG, FACP[1]

Functional gastrointestinal disorders (FGIDs) are characterized by the presence of chronic or recurrent symptoms that are felt to originate from the gastrointestinal (GI) tract, which cannot be attributed to an identifiable structural or biochemical cause. Food is associated with symptom onset or exacerbation in a significant proportion of FGID patients. Despite this, the role of food in the pathogenesis of the FGIDs has remained poorly understood. For this reason, diet has largely played an adjunctive rather than a primary role in the management of FGID patients. In recent years, there has been a rapid expansion in our understanding of the role of food in GI function and sensation and how food relates to GI symptoms in FGID patients. In a series of evidence-based manuscripts produced by the Rome Foundation Working Group on the role of food in FGIDs, comprehensive reviews of the physiological changes associated with nutrient intake, and the respective roles of carbohydrates, fiber, protein, and fats are provided. The series concludes with a manuscript that provides guidance on proper clinical trial design when considering the role of food in FGIDs.

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INTRODUCTION

The Merriam-Webster dictionary defines food as "material consisting essentially of protein, carbohydrate, and fat used in the body of an organism to sustain growth, repair, and vital processes and to furnish energy (1)." Along with air and water, food is essential to the normal development and health of all mammals. Though essential for life, it has long been recognized that under the right circumstances, food can cause disease. Perhaps the most obvious example is "food poisoning," where the ingestion of tainted food leads to the development of acute gastroenteritis (2,3). However, food is increasingly recognized as a critical factor not only in gastrointestinal (GI) diseases but also in a wide variety of non-GI diseases (i.e., cardiovascular disease, systemic arterial hypertension, obesity, and diabetes mellitus).

Functional gastrointestinal disorders (FGIDs) are characterized by the presence of chronic or recurrent symptoms that are felt to originate from the GI tract. By definition, FGID patients should have no identifiable organic, systemic, or metabolic disease that provides an explanation for their symptoms. The biopsychosocial model suggests that a complex web of predisposing genetic factors, influenced by early (i.e., maternal deprivation or abuse) and later (i.e., acute gastroenteritis and abuse) life events as well as psychosocial factors lead to abnormalities in motility, visceral sensation, and brain–gut interactions, manifesting clinically as GI symptoms (4). More recently, groups have reported data to support a role for alterations in the gut microbiome and immune activation in the pathogenesis and treatment of FGIDs such as irritable bowel syndrome (IBS) (5–9).

For many years, the role of food in the development of FGIDs has been poorly defined. Related to the paucity of empirical data, most primary care physicians and gastroenterologists have received little formal training regarding the role of nutrition in the management of FGID patients. In addition, most of the traditional dietary recommendations for FGIDs have been rudimentary and largely based upon expert opinion and common sense rather than credible scientific evidence. More recently, the potential role of food in the FGIDs has been revisited (10–12). This renewed interest in food represents a logical extension of our expanding understanding of the pathophysiology of IBS. It is only within the context of understanding how abnormalities in motility, visceral sensation, psychosocial functioning, gut microbiome, and gut immune system lead to GI symptoms that the potential importance of food can be fully appreciated. One needs to look no further than lactase deficiency for an example of this concept. Investigators and providers have argued about the potential relevance of lactase deficiency to IBS for decades. Investigations focusing on whether the prevalence of lactase deficiency is higher in patients with FGIDs, such as IBS, compared with controls have yielded mixed results (13). Another source of confusion stems from the observation that many persons with documented lactase deficiency do not experience GI symptoms after consuming lactose containing foods (14). Several recent observations have helped to lend some per-

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spective to this apparent confusion. For example, one study found that individuals with *lactose intolerance* (persons with lactase deficiency who develop symptoms after consuming lactose) develop symptoms and hypersensitivity to rectal balloon distention following ingestion of the non-absorbed carbohydrate, lactulose. On the other hand, the same was not the case for controls and persons with lactase deficiency but no lactose intolerance (15). These findings demonstrate that it is not lactase deficiency *per se* that is the problem. Rather, lactase deficiency is more likely to become clinically relevant in persons with underlying abnormalities of motility and visceral sensation as is the case in patients with IBS. This concept was validated by Ong *et al.* (16) who reported that the ingestion of FODMAPs (Fermentable Oligo, Di, Monosaccharides, And Polyols) caused flatulence but no other significant GI symptoms in healthy individuals. In contrast, a FODMAP-rich diet was associated with the generation of characteristic symptoms in IBS patients. It is also quite likely that many FGID patients with food-related symptoms develop a conditioned response, which can exaggerate their GI symptoms. It is certainly not hard to imagine how some individuals with food-related symptoms might develop anticipatory anxiety in association with eating a meal. There is evidence to suggest that stress and anxiety can amplify gut motor and sensory responses (17–19). Further, it is now apparent that food plays a critical role in determination of the host microbiome (20). In fact, some have argued that food has an even greater role in shaping the gut microbiome than genetics (21). There is mounting evidence that alterations in gut immune function can be identified in a subset of IBS sufferers. Increased numbers of mast cells, lymphocytes, and/or eosinophils have been identified in some IBS patients (5,6,22). The stimuli responsible for this immune activation remain to be fully defined, but it is reasonable to hypothesize that food is a candidate. This suggestion is supported by recent work published by Carroccio *et al.* (23), which found increased numbers of eosinophils in duodenal and colonic mucosal biopsies from patients with multiple food sensitivities. The notion of "functional" or even "therapeutic" foods is in its infancy but will rely upon the direct effects of food, the effects of the by-products of digestion/fermentation, and the prebiotic effects of food. Conversely, it is equally fascinating to speculate about the potentially negative effects of food in regards to GI and indeed, non-GI symptoms (24). In aggregate, it is growing increasingly clear that food serves as an important trigger for symptoms in FGID patients who have underlying alterations in physiology, which render them hypersensitive to a variety of external cues and stimuli (**Figure 1**).

