NUTRITIONAL APPROACHES FOR FUNCTIONAL BOWEL DISORDERS IN AN INTEGRATIVE MEDICINE CLINIC

BY

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ABSTRACT

Introduction Functional bowel disorders (FBDs) are gastrointestinal (GI) conditions based on patient-reported symptoms. Irritable bowel syndrome (IBS) is the most common FBD and despite extensive research on IBS, pathophysiology, etiology, and treatments for FBDs are still being researched. Treatment of FBDs involves a range of therapies including pharmaceutical treatments, psychological treatment, and lifestyle interventions like physical activity and dietary interventions. The evidence for efficacy of lifestyle interventions is still sparse. Integrative Medicine (IM) is a medical specialty that emphasizes lifestyle interventions, including dietary therapies. Studying lifestyle interventions in an IM clinic is useful because IM therapies are often sought out in addition to conventional medical treatment, thus patients may be more motivated to follow recommendations given by providers. The aims of this study include describing the interventions for FBDs in an IM clinic at an academic medical center (University of Kansas (KU)), and determining if the FBD interventions were effective. Finally, because little is known about the nutritional status (micronutrient) of patients with FBDs, we describe the vitamin and mineral status (vitamins B6, B12, D and zinc, magnesium and copper) of FBD patients. **Methods** This was a retrospective chart review in a population of 74 IM patients at KU IM. Charts were reviewed to collect data about FBD interventions, demographics, symptoms measurement (via medical symptoms questionnaire (MSQ), and micronutrient status. **Results** IM providers used 9 common interventions: elimination diets, vitamin/mineral supplementation, GI-related supplementation (probiotics, etc.), magnesium supplementation, non-dietary lifestyle intervention, GI-related prescriptions, water, referral to other healthcare providers, and fermented foods. The 3 most common interventions for patients with FBDs were (in descending order): elimination diets, vitamin/mineral supplementation and GI-related supplementation. FBD interventions by IM practitioners were effective (75.4% of patients had symptom improvement).

For all patients, digestive tract symptoms improved by an average of 3.0 points ($p<0.0000001$) on a scale from 0-28. Symptoms of IBS patients also improved significantly: IBS-C ($p=0.005$), IBS-D ($p=0.0004$), and IBS-M ($p=0.02$). Micronutrient status of FBD patients was generally adequate except for vitamin D deficiency among 23% (n=17) of FBD patients. Most patients (50.7%, n=36) had elevated levels for vitamin B6 and several (14.9%, n=11) had elevated vitamin B12 levels; both vitamins being elevated were likely related to patients taking nutritional supplements before their IM consultation. **Conclusion** IM interventions for FBD primarily center on diet and nutrition-based interventions. These interventions are effective for lowering GI-related symptoms; GI specialists should consider referring IBS patients to RDNs who are skilled at elimination and exclusion diets and may be knowledgeable about dietary supplement use and monitoring. Micronutrient status of FBD patients in this IM clinic was adequate except for vitamin D deficiency. Nutritional adequacy may be related to baseline supplement intake prior to IM consultation among 85% of the patients.

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LIST OF ABBREVIATIONS

Abbreviation	Full Name
FBD	functional bowel disease
IBS	irritable bowel syndrome
FB	functional bloating
FC	functional constipation
FD	functional diarrhea
IM	integrative medicine
MSQ	medical symptoms questionnaire
IBS-D	diarrhea-dominant IBS
IBS-C	constipation-dominant IBS
IBS-M	mixed type IBS (alternating diarrhea and constipation)
PI-IBS	post-infectious IBS
PEG	polyethylene glycol
GERD	gastroesophageal reflux disease
TNFSF15	tumor necrosis factor superfamily member 15
NCGS	non-celiac gluten sensitivity
NCWS	non-celiac wheat sensitivity
NCWPS	non-celiac wheat protein sensitivity
CD	celiac disease
FODMAPs	fermentable oligosaccharides, disaccharides, monosaccharides and polyols
HRV	heart rate variability
HRVB	heart rate variability biofeedback
GI	gastrointestinal
HAPC	High-amplitude propagated contractions

ANS	Autonomic Nervous System
SIBO	Small Intestinal Bacterial Overgrowth
CRH	corticotropin-releasing hormone
IL	interleukin
TLR	toll-like receptor
CDH1	cadherin-1
SLC6A4	solute carrier family 5 (neurotransmitter transporter), member 4 (aka 5HTT, 5-HTT, 5-HTTLPR, hSERT, HTT, OCD1, SERT, SERT1)
NT	Neurotransmitter
5-HT	5-hydroxytryptamine
GNbeta3	A gene associated with functional dyspepsia (aka GNβ3)
NPSR1	Neuropeptide S Receptor 1
FAAH C385A	fatty acid amide hydrolase C385A
KLB	klotho beta
TGR5	G protein-coupled bile acid receptor 1
ZO (Camilleri 2012)	Zonula occludens
EAACI	European Academy of Allergy and Clinical Immunology
IgG	immunoglobulin G
IgA	immunoglobulin A
IgE	immunoglobulin E
WA	wheat allergy
SIBO	small intestinal bacterial overgrowth
PPIs	proton pump inhibitors
CFU	colony forming units

CHAPTER 1

INTRODUCTION

I. Significance of Nutrition for Functional Bowel Disorders in Integrative Medicine

Functional bowel disorders (FBDs) include irritable bowel syndrome (IBS), functional bloating (FB), functional constipation (FC), functional diarrhea (FD), and FBD not otherwise specified (FBD-U) [1]. Conventionally, FBDs are diagnosed based on patient-reported gastrointestinal (GI) symptoms despite a lack of physically identifiable etiology, but the idea that FBDs lack physical abnormalities may be an outdated concept [2]. IBS – the most common FBD – is characterized by either constipation-dominance (IBS-C) or diarrhea-dominance (IBS-D) or mixed symptomatology (IBS-M), and patients' symptoms are related to defecation [3].

About 11% of adults, worldwide are diagnosed with IBS. In North America, the most likely prevalence range is between 10-15% [4]. The syndrome is more common in women [3] and those of middle age. IBS has a detrimental effect on quality of life in those who report symptoms [5].

In addition to FBDs decreasing patients' quality of life, they also pose a burden on primary care physicians and gastroenterologists who spend more time caring for these patients relative to sicker patients [6]. In addition to the time burden, FBDs also pose a financial burden on patients [7]. Although the direct and indirect costs per patient of FBDs vary [8], the overall annual cost of FBDs in the US is likely more than $26 billion US dollars [9]. Interestingly, IBS experts more accurately diagnose IBS than non-expert practitioners, and experts spend less money on testing than non-experts to reach an accurate diagnosis ($297 vs. $658) [10].

IBS treatment includes both lifestyle recommendations (diet and physical activity), medication recommendations [11 12], and other therapies [13]. Most patients report more confidence that lifestyle recommendations would help them, but patients are more likely to

adhere to medication recommendations [11]. Although nutrition-based therapies and treatments for FBDs exist, researchers have not conducted a comprehensive investigation of the effectiveness of these interventions. Efficacy of these interventions has been measured in various settings, but the effectiveness of these therapies in an integrative medicine clinical setting is unknown. Patients in an integrative medicine setting may be more willing to make lifestyle changes because they seek this additional healthcare, thus I chose an integrative medicine clinic to study the efficacy of lifestyle interventions.

II. Functional Bowel Disorders: Definition, Prevalence, Diagnosis and Treatment

FBDs are digestive disorders that include IBS, functional bloating (FB), functional constipation (FC), functional diarrhea (FD), FBDs not otherwise specified (FBD-U) [1], and more recently, opioid-induced constipation [14]. FBDs are clinical conditions without a known structural or biochemical basis. Instead, FBDs are based on clinical, patient-reported symptoms of the middle and lower GI tract. Prevalence of FBD Functional bowel disorders is estimated between 10-20% of adults, worldwide [3]. A 2012 meta analysis reports IBS prevalence is about 11% worldwide and varies from 1% to 45% among countries [15]; worldwide prevalence is questionable due to heterogeneous study methods [16]. IBS is most common among women and between the ages of 30-50 years [17].

Currently, providers do not agree upon specific biomarkers to diagnose IBS, and symptom-based diagnosis remains the standard [18]. However, IBS's definition is debated as a functional disorder as some evidence suggests IBS has organic pathophysiology [19-21]. The physical intestinal barrier of people with IBS is altered, suggesting the condition may not be merely clinical [22]. Additionally, physical biomarkers like fecal short chain fatty acids [23] and

hydrogen sulfide in exhaled breath [24], and small intestinal bacterial overgrowth (SIBO) [25] are suggested by emerging research.

De Giorgio and colleagues [26] describe IBS as a "prototype of all functional bowel disorders for its high prevalence worldwide and impact on patients' quality of life." Thus, most of the evidence in this literature review is from IBS-related research due to its disproportionate presence in the literature.

In a survey of internal medicine physicians, family physicians, and gastroenterology physicians, the internal medicine physicians and family physicians reported the need to refer about one third of IBS patients to a gastroenterology physician [6]. Gastroenterologists reported that IBS patients are less ill than other patients but require more of their time [6], possibly reflecting some of the psychosocial effects of IBS. Thus, IBS patients pose a disproportionate time burden on physicians who also need to care for more critically ill patients.

Diagnosis of FBDs is based on Rome IV criteria (i.e. fourth version). The Rome Criteria are established by The Rome Organization (a 501c3 tax-exempt organization) [27]. Gastroenterologists use the Rome Criteria as standard diagnostic criteria for IBS. The diagnostic criteria for FBDs, including IBS (Rome IV) are shown in Table 1. To ensure patients do not have more severe GI-related disease than a FBD, clinicians note "red flag" or "alarm" signs during their assessment. These signs include: bloody stools, symptoms that wake a patient at night, unintentional weight loss, use of antibiotics, and family histories like celiac disease, colon cancer or others [28].

Although FBD diagnostic guidelines suggest FBD diagnosis should be based on clinical symptomatology and the Rome criteria, in practice the Rome criteria is used by just over 1/3 of

European primary care physicians [29]. Another challenge to using the Rome criteria is the emergence of physical biomarkers as potential diagnostic markers [30]. Proposed IBS biomarkers include elevated bile acid in stool and altered colonic transit time [30]. Mast cells have also been implicated as possible biomarkers of IBS pathophysiology [31].

Table 1: Rome IV Diagnostic Criteria for Irritable Bowel Syndrome [32].

