Rome Foundation Working Committee Statement:

The Role of Food in Functional Gastrointestinal Disorders

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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 in not only gastrointestinal (GI) diseases but also 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, 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 gut immune activation and alterations in the gut microbiome in the pathogenesis and treatment of FGIDs such as 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. In recent years, the potential

role of food in the FGIDs has been revisited. A rapidly growing body of literature provides compelling support for the critical role of diet in the pathogenesis and treatment of FGIDs (10-12). Unfortunately, this information is widely distributed amongst 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 physiology of food intake, processing and nutrient sensing:

  Farre and Tack (13) discuss the complex "end to end" response of the gastrointestinal tract (GIT) 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 & intrinsic neural pathways and entero-endocrine pathways and their putative role in gastrointestinal function and sensation.

- The role of carbohydrates in the pathogenesis and treatment of FGID patients:

  Shepherd, Lomer and Gibson (14) 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 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 (Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols) as a primary management strategy for patients with irritable bowel syndrome (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 (15) 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 & 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 (16) 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 down-regulation of the immune response to the agents

that do cross, leading to what is termed '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 food sensitivities or food intolerance. Food toxicity, as well as pharmacological, metabolic, physiological and psychological food sensitivities are 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 (17) 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 which assess the benefits of dietary treatments for FGID patients.

Yao, Gibson and Shepherd (18) conclude the series with an illuminating manuscript which provides recommendations for the conduct of studies evaluating food interventions in patients with FGIDs. They highlight the innate differences and unique challenges which confront trials comparing the efficacy of dietary versus 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 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 discretionary food intake and record 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 which utilize food elimination and re-challenge 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

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.

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16. Boettcher and Crowe…
17. Feinle-Bisset and Azpiroz…
18. Yao, Gibson and Shepherd…

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