Unfortunately, the rapidly growing body of literature on the role of diet in the FGIDs is widely distributed among a number of different disciplines and thus, is not universally recognized or even accessible to scientists and providers with an interest in FGIDs. Because of the rapid evolution of the literature and the general lack of knowledge and training on the part of most medical providers in regards to the role of nutrition in FGIDs, the Rome Foundation convened a working group to prepare a series of evidence-based, narrative reviews on this important topic. The Working Group was comprised of eight international members who were selected based upon publication record and recognition

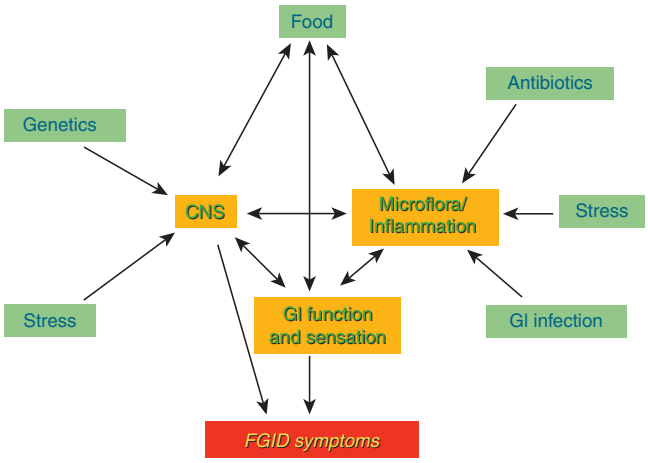

Figure 1. Evolving conceptual model of FGIDs. CNS, central nervous system; FGID, functional gastrointestinal disorder; GI, gastrointestinal.

for their expertise in the subject matter. Primary members of the working group included William D. Chey, MD (Co-chair, University of Michigan Health System, Ann Arbor, MI, USA), Jan Tack, MD (Co-chair, University of Leuven, Leuven, Belgium), Fernando Azpiroz, MD (Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain), Sheila Crowe, MD (University of California of San Diego, San Diego, CA, USA), Shanti Eswaran, MD (University of Michigan Health System, Ann Arbor, MI, USA), Peter Gibson, MD (The Alfred Hospital and Monash University, Melbourne, Victoria, Australia), Miranda Lomer, PhD (Nutritional Sciences Division, King's College London, London, UK), and Susan Shepherd, PhD (La Trobe University, Bundoora, Victoria, Australia). Primary members of the working team collaborated with other content experts to produce the following series of narrative reviews:

- The physiology of food intake, processing, and nutrient sensing:
  Farré and Tack (25) discuss the complex "end to end" response of the gastrointestinal tract to ingestion of food, which encompasses a wide range of functions including optimization of motility, digestion, absorption of nutrients, and disposition of indigestible remnants of food. This manuscript also reviews the growing literature addressing nutrient-sensing receptors, extrinsic and intrinsic neural pathways and entero-endocrine pathways, and their putative role in GI function and sensation.
- The role of carbohydrates in the pathogenesis and treatment of FGID patients:
  Shepherd, Lomer, and Gibson (26) provide a comprehensive review of how commonly consumed carbohydrates, such as grains, vegetables, fruits, and legumes, can contribute to symptoms in patients with FGIDs. They review how differences in digestibility and absorption of commonly ingested short-chain carbohydrates can lead to

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intrinsic osmotic effects as well as the production of gas and short-chain fatty acids through bacterial fermentation. The resulting increased stool biomass, decreased stool consistency, and luminal distension can cause an exaggerated symptom experience in FGID patients who frequently have underlying abnormalities in GI motility and visceral sensation. The authors critically discuss the generally poor quality evidence supporting the use of lactose and fructose-reduced diets in FGID patients. They develop the argument that all dietary, poorly absorbed, short-chain carbohydrates have similar and additive effects in the GI tract. The growing body of physiological and clinical evidence supporting the restriction of dietary FODMAPs as a primary management strategy for patients with IBS is reviewed. They conclude with a thoughtful discussion of the gaps in knowledge as well as potential concerns surrounding dietary FODMAP restriction.