Rome IV Diagnostic Criteria* for Irritable Bowel Syndrome *Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
Recurrent abdominal pain at least 1 day per week over the past 3 months associated with two or more of the following: 1. Related to defecation 2. Associated with a change in frequency of stool 3. Associated with a change in form (appearance) of stool

Treatment for FBDs differs based on the type of FBD and the accompanying symptomatology. Evidence for food-based therapies to improve FBD-related symptoms is promising [26 33]. General FBD treatments include diet changes [34], and, specifically for IBS, include psychological, pharmacological, diet changes, and dietary supplement treatments [35]. Diet therapies for IBS include avoidance of food allergies using elimination diets and changes in fiber or specific carbohydrate intake [33 35]. Psychological IBS treatments include short- and long-term psychotherapies [13]. According to The Mayo Clinic, there are two current pharmacological treatments approved specifically for IBS: Alosetron (Lotronex) [36] (prescribed for IBS-D) and Lubiprostone (Amitiza) (for IBS-C and chronic constipation) [37]. Clinicians are also using a new prescription medication, Linaclotide (Linzess), for IBS-C and chronic

constipation [38]. Other medical treatments for IBS symptoms include fiber supplements, anti-diarrheal medications, anticholinergic and antispasmodic medications, antidepressants, antibiotics, polyethylene glycol (PEG) [39], lactulose [39], and psychological counseling for mental health features of IBS [37]. Interestingly, non-concealed placebo treatment for IBS is also effective at relieving symptoms [40]. Although the placebo effect is an effective IBS treatment, it seems to last only about 12 weeks [41]. Variable research methods for yoga as an intervention for IBS suggest that yoga is a safe and possibly effective adjuvant to IBS treatment [42]. Dietary supplement treatments for IBS include magnesium [43], melatonin [44], peppermint oil [45 46], probiotics and fiber supplements [45].

III. Burden of FBDs and IBS

A. Symptomatology of FBDs

FBDs are characterized by symptoms that patients report to their diagnosing healthcare providers. IBS is specifically characterized by lower gastrointestinal symptoms, including bloating, cramping below the belly button, stomach pain, constipation and/or diarrhea [47]. When compared to asymptomatic controls and US norms, people with IBS symptoms report poorer physical and mental health based on the Short Form-36 (SF-36) (a quality of life questionnaire) [48]. Patients with FBD report symptoms including change in stool form and frequency, abdominal pain, bloating and/or distension, and other symptoms. See Table 2 for FBD symptoms. [49].

Table 2: Symptoms of Functional Bowel Disorders. Adapted from The University of Michigan website [47], Tack 2006 [50], Lacy 2016 [14]

Symptoms of FBDs
IBS symptoms
Abdominal bloating and/or distension
Pain in mid-to-lower abdomen
Constipation (IBS-C and/or IBS-M)
Diarrhea (IBS-D and/or IBS-M)
FD symptoms
Repeated loose or watery stools
Possible abdominal pain/bloating (but less likely than IBS)
FC symptoms
Difficult, infrequent or incomplete defecation
Possible abdominal pain/bloating (but less likely than IBS)
FB symptoms
Repeated abdominal fullness, feeling of trapped gas, pressure, and/or objective increase in abdominal circumference (distension)
Unspecified FBD symptoms
Symptoms do not meet IBS or other FBDs, but patient does not have physical evidence of disease
Opioid-induced constipation symptoms
Change in baseline bowel and defecation habits after starting opioid medications
Less frequent bowel movements
Increase in straining
Feeling of incomplete evacuation

B. Comorbidities of IBS

IBS patients often have overlapping FBD-related symptoms [51]. About half of patients with IBS also have gastroesophageal reflux disease (GERD) or symptoms of functional dyspepsia [51-53].

In addition to the burden of GI-related symptomatology in IBS, patients with IBS have higher rates of anxiety and depression [54], chronic headaches, and fibromyalgia [55]. In fact, anxiety independently predicts whether IBS patients seek healthcare [56]. Other conditions commonly seen among persons with IBS include chronic fatigue syndrome, interstitial cystitis, tension headaches and others [51 57 58].

C. Quality of Life and Economic Burden of FBDs

Patients with FBDs and, specifically, IBS-C and IBS-D have lower health related quality of life (HRQOL) [7 59]. This decreased quality of life translates to increased direct costs (over the counter medications, cost of alternative treatments) and indirect costs (lost work productivity, including absenteeism and presenteeism, i.e. working while sick) [7].

The costs to patients with FBDs include costs of over-the-counter and alternative treatments, cost and time spent for healthcare visits, time off work, and others. Although the direct and indirect costs per patient of FBDs vary [8], the overall (direct and indirect) annual cost of FBDs in the US is likely more than $26 billion US dollars [9]. Specifically, IBS-D has a significantly higher cost burden for medical service use (not pharmaceuticals) when compared to matched controls [60].

IV. Factors Contributing to Diagnosis of FBDs

Functional bowel disorders (FBDs) are a group of conditions that includes irritable bowel syndrome (IBS), functional bloating (FB), diarrhea (FD), functional constipation (FC), and unspecified functional bowel disorders (FBD-U) [61]. FBDs are not life-threatening conditions, but they negatively impact patients' the quality of life [62]. FBDs are diagnosed based on

patient-reported gastrointestinal (GI) symptoms despite a lack of physically identifiable etiology. Although IBS diagnosis is often called a "diagnosis of exclusion," IBS experts suggest the condition is not a disease of exclusion [10]. IBS is the most common FBD. Patients with IBS report pain and their symptoms are related to defecation or a change in bowel habits. IBS symptoms are characterized by either constipation-dominance (IBS-C), diarrhea-dominance (IBS-D), mixed symptomatology (IBS-M), or are unclassified (IBS-U) [14]. IBS has both complex pathophysiology and treatment [63].

Diagnosis of FBDs can be difficult; the various FBDs share common symptomatology with other GI conditions [64-66]. For example, both FC and IBS-C have constipation in Rome criteria for diagnosis, but a distinction between them is the presence of pain with IBS-C compared to chronic constipation [38].

A. Symptom Profile

Altered gastrointestinal function and accompanying symptoms define FBDs. The Rome IV Criteria is the most current and widely accepted diagnostic criteria for FBDs. See Table 1 for Rome IV Criteria for IBS diagnosis [32]. IBS is distinct from other FBDs because IBS patients more often report pain and report symptoms related to defecation.

B. Psychological Health, Sleep and FBDs

Psychological abnormalities are common among persons with IBS, including anxiety [67 68], depression [68], somatization [68 69], and hypochondria [35]. Persons with FBDs score higher on personality measurements of neuroticism and introversion [70]. IBS patients more often report chronic stressors [71], and their perceived stress is negatively associated with quality of life factors [72]. In fact, anti-depressants effectively alleviate IBS symptoms (both physical

and psychological) [73]. Although persons with IBS have psychological abnormalities, evidence from a case-control sleep study of IBS patients suggests IBS patients have higher sympathetic dominance. Thus, the characterization of increased anxiety and sympathetic dominance may be inherent and not solely psychosocial [74 75]. Psychological aspects of FBDs are complex, and we do not know whether psychological abnormalities initiate FBD pathophysiology or FBD-related symptoms lead to psychological problems.

IBS patients also exhibit disturbed sleep [76]; they sleep more hours, but they have more waking episodes and report less restful sleep. In addition to abdominal symptomatology, IBS affects quality of life related to sleep habits.

C. Genetics and FBDs

Tumor necrosis factor superfamily member 15 (TNFSF15), which has been called the "IBS gene" [19], is associated with IBS. Other IBS-related genes are linked to inflammation, neurotransmitters and synthesis of bile acids, and can play roles in IBS pathophysiology [19]. In a systematic review, Infante-Molina [77] reported that 44% of non-celiac gluten sensitivity (NCGS) patients (often exhibiting IBS-like symptoms) had HLADQ2/DQ8 (celiac-related) haplotypes. Thus, genes likely play a role in IBS pathophysiology, but more research is needed to make clinical recommendations for genetics-based treatment.

D. Food intolerances/sensitivities and allergies in Functional Bowel Disorders

About 50% of patients with IBS have true, IgE-based food allergies [78], and the idea that persons with IBS may have underlying food sensitivities is not new [79 80]. Common food sensitivities include gluten intolerance or sensitivity, wheat intolerance or sensitivity, lactose intolerance, fructose malabsorption, and sensitivity to a group of carbohydrates referred to as

"FODMAPs" (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) [33 81 82]. FODMAPs are a group of short-chain, easily fermentable carbohydrates that can contribute to IBS symptoms. Persons with food sensitivities who have IBS can be alleviate their symptoms by eliminating the offending food or foods [33]. Lowering FODMAPs in the diet reduces IBS symptoms [83]. Other food components that can elicit IBS-like symptoms include benzoates, amines, glutamate, and salicylates [26].

In 2015, Pasqui and colleagues [84] proposed a therapeutic algorithm to diagnose and treat food allergy and intolerances related to functional GI symptoms. Their algorithm is a "diagnostic-therapeutic protocol" that is used to assess food allergy or intolerance. Their therapeutic algorithm guides a practitioner through presenting symptoms (GI-related) and recommended lab testing: IgE allergy testing, lactose breath testing, IgA measurement, and endoscopic testing. Based on the results of lab testing, recommendations for therapies are made (lactose-free diet, gluten-free diet or elimination of any other allergenic food).

In a tutorial by Mullin and colleagues [33] that reviews nutritional therapies for IBS, investigators suggested that addressing adverse food reactions and intolerances (e.g. lactose, gluten, wheat, FODMAPs) and using dietary supplements (e.g. peppermint oil, herbs, pre- and probiotics, fiber) are all evidence-based therapies for IBS. They provided a nutrition-based care algorithm for providers treating IBS patients. See Figure 1.

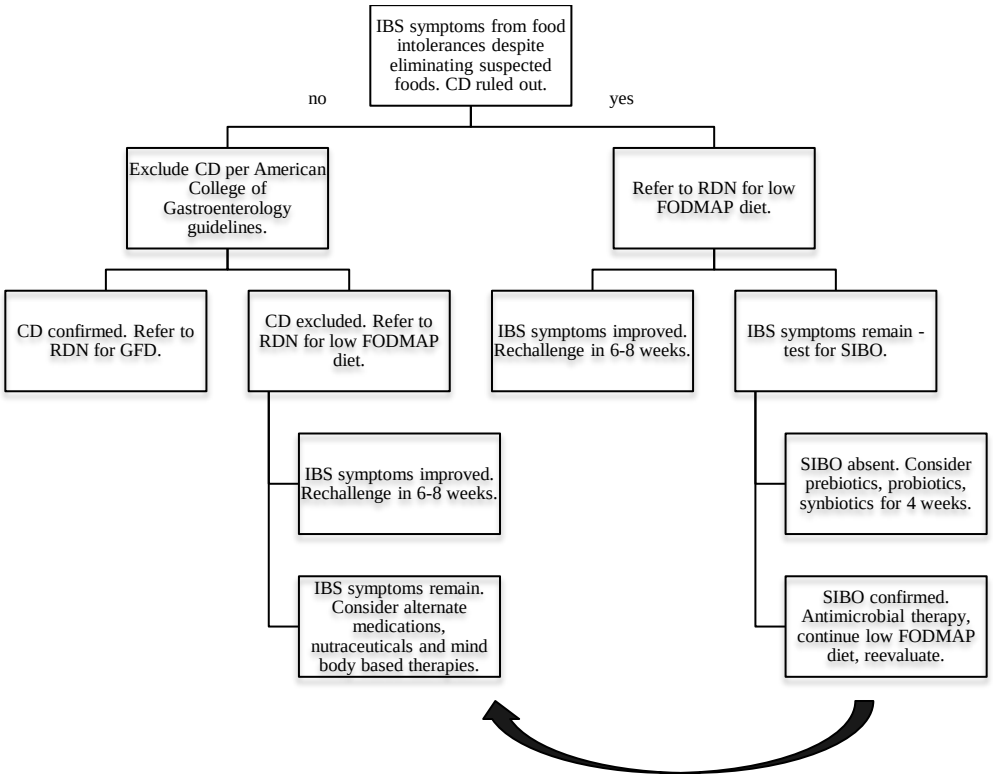

Figure 1: Care algorithm for using diet-related interventions for patients with IBS. Figure adapted from Mullin et al 2014 [33]. IBS, irritable bowel syndrome; CD, celiac disease. RDN, registered dietitian-nutritionist. GFD, gluten-free diet; FODMAP, fermentable oligo- di- monosaccharides and polyols; SIBO, small intestinal bacterial overgrowth.

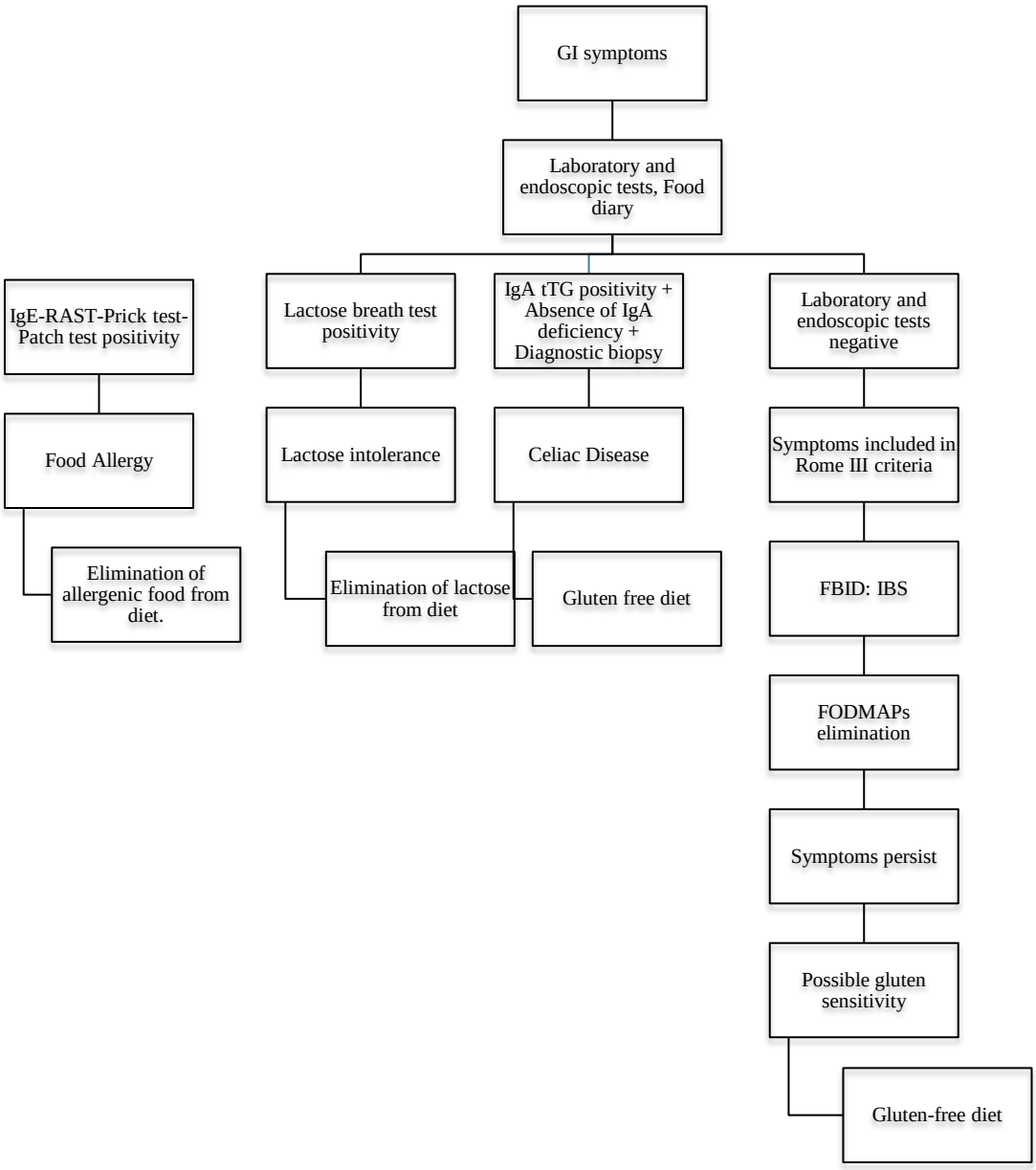

Figure 2: Diet-related care algorithm for patients with GI symptoms. Adapted from Pasqui 2015 [84]. GI, gastrointestinal.

E. IBS and Non-Celiac Gluten Sensitivity

IBS symptoms often overlap with symptoms reported by persons with NCGS [85], and some suggest that a portion of IBS patients have NCGS [86]. NCGS is of growing concern for healthcare providers in the US and around the world [77 87-89]. Doctors and other diagnosing

healthcare professionals are beginning to characterize the diagnostic criteria for NCGS as distinct from Celiac Disease (CD) and wheat allergy [90]. In persons with NCGS, gluten appears to trigger the innate immune system [90], which may help explain the effectiveness of elimination diets based on IgG food sensitivity testing [91]. Prevalence of NCGS may range between 0.5% and 13%, the higher range exceeding that of CD prevalence [77]. However, gluten may not be the cause of patients' symptoms but more of a nocebo effect [92].

Presence of both celiac-related genes (HLA-DQ2) and elevated IgG anti-gliadin antibodies in persons without CD diagnosis are more predictive of the effectiveness of a gluten-free diet than either marker alone (56% positive predictive value compared to 44% and 45% of each HLA-DQ2 and gluten antibodies, respectively). In other words, patients with both HLA-DQ2 genes and elevated anti-gliadin antibodies with IBS-D are more likely to benefit from a gluten-free diet than those without the celiac-related gene and antibody markers [93 94]. However, evidence suggests that expression of HLA-DQ2 or DQ8 may not be a useful marker of wheat sensitivity [95]. NCGS is one of many possible contributors to GI symptoms in IBS patients.

Adherence to a gluten-free diet is variable, even in patients with CD adherence ranges between 42-91% [96]. Thus, adherence will likely vary among persons with NCGS. Leffler and colleagues [97] found that self-reported adherence and serological measurements of adherence to a gluten free diet were associated, therefore, self-reported adherence may be a useful proxy measurement for adherence to a gluten free diet.

V. Etiology and Pathophysiology of FBDs

A. Etiology of IBS

The etiology of IBS is elusive, but several factors have been proposed to contribute to IBS. Evidence suggests an imbalance of the autonomic nervous system (ANS) may contribute to IBS pathophysiology [98]. Patients with IBS-C have lower parasympathetic modulation based on heart rate variability (HRV) measurement [99]. However, evidence for HRV in IBS patients versus controls varies widely, especially when comparing IBS subgroups [100 101]. Evidence in children with IBS demonstrates that HRV biofeedback (HRVB) alleviates IBS-related symptoms [102]. Mucous layer damage may also be a contributing cause of both IBS and inflammatory bowel disease (IBD) [103].

Historically, IBS was believed to be a predominantly psychosomatic condition. However, in the last decade, evidence suggests that alterations in the microbiota are associated with IBS pathophysiology [104 105]. Related to this idea: post-infectious IBS is triggered after a GI infection [19] and patients' IBS symptoms are alleviated by antibiotics [106]. In fact, IBS-D patients who took the probiotic Lactobacillus brevis KB290 with beta carotene for 12-weeks reported less severe abdominal pain and higher levels of circulating interleukin-10 (an anti-inflammatory cytokine) [107] Thus, IBS may be an infectious disease [106]. See Table 3 for background on IBS pathophysiology.

B. Pathophysiology of Irritable Bowel Syndrome

The full picture of IBS pathophysiology remains unknown, but many factors contribute to IBS pathophysiology [19]. See Table 3 for a short summary of different aspects of IBS pathophysiology. These physical abnormalities support that IBS may not be "idiopathic."

Table 3: Short summary of IBS pathophysiology

IBS Pathophysiology	
Altered GI motility[1] or "Motor Dysfunction"[2]	High-amplitude propagated contractions (HAPCs) are common in IBS-D pathophysiology (rare in IBS-C). Similarly, transit time is longer for persons with IBS-C and shorter for IBS-D. Both IBS-D and IBS-C patients report incomplete bowel evacuation. Other data suggest pelvic floor abnormalities as contributing to IBS symptoms [108].
Autonomic Nervous System Dysregulation[2]	IBS-D patients have abnormal sympathetic adrenergic nervous system activity while IBS-C patients have abnormal vagal parasympathetic activity.
Visceral hypersensitivity[1]	Persons with IBS have increased sensitivity in their GI tract [109]: esophageal, gastric, small intestinal, colonic and rectal [19]. This increased sensitivity has been associated with increased stress and food ingestion [19] and is related to both internal and external (environmental) factors.
Gut-Brain Interaction[1]	Hormones facilitate the communication between the gut-brain axis. Specifically, corticotropin-releasing hormone (CRH) controls stress communication. Evidence from brain imaging research shows increased brain activation with GI distension [19].
Inflammation[1]	The intestinal mucosa of IBS patients has elevated inflammatory markers like T-lymphocytes, neutrophils, mast cells, and plasma cells [19].
Post-infectious low-grade inflammation[1]	PI-IBS is characterized by IBS symptoms that do not meet Rome criteria but are preceded by any two of the following: fever, emesis, diarrhea, culture positive for GI bacterial overgrowth. Low-grade inflammation characterizes PI-IBS pathophysiology [19].
Small Intestinal Bacterial Overgrowth (SIBO)[3]	SIBO shares similar symptomatology of IBS and some suggest that IBS may actually be an infectious disease [106].
Genetic Factors of Inflammation[1]	Genetic factors related to IBS pathophysiology are characterized by inflammation, neurotransmitters and synthesis of bile acids. TNFSF15 is called the "IBS gene." Variants of genes TLR9, IL-6 and CDH1 were associated with increased risk for PI-IBS [110]. Controversy exists for the relationship between IBS and genetic variants of the IL-10 gene.