- The role of fiber in the pathogenesis and treatment of FGID patients:
  Dietary fiber supplementation remains a treatment mainstay for patients with FGIDs. Eswaran, Muir, and Chey (27) provide clarification on the different types of fiber and how fiber is processed by the GI tract. They explain that fiber can broadly be divided into short-chain and long-chain carbohydrates or categorized based upon their solubility and fermentation characteristics. A review of how fiber impacts GI function and sensation through effects on stool mass, fermentation with the production of gas and short-chain fatty acids, the microbiota, and possibly gut immune function and permeability follows. The paper concludes with an evidence-based review of the role of fiber as a treatment for chronic constipation and IBS.
- The role of proteins in the pathogenesis and treatment of FGID patients:
  Boettcher and Crowe (28) discuss the distinctions between true food allergies and food sensitivities and the role that proteins plays in each set of conditions. They point out that with an intact mucosal barrier, only small quantities of antigen or pathogen cross beyond the epithelium and a mechanism exists for downregulation of the immune response to the agents that do cross, leading to what is termed as "oral tolerance." An "allergy" occurs in the face of altered immunologic reactivity to various antigens that may be IgE mediated or non-IgE mediated. Foods or food components that elicit an adverse reaction but have no established immunologic mechanism are termed as food sensitivities or food intolerance. Food toxicity, as well as pharmacological, metabolic, physiological, and psychological food sensitivities is discussed. Examples of true allergic disorders and food sensitivities are provided. This is followed by a more detailed discussion of celiac disease, non-celiac gluten sensitivity, and cow's milk protein intolerance. The authors provide advice on distinguishing between and utilizing exclusion diets to treat these groups of patients.
- The role of lipids in the pathogenesis and treatment of FGID patients:
  Feinle-Bisset and Azpiroz (29) start by defining the process by which lipids are digested and absorbed in the GI tract. The authors provide a detailed discussion of how fat modulates the responses of the gut to various stimuli and how these modulatory mechanisms can be abnormal in patients with gastroesophageal reflux disease, functional dyspepsia, gastroparesis, and IBS. They offer persuasive evidence to suggest that a subset of FGID patients demonstrate a hypersensitivity to lipid perhaps through alterations in gut hormones, including cholecystokinin from the proximal, and glucagon-like peptide-1 and peptide YY from the distal, small intestine, as well as suppression of ghrelin secretion from the stomach. They also review the sparse and often conflicting clinical studies evaluating dietary patterns, eating behaviors, and response to dietary modification in regards to lipids in FGID patients.
- Recommendations for the design of clinical trials that assess the benefits of dietary treatments for FGID patients:
  Yao, Gibson, and Shepherd (30) conclude the series with an illuminating manuscript that provides recommendations for the conduct of studies evaluating food interventions in patients with FGIDs. They highlight the innate differences and unique challenges that confront trials comparing the efficacy of dietary vs. pharmaceutical interventions. Important issues such as inherent biases arising from personal and/or societal beliefs and the fact that food is composed of numerous constituent components rather than a single agent are important issues that can confound the design of food intervention trials. As adherence to the dietary intervention is the biggest determinant of its effectiveness, study design should maximize adherence. A controlled-feeding trial is considered as the gold standard as it maximizes participant adherence and minimizes the potential impact of confounding dietary habits. Optimal trial design should incorporate specific strategies to limit the discretionary food intake and to record the details of the control and experimental diets so that between trial data can more easily be compared. Challenges in designing a placebo or sham diet intervention, blinding of patients and investigators, appropriate measurement of adherence, and assessment of safety are discussed. The authors provide detailed advice in regards to trials that utilize food elimination and rechallenge to identify patients with food sensitivities. The pros and cons of less rigorous but more practical study designs are also reviewed.

This comprehensive series of evidence-based reviews will provide the busy clinician with a "one stop shop" to better understand the emerging role of specific dietary constituents in the pathogenesis and treatment of FGID patients. These documents will also allow the interested clinical investigator to quickly review the available literature and provide advice on clinical trial design, which will

allow the transformation of innovative ideas to scientific evidence. We hope that this series of articles increases the awareness of the importance of food in the pathogenesis and treatment of FGIDs and plants the seeds for the next crop of innovations in clinical research and patient care.

CONFLICT OF INTEREST

Guarantor of the article: William D. Chey, MD, AGAF, FACG, FACP.
Specific author contributions: Initiated the manuscript concept and design, drafted the manuscript, and critically revised and approved the final manuscript: William D. Chey.
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Potential competing interests: William D. Chey, MD is a consultant for Nestlé/Prometheus.

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