Immunologic Factors[1]	The immune system is activated in IBS leading to increased expression of immune factors: TLR2, TLR4, IL-1, IL-8, TLR5, TLR9, IL-6, CDH1.
Genetic Factors of Neurotransmitters and Cytokines[1]	NT and cytokine-related genetic polymorphisms associated with IBS: SLC6A4 (a SERT gene), GNbeta3, NPSR1, FAAH, and C385A.
Genetic Factors of Bile Acid Synthesis[1]	Bile acid synthesis-related genetic polymorphisms associated with IBS: KLB gene (rs17618244), TGR5.
Altered Microbiota[1]	Altered GI bacteria may lead to IBS pathophysiology. SIBO is common in certain IBS subsets. Elevated dysbiotic bacteria and lower lactobacillus and bifidobacterium are common in IBS patients [111].
Diet-related Factors[1]	*Food allergies & intolerances*: Little evidence exists for the role of food allergies in IBS pathophysiology. Evidence supports the role of intolerances in IBS pathophysiology (though still debated) due to elimination of certain foods resulting in alleviation of IBS-symptoms. *Altered absorption*: Poor absorption of certain food components, like short-chain carbs (e.g. fructose) and FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) can lead to IBS-symptoms. Gut flora also contributes to altered nutrient absorption and gas-forming fermentation (leading to IBS symptoms). *Gluten intolerance*: Conflicting evidence exists [112 113] for the role of gluten intolerance in IBS-related symptoms. Some report gluten withdrawal alleviates IBS symptoms [113] while others refute that claim [112].
Enteroendocrine Cells[1]	Gastrin, secretin, stomatostatin, cholecystokinin, chromogranins, and serotonin are all bioactive substances released by enteroendocrine cells. Abnormal levels of some of these compounds are found in IBS patients. E.g. elevated release of serotonin in IBS-D and PI-IBS; elevated 5-HT is associated with GI inflammation; abnormal levels of chromogranin A are found in IBS patients.
Intestinal Barrier[4]	Patients with IBS-D and PI-IBS have increased intestinal permeability (altered GI barrier function and risk of bacterial translocation). Zonula occludins (ZO) proteins play a role in gut

	barrier function and zonulin specifically regulates tight junctions. *Triggers of altered intestinal permeability*: stress, foods, infections.
Altered bile acid metabolism[5]	Abnormalities in bile acid metabolism are common in patients with IBS-D [2]. Patients with IBS-D often have elevated bile acid levels in their stool [114].

[1]Lee 2014, [2]Hasler 2011, [3]Thompson 2016, [4]Camillerei 2012, [5]Holtmann 2016
IBS, irritable bowel syndrome; GI, gastrointestinal; HAPCs, High-amplitude propagated contractions; IBS-D, diarrhea-dominant IBS; IBS-C, constipation-dominant IBS; CRH, corticotropin-releasing hormone; PI-IBS, post-infectious IBS; SIBO, small intestinal bacterial overgrowth; TLR, toll-like receptor; IL, interleukin; CDH1, cadherin-1; NT, neurotransmitter; SLC6A4, Solute Carrier Family 6 Member 4; SERT, serotonin transporter; GNbeta3, A gene associated with functional dyspepsia (aka GNβ3); NPSR1, Neuropeptide S Receptor 1; FAAH C385A, fatty acid amide hydrolase C385A; KLB, klotho beta; TGR5, G protein-coupled bile acid receptor 1; FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; ZO, zonulin.

VI. Modifiable Lifestyle Factors for FBDs

Some lifestyle approaches can alleviate FBD-related symptoms. Those include dietary approaches like limiting or eliminating specific food triggers, psychotherapy, stress reduction, and others [33]. In fact, ingestion of food, alone, can trigger IBS symptoms [115].

A. Dietary Approaches, Food Intolerances, Food Sensitivities and IBS

i. Elimination Diets

Elimination or "exclusion" diets have been used for years to alleviate IBS symptoms [116]. Elimination diets can help identify both IgE and non-IgE-mediated food allergies or sensitivities [117]. The European Academy of Allergy and Clinical Immunology (EAACI) recommends a 2-4 week elimination diet is sufficient to identify food allergies for IgE-related food allergies, while non-IgE-related allergy (food sensitivity) requires up to 6 weeks [117]. For non-IgE-mediated food sensitivities, studies in children suggest nearly all of patients (98.4%)

report symptom improvement after 4 weeks [118]. To my knowledge, no comparable recent data [119] exist for adults regarding symptom improvement following elimination diets for non-IgE-mediated GI food sensitivities.

In addition to elimination diets, clinicians use other methods to identify food sensitivities. Food sensitivity laboratory testing includes the mediator release test (MRT®) testing, serum IgG testing, and others. Symptoms of patients with IBS improve when they eliminate foods that are identified as abnormal per serum IgG testing [120]; personalized elimination diets based on IgG blood testing improved IBS-related symptoms and self-reported quality of life in IBS patients [91]. Little is known about the efficacy of treatment based on the other methods of testing.

In 2014 Kabbani and colleagues [121] created a diagnostic model to guide healthcare practitioners to diagnose CD, NCGS, or Non-Celiac Enteropathy. The algorithm starts with identifying patients who report symptoms responsive to a gluten-free diet [121], then leads the clinician through lab testing algorithms, and finally ends with potential gluten-related diagnoses (e.g. CD, NCGS, serological-negative CD, non-celiac enteropathy and indeterminate diagnosis).

Beyond diagnostic criteria, Pasqui and colleagues [84] created a diagnostic and therapeutic algorithm to assist healthcare practitioners in the accurate diagnosis and therapy for adverse food reactions. They distinguish food allergies, food intolerances, sensitivities, and different methods to diagnose these conditions. Additionally, they provide algorithms to assist decision-making for therapeutic diet recommendations. Pasqui and colleagues' [84] diagnosis and dietary care algorithm (see Figure 2), leads to recommendations for use of specific elimination diets.

ii. Low FODMAP Diet

Similar to the use of tailored food withdrawal diets, lowering intake of FODMAP foods alleviates IBS-related symptoms [112 122 123]. Clinical evidence suggests that a low-FODMAP diet can alleviate IBS symptoms [83], and one review concluded that evidence for use of low-FODMAP diets in FBDs is "sufficiently strong to recommend its widespread application" [82]. Foods with high amounts of FODMAPs contain easily fermentable, short-chain carbohydrates. Table 4 lists foods with high amounts of different categories of FODMAPs [33].

Table 4: Common foods high in FODMAPs [33 84]

Fructose	Lactose	Fructans	Mannitol	Sorbitol	Galactans
Fruit: apples, mango, pear, watermelon *Vegetables*: asparagus, artichokes, sugar snap peas. *Other*: agave, high-fructose corn syrup, honey	Dairy (Cow, goat, sheep)	*Fruit*: custard apples, white peaches, nectarines, persimmon, watermelon *Vegetables*: artichokes, garlic, leek, onion, spring onion (white part only), shallot *Grains/Cereals*: Barley, rye, wheat-based food products *Nuts & Legumes*: Cashews, pistachios, chickpeas, legumes, lentils *Other*: Fructo-oligosaccharides, inulin	*Fruit*: stone fruits, peach, watermelon *Veggies*: cauliflower, mushrooms, snow peas *Other*: mannitol	*Fruit*: apples and stone fruits; sugar-free candies & gum *Other*: Sorbitol	*Legumes*: chickpeas, lentils, legumes (e.g. kidney beans, soy beans)

Although low-FODMAP diets are effective for IBS, evidence from one randomized controlled trial suggests that a low-FODMAP diet was no more effective at improving IBS symptoms than traditional dietary advice (eating smaller meals at consistent times, decreasing fat, indigestible fiber, caffeine, and gas-producing foods like cabbage, onions and beans) [124]. Concerns about a low-FODMAP diet include an unknown effect on the GI flora, long-term effects and nutritional adequacy [122 125].

iii. Gluten-Free Diet Non-Celiac Gluten Sensitivity, Non-Celiac Wheat Sensitivity or Non-Celiac Wheat Protein Sensitivity

NCGS is a new condition of growing concern for healthcare providers in the United States and around the world [77 86 88-90 112 121 126-129]. Published reviews related to NCGS span disciplines that include gastroenterology [86 121 128], clinical nutrition [126], nutritional metabolism [130 131], nursing [127], and cellular and molecular immunology [89]. Similar to IBS, NCGS is more common among women and between the ages of 30-50 years [130]. NCGS diagnosis is difficult due to symptomatic similarities between NCGS and CD [121]; some suggest that a subpopulation of IBS patients likely have NCGS [86]. Doctors, Nurse Practitioners, and other diagnosing healthcare professionals are just starting to characterize diagnostic criteria for non-celiac gluten sensitivity, which is important because NCGS is distinct from CD and wheat allergy [90 121 127]. Recognition of NCGS is recent enough that there is still discussion regarding the accurate terminology for the condition [132]. Nomenclature surrounding the condition has been discussed, suggesting “Non-Celiac Wheat Sensitivity” as a more appropriate label than “Non-Celiac Gluten Sensitivity” since the exact component of wheat that elicits symptoms has not been identified [132].

In a double blind, randomized, placebo-controlled trial, Biesiekierski and colleagues [133] tried to determine whether gluten intake could elicit symptoms in persons without CD. The investigators studied a group of 34 patients with IBS and non-celiac who controlled their symptoms on a gluten-free diet. At baseline, patients reported symptoms on a visual analog scale for pain, bloating, stool consistency satisfaction, and tiredness. Researchers also measured GI biomarkers of inflammation, immune activation and injury. Participants followed a gluten free diet throughout the 6-week trial and were divided into two groups: one group consumed gluten-containing bread and muffins, and the other was given gluten-free bread and muffins. After the 6-week intervention, participants again completed the symptom reports and biomarker lab tests. Sixty percent of the participants given gluten reported significantly poorer symptom control (overall symptoms, pain, bloating, stool consistency satisfaction and tiredness) while fewer of the placebo group (40%) reported poorly controlled symptoms. Investigators concluded that NCGS likely exists, but the mechanism remains unknown [134].

Data from a more recent study by Biesiekierski and colleagues [112] with 37 subjects suggest there is no effect of gluten on patients with self-reported NCGS when compared to improvement of symptoms following a low FODMAPs diet. Symptoms were well controlled following the low-FODMAPs diet, but upon the “food challenge” period (reintroducing gluten), symptoms were not significantly different between the study arms. Although data from clinical trials are variable, it is reasonable to consider a gluten-free diet for patients with IBS symptoms. However, it will be important to characterize patients who benefit the most from this dietary treatment.

De Giorgio and colleagues [26] summarized results from double-blind placebo-controlled trials among non-celiac patients with gluten or wheat sensitivity and IBS symptoms [112 134-

138]. They also summarized the clinical trial results for low FODMAP diets' effectiveness in IBS symptoms [83 139-144].

Fasano and colleagues [86] created a figure showing the varying pathogenesis of gluten-related disorders [autoimmune, allergic and non-autoimmune/non-allergic (possibly involving the innate immune system)]. See Figure 3 below.

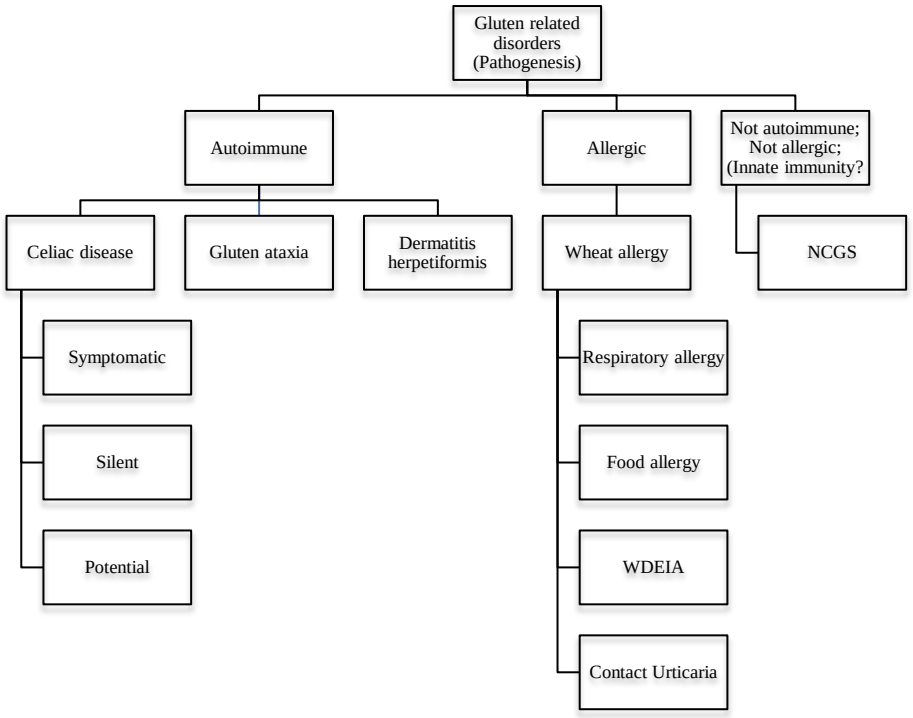

Figure 3: Characterization of the pathogenesis of gluten-related disorders. Figure adapted from Fasano and colleagues, 2015 [86]. WDEIA: wheat-dependent induced anaphylaxis.

Czaja-Bulsa [126] created an algorithm to understand if the etiology of a patient presenting with IBS-like syndrome, includes a gluten-related disorder (CD, wheat allergy, NCGS), IBS, bacterial overgrowth, or a non-gluten adverse food reaction (lactose intolerance, food allergy, FODMAPs intolerance, or food chemical intolerance). See Figure 4 for algorithm.

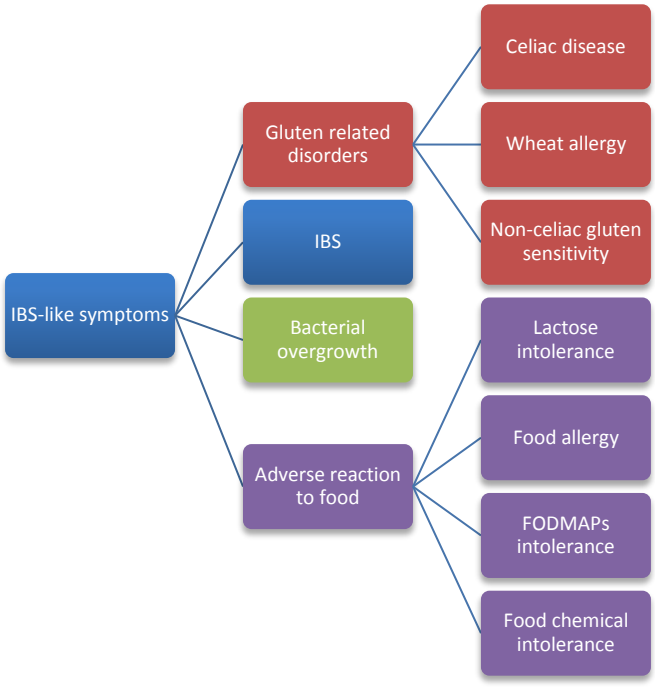

Figure 4: Modified from Czaja-Bulsa, 2015: Clinical presentation of IBS to guide clinical action [126]. IBS: Irritable Bowel Syndrome; FODMAPs: fermentable oligosaccharides, disaccharides, monosaccharides and polyols.

B. Psychiatric Health (Anxiety and Depression)

Anxiety and depression are common in FBDs [54]. Evidence from a recent meta analysis of persons with IBS suggests that these patients benefit from both short- and long-term psychotherapy [13]. Thus, persons with IBS may be recommended to seek therapy.

C. Stress and FBDs

It is well known that stress and FBDs are related. In fact, psychological stressors trigger IBS symptoms [33 145]; and women with IBS more often report early traumatic life events (physical, emotional, and sexual abuse) than women without IBS ($p<0.001$) [146]. To further reinforce the relationship between stress and IBS, healthcare providers (physicians and nurses)

have a significantly higher prevalence of IBS compared to controls [147] with their stressful work environments explaining the relationship.

VII. The Placebo and Nocebo Effects and IBS

There is a placebo effect on IBS symptoms, however Spiller and colleagues [41] found that the placebo effect for IBS patients diminishes after 12 weeks. Thus, a follow up period beyond 12 weeks may be ideal for the assessment of the efficacy of IBS-related interventions.

As mentioned above, the nocebo effect of gluten-free diet may contribute to its seeming effectiveness [92], but this should be further explored.

Based on results from a systematic review, there is a placebo effect of psychotherapy on IBS patients that is similar to that of other IBS treatments (medications, dietary and alternative interventions) [148].

VIII. Alterations of the Gastrointestinal Environment and FBDs

Small Intestinal Bacterial Overgrowth (SIBO) is a condition defined as an overgrowth of bacteria with a minimum of 10^5 colony-forming units (CFU) per milliliter on a culture of an upper gastrointestinal aspirate [149]. SIBO symptoms are similar to those with IBS, so persons with SIBO may be misdiagnosed as having IBS [149]. There is evidence of a direct relationship between IBS and SIBO [150]. Thus, SIBO should be considered as a possible contributing factor in persons reporting IBS symptoms, but diagnostic-testing methods for SIBO needs improvement [151].

One factor that affects SIBO risk is patients' use of Proton Pump Inhibitors (PPIs) to control reflux symptoms. By blocking acid production in the stomach, PPIs change the pH of the

stomach and increase patients' risk for SIBO [152]. Patients on long-term PPIs should be monitored for IBS symptoms that may be affected by an elevated pH and, as a result, increased susceptibility for SIBO.

IX. Nutritional Considerations and IBS

A. Nutritional Status and IBS

With several dietary interventions for IBS treatment, some investigators have looked at the possible connections between nutrient intake and IBS. New evidence suggests that the severity of IBS symptoms is inversely related to vitamin D status in persons with IBS and that the majority of people with IBS may have vitamin D deficiency [153]. Magnesium is another possible nutrient deficiency among persons with IBS as magnesium supplementation can effectively alleviate symptoms of IBS [43]. A study of the 7-day dietary and nutrient intake of IBS patients suggests that patients with IBS have a lower intake of vitamin B6 but no other nutrients emerged as significant [154].

Nutritional deficiencies are more common in CD than NCGS. In a retrospective chart review, Kabbani and colleagues [121] found that 57.4% of CD patients had nutrient deficiency (defined as one or more of the following: vitamin D, iron deficiency anemia, vitamin B12 or zinc deficiency) compared to patients with NCGS. Persons with CD may be nutritionally deficient due to their restricted diet (gluten withdrawal removes b-vitamins from the diet) or from malabsorption inherent in CD.

Magnesium is a mineral (Mg^{2+}) with multiple functions: enzyme cofactor, chelates adenosine triphosphate (ATP), competes with calcium (Ca^{2+}) for binding sites to regulate intracellular and extracellular calcium concentrations, and other functions. Homeostasis of

magnesium is maintained by balancing gastrointestinal absorption with renal excretion of the mineral. Magnesium deficiency alters gut microbiota and contributes to anxiety pathophysiology in mice [155]. Magnesium-deficient mice have abnormalities in the hypothalamic-pituitaryadrenal (HPA) axis, leading to increased anxiety-related behaviors [156], and these magnesium-deficient mice serve as a model to study anxiety [156]. Comorbidity of IBS includes other diseases that are characterized by magnesium deficiency including anxiety [156], chronic headache [157], fibromyalgia [158]. Thus, it is reasonable to suggest that magnesium deficiency may play a role in patients with both IBS and anxiety.

Other nutrients may be implicated in the pathogenesis of IBS. In zinc metabolism, specifically, IBS pathogenesis may follow a different course depending on the patient's blood levels of zinc or the amount of fecal zinc excretion [159]. Deficiencies of both zinc and magnesium have been suggested as possible factors implicated in pathophysiology of fibromyalgia, a comorbidity of IBS, but there is not similar evidence for the pathophysiology of IBS or other FBDs [160].

X. Patient Satisfaction with IBS Treatment

Patients with severe IBS were interviewed (n=10, 4 women, 5 men, 1 transgender) about their healthcare encounter experiences for treatment of IBS [161]. These patients had negative emotions related to both their symptoms and the perception that their healthcare providers did not believe the reality of their symptoms. In addition to these negative experiences, these IBS patients demonstrated strengths like perseverance (not giving up), finding solutions, and seeking information and social support. Thus, patients with IBS may be more likely to seek alternative therapies for their symptoms.

Dorn and colleagues [162] developed and validated an instrument to determine patients' satisfaction with IBS care (IBS-SAT). They measure 5 subscales, including: connection with provider, education, benefits of visit, office attributes (wait time, office staff, etc.), and access to care. The IBS-SAT would be a helpful tool to determine why patients might seek care outside of conventional healthcare.

XI. Integrative Medicine: Practice, Patients, and Interventions

Definitions of integrative medicine (IM) vary widely. Hu and colleagues [163] summarized 17 different IM definitions by measuring the frequency of 11 different components. The 4 most common were that IM: 1) has aspects of both complementary and alternative medicine (CAM) and conventional medicine; 2) emphasizes the importance of the therapeutic relationship between practitioner and patient; 3) emphasizes goals of health and healing; 4) takes a holistic approach to health. In another study of 29 IM centers across the U.S. (The Bravewell Report), one IM program described their approach to patient care as "a commitment to find and treat the root causes of the patient's condition." [164]

The Academic Consortium for IM and Health states that "integrative medicine and health reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic and lifestyle approaches, healthcare professionals and disciplines to achieve optimal health and healing" [165]. And, IM practitioners spend more time with patients [166] so an IM clinic is an optimal setting to care for and study FBD patients, especially since GI specialists have limited time [6].

One of the foundational therapies used in IM practice is nutrition-based interventions [164]. Since many IM interventions are based on lifestyle changes (e.g. sleep, exercise, diet), an

IM clinic is an appropriate population to investigate the impact of dietary interventions on persons with FBDs. For example, adherence to a Mediterranean style diet has a positive impact on the gut microbiota of consumers [167], which may impact IBS symptoms.

Spending on alternative medicine appointments is estimated around $10 billion US dollars annually in the US [168 169] and tens of billions more, if you include products, classes and materials [169]. IM appears to be a growing specialty in medicine that has a financially promising future, thus investigating the efficacy of integrative therapies is important.

XII. Purpose of Dissertation

The main purpose of this dissertation was to characterize nutrition-based therapies for FBDs used in an IM clinic at an academic medical center. Furthermore, I wanted to determine the efficacy of these therapies. A final goal of the study was to determine whether FBD patients seen in an IM clinic present with any nutritional deficiencies.

My central hypothesis was that persons with FBDs who visit The University of Kansas (KU) IM will receive nutrition-based interventions to address FBD, and most patients will report improved symptomatology from these nutrition-related interventions. I tested my central hypothesis by pursuing the following specific aims and hypotheses:

XIII. Specific Aims and Hypotheses

Specific Aim 1: To determine and describe the types of interventions used for patients with FBDs at KU IM.

Specific Aim 2: To determine the change in digestive tract symptom score (based on the Medical Symptoms Questionnaire (MSQ)) from baseline to post-intervention follow up in

patients with FBDs treated at KU IM. *Hypothesis:* I hypothesize that patients will report a significantly lower MSQ digestive tract symptom score from baseline to follow up.

Specific Aim 3: To determine whether there are common micronutrient deficiencies among patients with FBDs who present at an IM clinic for care, and specifically, if there are deficiencies of zinc, copper, magnesium, vitamin B12, vitamin B6, or vitamin D.

XIV. Justification and Significance

FBDs are common in the US and globally [14 61]. Although overall prevalence of FBDs is unknown, about 11% of the world population is diagnosed with IBS (the most common FBD) [170]. There is growing interest in nutrition-related interventions and research on FBDs. For two main reasons, KU IM is an ideal population to test these hypotheses: 1) KU IM sees many clients with FBD diagnoses (often without relief following conventional treatment) and 2) KU IM is a healthcare clinic that primarily uses nutrition-based therapies and interventions.

CHAPTER 2

METHODS

I. Data Collection Overview

To investigate the efficacy of nutrition-based interventions for FBDs, I conducted a retrospective chart review. I screened patient charts beginning May 1, 2016 and moved backward in time.

II. Study Population and Chart Selection

I reviewed patient charts from the Integrative Medicine clinic at The University of Kansas Medical Center (KU Integrative Medicine). I randomly selected charts from KU Integrative Medicine beginning May 1, 2016 and moved backward in time.

Charts were reviewed for study inclusion if the patient fit study criteria (See Table 5). For aims 1 and 3, all 74 patients who fit study criteria were included in the final analysis to answer the research questions. For aim 2, 17 charts were omitted from the original 74, leaving 57 charts in the final analysis. The 17 additional charts were omitted because: 1) patients filled out the second MSQ at the intervention visit (n=6), 2) patients completed the first MSQ after the intervention visit (n=3); 3) a patient left the 2nd MSQ blank (n=1); 4) the time between the first and second MSQs was longer than 18 months (n=3); 5) a patient did not complete a post-intervention MSQ, or 6) patients completed the MSQ incorrectly (n=3).

III. Sample size determination

The number of charts reviewed was determined based on a power calculation. I planned to review at least 40 charts of patients with IBS to reach statistical power for Aim 2. Using a two-sided paired t-test, this study has 80% power at an alpha of 0.05 to detect a moderate effect size of 0.45 (Cohen's d).

Based on these numbers, I collected data for aims 1 and 3.

IV. Inclusion and Exclusion Criteria

Patients' charts were selected for the retrospective chart review (or excluded from the study) based on the following inclusion and exclusion criteria (Table 5).

Table 5: Study inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• 21-89 years of age • Diagnosed with "functional bowel disorder" and/or "irritable bowel syndrome" and/or other functional digestive disorder • Attended 3 or more appointments at KU Integrative Medicine with a "provider" (medical doctor, advanced practice registered nurse, physician assistant or registered dietitian) • Followed up within 18 months of intervention consultation (applicable to aim 2) • Third follow up occurred on or before May 1, 2016 • Completed at least 2 Medical Symptoms Questionnaires (baseline and follow up after intervention) (applicable to aim 2)	• Only consultation at KU Medical Center was with a Registered Dietitian (likely no medical diagnoses in the chart) • Attended fewer than 3 appointments • Follow up occurred longer than 18 months after intervention consultation (applicable to aim 2) • Completed fewer than 2 Medical Symptoms Questionnaires (applicable to aim 2)

V. Study Variables

A. Measuring Symptom Change: The Medical Symptoms Questionnaire (MSQ)

The MSQ is a clinical and research tool [171-173], organized by body systems (e.g. head, nose, digestive tract, emotions, etc.), and is used to measure patient-reported symptoms. See Appendix A for the MSQ. The MSQ asks patients to rate symptoms on a scale from 0-4 (0 means the patient never or almost never has the symptom, and 4 means the patient experiences

the symptom frequently and the symptom's effect is severe). Although the MSQ has not been validated, other investigators have used it to detect a change in symptoms over time [172 173]. Lerman and colleagues [172] used the MSQ joint/muscle sub-category to detect change over time in joint pain and arthritis. The digestive tract symptoms on the MSQ include diarrhea, constipation, bloating, and intestinal pain, which are appropriate symptoms to assess in patients with FBDs.

B. Measuring Micronutrients

Micronutrient levels were measured via serum or plasma testing by a commercial laboratory using validated procedures. Practitioners gave patients orders to have their blood drawn and analyzed at one of several different laboratories (e.g. Quest Diagnostics, Lab Corp, KU Medical Center, or others).

VI. Analysis of Data

Quantitative data was analyzed using statistical software.

Analysis of Specific Aim 1: Aim 1 is a descriptive aim. I used descriptive statistics for the various treatments used to treat FBDs at KU Integrative Medicine.

Analysis of Specific Aim 2: I used a paired 2-sample t-test to compare the baseline and post-treatment MSQ scores for the IBS patients' digestive tract sub-scores. For non-parametric data, I used a Wilcoxon Signed Rank Test to analyze the Functional Bloating, Constipation and Diarrhea patients' digestive tract sub-scores.

Analysis of Specific Aim 3: Aim 3 is a descriptive aim. I used descriptive statistics to describe the nutrient results for aim 3

CHAPTER 3

TREATMENT OF FUNCTIONAL BOWEL DISORDERS IN AN INTEGRATIVE MEDICINE CLINIC

Abstract

Background Functional bowel disorders (FBDs), like irritable bowel syndrome (IBS) and others, are often difficult to treat because they have complex pathophysiology and do not necessarily have a physical abnormality. Patients often seek alternative options for treatment when they experience medication side effects or no relief. Integrative Medicine (IM) is an ideal specialty to investigate these alternative interventions for IBS and other FBDs. **Aim** The purpose of this study was to characterize IM interventions for FBDs in an IM clinic at an academic medical center. **Methods** We performed a retrospective chart review to describe IM interventions for FBDs at an IM clinic in an academic medical center. **Results** Most patients were told to take dietary supplements (94.6%) and next most often were told to follow an elimination diet (87.8%). Patients told to follow an elimination diet were most often suggested to avoid gluten (96.9%) or dairy (80%). **Conclusions** IM providers at this academic medical center frequently recommended lifestyle-based (diet, exercise) interventions for patients diagnosed with FBDs. Gluten and dairy were the two most commonly eliminated food categories. IM providers at this clinic have an opportunity to employ additional evidence-based interventions to their patient interventions, including peppermint oil, herbs, and others. Our results may contribute to a protocol that could be used in this and other IM clinics for treatment of FBDs.

Introduction

Functional bowel disorders (FBDs) are often difficult to treat, as they have complex pathophysiology and do not necessarily have a physical abnormality. FBDs are diagnosed based on patient-reported symptoms. Patients report gastrointestinal (GI) symptoms and are subsequently tested for several possible physical abnormalities via colonoscopy, endoscopy,

celiac disease testing, abdominal ultrasound among other available tests, but test results are negative. Next, clinicians use patient-reported symptoms to determine whether a patient can be diagnosed with an FBD. In other words, a patient is often diagnosed with an FBD after physical evidence of disease has been ruled out. Although patients with FBDs do not necessarily live shorter lives (no increased mortality), FBDs do, however, decrease patients' quality of life, affect work attendance and impact patients' participation in normally pleasurable activities [1].

There are many FBDs; Irritable bowel syndrome (IBS) is the most common FBD, and IBS has been described by De Giorgio and colleagues [174] as the "the prototype of all functional bowel disorders" due to its negative effect on quality of life and wide prevalence. IBS encompasses different subtypes: diarrhea-dominant IBS (IBS-D), constipation-dominant (IBS-C), IBS with symptoms that alternate between constipation and diarrhea, called mixed-type (IBS-M), and unspecified IBS (IBS-U). IBS is defined by chronic GI pain with change in stool form and/or frequency. If a patient experiences diarrhea, constipation or bloating without pain and without other organic disease, these patients are diagnosed with other functional bowel disorders (e.g. functional diarrhea (FD), functional constipation (FC), or functional bloating (FB)) [14].

Although the direct and indirect costs per patient of FBDs vary [8], the overall (direct and indirect) annual cost of FBDs in the US are upwards of $26 billion US dollars [9]. Not only do FBDs have a physical and financial impact on patients, they cost healthcare providers more time than patients with other GI conditions [6]. Interestingly, IBS experts more accurately diagnose IBS than non-expert practitioners, and experts spend less money on testing than non-experts to reach an accurate diagnosis ($297 vs. $658) [10]. Contrary to common belief, IBS experts do not consider IBS a "diagnosis of exclusion" [10].

Treatment of FBDs depends on each patient's specific symptoms [14]. If a patient has loose stools, the physician might prescribe an anticholinergic, antispasmodic, or anti-diarrheal medication. If the patient reports constipation, the physician may prescribe polyethylene glycol (PEG) or fiber. Some physicians even prescribe antidepressants to patients with FBDs, especially when a patient reports pain. Non-medical treatments include dietary recommendations, nutritional supplements, and psychotherapy [35]. Patients often turn to these "alternative" therapies if they want to approach their symptoms without pharmaceuticals or if they experience negative medication side effects [175]. See Table 6 for a summary of IBS interventions. Interventions for IBS vary by the predominant symptom. For example, patients with IBS-C are often recommended to take fiber supplements while patients with IBS-D can sometimes have exacerbation of symptoms with high amounts of added fiber [176].

Since primary care physicians and gastroenterologists have limited time to spend with patients on nutrition or psychological-based counseling, there is an opportunity for other healthcare providers to offer alternative treatments. Integrative medicine (IM) is a medical specialty that emphasizes nutrition-based therapies [164]. The IM clinic at The University of Kansas (KU) – an academic medical center – specializes in nutrition-based treatments and often sees patients with gastrointestinal complaints. Thus, patients from KU IM were the ideal population to study alternative treatments for FBDs. This study aimed to describe the types of interventions for FBDs used by practitioners at an integrative medicine clinic at an academic medical center.

Table 6: Conventional and Integrative interventions for IBS.

	Conventional Therapies*	Integrative Therapies (Complementary, Alternative and Nutritional)**
IBS (general)	Pharmacological Therapies • Antibiotics (e.g. Rifaximin) • 5-HT_3 antagonist (e.g. Alosetron) • Antidepressants (TCAs and SSRIs) • Antispasmodics • Laxatives (e.g. PEG)	Mind-Body Interventions • Cognitive Behavioral Therapy • Gut-directed hypnotherapy Biologic and Nutritional Therapies • Elimination diets • Probiotics Dietary Supplements • Prebiotics and synbiotics • Fiber • Peppermint oil • L-glutamine • Zinc • Melatonin • Iberogast Other therapy • Cromolyn sodium
IBS-D	• Opioid agonists • Diet (Gluten-free, Low FODMAP) • Bile salt sequestrants • Probiotics • Antibiotics • 5-HT_3 antagonists • Mixed opioid agonists/antagonists	None specific to IBS-D
IBS-C	• Psyllium • PEG • Chloride channel activators • Guanylate Cyclase C agonists (e.g. Linaclotide) • Lubiprostone	None specific to IBS-C

Abdominal Pain	• Smooth muscle antispasmodics • Peppermint oil • Tricyclic antidepressants • SSRIs • Chloride channel activators • Guanylate cyclase C agonists • 5-HT_3 antagonists	Primarily in pediatrics: hypnosis, yoga, acupuncture, massage, guided imagery, biofeedback, and distraction.

*Modified from Lacy 2016 and Chang 2014 [14 177]

**IBS interventions based on reviews by Wald & Rakel 2008 and Mullin 2014 [33 178], Abdominal pain interventions based on review by Friedrichsdorf 2016 [179].

Methods

This study was conducted at KU IM as a retrospective chart review to determine how IM practitioners treat FBDs. Patients' charts were selected for the study based on the following inclusion and exclusion criteria (Table 7).

Patients

A total of 547 charts were screened for fit to study criteria. Patient charts were identified for inclusion in the study if the patient was diagnosed with any Functional Bowel Disorder (e.g. IBS, Functional Bowel Abnormality, Functional Constipation, etc.). Seventy-five patients fit study criteria (see Table 7 for inclusion/exclusion criteria). Based on initial diagnosis by integrative medicine practitioners (MD, PA, APRN), patients were given 1 of 10 different diagnoses (see Table 8). The initial 10 diagnoses included: IBS, IBS-D, IBS-C, IBS-M, FBD, Functional Disorder of Intestine, FBD-C, Irritable Bowel, Functional Bowel Abnormality, and Functional Diarrhea. A board-certified gastroenterologist reviewed all records and determined the final diagnosis based on the Rome IV diagnostic criteria, physician documentation, and patient-reported symptoms. The criteria for diagnosis were presence or absence of pain and presence or absence of constipation, diarrhea, or bloating. The 6 final diagnoses included IBS-C,

IBS-D, IBS-M, Functional Diarrhea (FD), Functional Constipation (FC), and Functional Bloating (FB) (See Table 9 below). Table 10 shows the patients' predominant symptom pattern irrespective of pain, and thus can be characterized with the following symptom patterns: 1) constipation, 2) diarrhea, 3) alternating or mixed symptomatology or 4) bloating. One of the patients who was initially identified for study inclusion was determined not to fit Rome Criteria IV for any FBD. That patient was excluded from the study. The remaining 74 patients were included for final study analysis.

Table 7: Study inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• 21-89 years of age • Diagnosed with "functional bowel disorder" and/or "irritable bowel syndrome" and/or "functional dyspepsia" • Has attended 3 or more appointments at KU IM with a "provider" (medical doctor, advanced practice registered nurse, physician assistant or registered dietitian) • Third follow up on or before May 1, 2016	• Only consultation at KU Medical Center was with a Registered Dietitian (likely no medical diagnoses in the chart) • Patient has attended fewer than 3 appointments

Table 8: Diagnoses in patient's medical record

Diagnosis	Number of patients diagnosed*
IBS	27
IBS-D	9
IBS-C	7
IBS-M	5
FBD	13
Functional disorder of intestine	13
FBD-C	5
Irritable bowel	1
Functional bowel abnormality	1
Functional diarrhea	1
Total Diagnoses	82*

* The total number of patient diagnoses is greater than 74 because some patients were given multiple FBD diagnoses.

Table 9: Diagnoses by Gastroenterologist

Diagnosis	Number of patients
IBS-C	23
IBS-D	19
IBS-M	14
Functional Constipation	11
Functional Bloating	4
Functional Diarrhea	3
Total Diagnoses	74

Table 10: Symptom pattern irrespective of pain

Predominant symptom	Number of patients
Constipation	34
Diarrhea	22
Mixed (Alternating diarrhea/constipation)	14
Bloating	4
Total	74

Retrospective Chart Review

This study was a retrospective chart review to describe interventions for patients with FBDs at an IM clinic at an academic medical center (KU IM). A patient chart was included in the study if he or she was diagnosed with a FBD. Once a patient was selected for study inclusion, the patient's chart was reviewed to characterize the interventions recommended to the patient. The "intervention appointment" was defined as the appointment that followed the initial or "baseline" appointment when the practitioner reviews lab results with the patient and makes a treatment plan or "intervention". The intervention might include recommendations from a diagnosing healthcare provider (provider) such as a medical doctor (MD), a nurse practitioner (APRN), or a physician assistant (PA) and/or a registered dietitian-nutritionist (RDN). Both the provider and RDN interventions were included if the appointments were within 6 months of each other.

The intervention was recorded, reviewed and coded to determine if the provider had recommended that the patient follow one of several interventions. Initially, 38 total interventions were identified, and subsequently collapsed into 9 intervention categories. The 9 categories included 1) elimination diet, 2) vitamin or mineral supplementation, 3) magnesium

supplementation, 4) GI-related supplement (including probiotic, digestive enzyme, betaine hydrochloric acid), 5) fermented foods, 6) water (hydration), 7) non-diet lifestyle modification (physical activity, stress management), 8) referral (non-RDN), and 9) GI-related prescription. Table 11 shows a summary and descriptions of the 9 categories of IM interventions for FBDs assessed in this study.

After the 9 IM intervention categories were defined, each patient's intervention appointment(s) were tallied for the intervention(s) he or she received. Once all charts were reviewed, totals for each of the 9 categories of integrative intervention were compiled to determine which interventions were most- and least-often recommended to IM patients.

Table 11: Summary and descriptions of the possible integrative interventions for FBDs used in this study population. IM: integrative medicine; RDN: registered dietitian-nutritionist; MD: medical doctor; APRN: advance practice registered nurse; PA: physician assistant.

IM intervention categories for treatment of Functional Bowel Disorders	Description of Intervention
Elimination Diet	MD, APRN, PA or RDN recommended that a patient eliminate a certain food or food group or to see a dietitian for this therapy. Example: recommend that a patient eliminate gluten, casein and eggs for a certain number or weeks to determine if symptoms resolve or improve.
Vitamin or mineral supplementation	MD, APRN, PA or RDN recommended that a patient start or continue taking any kind of vitamin or mineral supplement
Magnesium supplementation	MD, APRN, PA or RDN recommended that a patient start or continue taking magnesium.
GI-related supplementation (probiotic, digestive enzyme, betaine hydrochloric acid)	MD, APRN, PA or RDN recommended that a patient start or continue taking a probiotic, digestive enzyme or betaine

	hydrochloric acid (betaine HCl)
Fermented foods	MD, APRN, PA or RDN recommended that a patient consume fermented foods (example: sauerkraut).
Water (hydration)	MD, APRN, PA or RDN recommended that a patient increase water intake.
Lifestyle modification (non-diet: physical activity, exercise, stress management)	MD, APRN, PA or RDN recommended that a patient engage in physical activity or practice stress management
Referral (not including referral to RDN)	Referrals included any healthcare referral that was not a referral to an RDN (since RDN interventions were included in the integrative intervention data collection).
GI-related prescription	MD, APRN or PA prescribed a medication for a patient.

Results

Patients

Sixty-three (85.1%) of the patients were women. The mean age of patients at their baseline visit to KU IM was 50.8 years old (std. dev. 12.8 years) with a range between 22 and 80 years. The main reason patients reported coming to KU IM (either reported by the patient in paperwork or provider in the medical note) was for GI-related complaints in 33 of the 74 (44.6%) of patients in this study. The next most common reason for visiting was for pain-related issues (27%), hormone problems (24.3%), fatigue or energy issues (18.9%) and overall health, disease-prevention or wellness (16.2%).

Interventions at Clinic Appointments

The most common intervention recommended by IM providers was to follow an elimination diet. The recommendation was made to patients at 103 (78.6%) of the 131 total patient appointments. The second most common recommendation was vitamin or mineral supplements, recommended at 83 of 131 patient appointments (63.4%). Providers or RDNs recommended that patients take GI-related supplements (digestive enzymes, probiotics and/or betaine HCl) 48.9% of the time. A provider or RDN suggested magnesium supplementation at 45.0% of patient appointments. The next most common interventions for FBD patients were non-diet lifestyle interventions (32.1% of appointments), water drinking (29.0%), non-dietary referral (25.2%), and consumption of fermented foods (16.0%). GI-related medications were prescribed at 32.9% of appointments (24 out of 73 patient appointments with providers since RDNs are unable to prescribe medications.). See Table 12 for a summary of intervention data.

Since patients of KU IM seek consultations for more issues than gastrointestinal complaints, the interventions often involved recommendations that were not directly related to the GI tract. For example, some providers suggested that patients follow a detoxification program, eat organic foods, drink filtered water or take hormones. These interventions were collected but not included in the summary of interventions for FBD in this study since they were unrelated to FBD treatment.

Table 12: Frequency of recommended interventions to patients with FBDs.

Intervention	Frequency of recommendations (out of 131 total patient visits) n (%)
Elimination diet (% of 131 total patient visits)	103 (78.6%)
Vitamin and/or mineral supplementation (% of 131 total patient visits)	83 (63.4%)
GI-related supplementation (% of 131 total patient visits)	64 (48.9%)
Magnesium supplementation (% of 131 total patient visits)	59 (45.0%)
Lifestyle modification (non-diet) (% of 131 total patient visits)	42 (32.1%)
GI-related prescription (of 73 total patient visits)	24 (32.9%)
Water (hydration) (% of 131 total patient visits)	38 (29.0%)
Referral (not including referral to RDN) (% of 131 total patient visits)	33 (25.2%)
Fermented foods (% of 131 total patient visits)	21 (16%)

Interventions by FBD Diagnosis

Interventions for each diagnostic subtype are reported in Table 13 and include recommendations made by providers (MD, APRN, PA) and/or RDN. When analyzed by patients receiving any FBD diagnosis (n=74), the most common intervention was vitamin or mineral supplementation (94.6% of study patients) with the next most common intervention being an elimination diet (87.8% of patients) followed by magnesium and GI supplements (74.3% each), water intake (44.6%), non-diet lifestyle interventions and non-dietary referrals (43.2% each), and least-often recommended were prescription medications (37.7%).

Table 13: Frequency of therapies recommended for all patients with FBDs ("overall") in the study and by diagnosis.

	Overall FBD (n=74)	IBS-C (n=23)	IBS-D (n=19)	IBS-M (n=14)	FC (n=11)	FB (n=4)	FD (n=3)
Elimination Diet	87.8% (65/74)	82.6% (19/23)	94.7% (18/19)	85.7% (12/14)	100% (11/11)	50% (2/4)	100% (3/3)
Vitamin or Mineral Supplementation	94.6% (70/74)	95.7% (22/23)	89.5% (17/19)	85.7% (12/14)	90.9% (10/11)	100% (4/4)	100% (3/3)
Magnesium	74.3% (55/74)	78.3% (18/23)	73.7% (14/19)	71.4% (10/14)	81.8% (9/11)	50% (2/4)	66.7% (2/3)
GI Supplement	74.3% (55/74)	69.6% (16/23)	63.2% (12/19)	78.6% (11/14)	100% (11/11)	100% (4/4)	66.7% (2/3)
Fermented Food	21.6% (16/74)	26.1% (6/23)	21.1% (4/19)	28.6% (4/14)	9.1% (1/11)	25% (1/4)	0% (0/3)
Water	44.6% (33/74)	43.5% (10/23)	36.8% (7/19)	50% (7/14)	54.5% (6/11)	25% (1/4)	100% (3/3)
Non-Diet Lifestyle	43.2% (32/74)	43.5% (10/23)	36.8% (7/19)	42.9% (6/14)	54.5% (6/11)	25% (1/4)	100% (3/3)
Referral	43.2% (32/74)	47.8% (11/23)	42.1% (8/19)	42.9% (6/14)	36.4% (4/11)	50% (2/4)	33.3% (1/3)
GI-related Prescription Medication	37.7% (26/69)	43.5% (10/23)	35.3% (6/17)	38.5% (5/13)	33.3% (3/9)	25% (1/4)	33.3% (1/3)

Frequency of recommendation of various types of elimination diets.

Practitioners at KU IM recommended that 65 of the 74 total patients (87.8%) follow an elimination diet. Of these 65 patients told to follow an elimination diet, 59 patients (90.8%) were instructed to eliminate gluten and/or wheat, 52 (80%) to eliminate dairy and/or casein, 28 (43.1%) were told to avoid eggs, and 22 (33.9%) were told to avoid soy. KU IM practitioners

suggested that 25 patients (38.5%) follow a grain-free diet (e.g. wheat, rye, barley, corn, oats, rice, etc.). If you combine the patients who were told to avoid gluten and/or grains (which would also include gluten), then 63 patients (96.9%) were told to avoid gluten (whether directly or via grain elimination). In other words, 96.9% of patients who were told to follow an elimination diet were instructed to eliminate gluten.

Table 14: Elimination diet recommendations by diagnosis and the specific food(s) providers recommended that patients eliminate.

Specific food(s) to be eliminated	Overall FBD n=65/74 (87.8%)	IBS-C n=19/23 (82.6%)	IBS-D n=19/20 (95%)	IBS-M n=12/14 (85.7%)	FC n=10/10 (100%)	FB n=2/4 (50%)	FD n=3/3 (100%)
Gluten	60/65 (92.3%)	17/19 (89.5%)	19/19 (100%)	11/12 (91.7%)	10/10 (100%)	2/2 (100%)	3/3 (100%)
Grains	25/65 (38.5%)	8/19 (42.1%)	5/19 (26.3%)	7/12 (58.3%)	4/10 (40%)	0 (0%)	1/3 (33.3%)
Gluten and/or Grains	64/65 (98.5%)	18/19 (94.7%)	19/19 (100%)	12/12 (100%)	10/10 (100%)	2/2 (100%)	3/3 (100%)
Dairy and/or casein	53/65 (81.5%)	16/19 (84.2%)	15/19 (78.9%)	11/12 (91.7%)	6/10 (60%)	2/2 (100%)	3/3 (100%)
Soy	23/65 (35.4%)	9/19 (47.4%)	4/19 (21.1%)	5/12 (41.7%)	3/10 (30%)	1/2 (50%)	1/3 (33.3%)
Egg	28/65 (43.1%)	8/19 (42.1%)	9/19 (47.4%)	7/12 (58.3%)	3/10 (30%)	1/2 (50%)	1/3 (33.3%)
Other foods	48/65 (73.8%)	12/19 (63.2%)	14/19 (73.7%)	11/12 (91.7%)	6/10 (60%)	2/2 (100%)	3/3 (100%)

FBD, functional bowel disorder; IBS, irritable bowel syndrome; IBS-C, constipation-dominant IBS; IBS-D, diarrhea-dominant IBS; IBS-M, mixed type IBS; FC, functional constipation; FB, functional bloating; FD, functional diarrhea.

Discussion

IM "care plans" (referred to here as "interventions" or "therapies") have been described by the 2012 Bravewell report ("Integrative Medicine in America: How Integrative Medicine Is Being Practiced in Clinical Centers Across the United States") [164]. The Bravewell report was a study of 29 IM clinical centers across the U.S. and described IM use in the U.S. Per the Bravewell report, lifestyle interventions include recommendations for diet, exercise, provision of

clean air and water, eliminating toxins from home and work environments, and stress reduction. Sixty-two percent of US IM centers include lifestyle interventions in their care plans. Based on our study, 91.9% (68 of 74) patient appointments at KU IM resulted in recommendations for lifestyle interventions. Based on my findings, I created a KU Integrative Medicine Care Algorithm (see Appendix B).

Although others have described IM therapies for gastrointestinal disease (including IBS), diet-related interventions outside of supplementation (peppermint oil, ginger, probiotics and others) have seldom been described [175]. Thus, this study provides evidence for the use of therapeutic diets (specifically elimination diets) to address FBDs.

Our study demonstrates the frequent use of dietary and nutrition-based interventions by IM providers and RDNs at an academic medical center. Previous evidence by Zar [180] and Drisko [91] suggest that elimination diets based on IgG food sensitivity testing are effective to alleviate GI symptomatology and improve quality of life. A small study (n=21) of patients with IBS and migraine had significantly lower symptoms of both conditions following elimination diet [181].

This academic IM clinic less frequently used some of the more cited FBD interventions like peppermint oil, melatonin, and/or iberogast [33]. More frequently, KU IM practitioners recommended probiotics to patients. Despite efficacy of some integrative therapies (i.e. peppermint oil, fiber supplements, mind-body therapies (e.g. CBT, prebiotics, l-glutamine, zinc, melatonin, iberogast, cromolyn) [33], some available therapies were not recommended to patients in this study population. Mindfulness is another approach that, when taught to patients,

may lessen the severity of IBS symptoms [182]. This suggests not all evidence-based options available to providers at this academic IM clinic were utilized in recommendations.

The interventions described in this study are a glimpse into the total care process at this academic medical center IM clinic. Since IM takes a holistic approach to health, there are often several visits for each client, at which several therapy recommendations are made. Along those lines, interventions in this study may seem falsely comprehensive since we included interventions from both RDNs and other providers' (MD, PA, APRN).

The conclusions from this study are limited to a single IM clinic. Several different approaches to FBDs are available, and each IM clinic may practice differently [33], especially when IM practices have different provider types; if a clinic did not have RDNs, we might assume that dietary interventions would be used less frequently. Interventions from this one clinic may not be representative of other academic medical center IM clinics.

Per the Bravewell Collaborative, the health conditions for which IM treatments are the most clinically successful, include, in descending order: chronic pain (75%), gastrointestinal disorders (59%), depression/anxiety (55%), cancer (52%) and stress (52%). Thus, based on the effectiveness of IM treatments of gastrointestinal disorders, the patients from this study who sought help for GI complaints were likely to find the interventions were effective. A practical next-step to investigate would be to measure the efficacy of these interventions.

Conclusions & Future Directions

IM providers at this academic medical center most often recommended that FBD patients follow an elimination diet and/or take dietary supplements. The most common food category recommended to eliminate was gluten, followed by dairy. There is an opportunity for IM

providers to consider additional approaches, like peppermint oil or other evidence-based, alterative approaches to FBDs. Providers in this clinic widely suggested lifestyle-based interventions to patients, which are low-risk approaches to address FBD symptoms. A logical next step would be to measure the efficacy of these IM interventions.

CHAPTER 4

EFFICACY OF TREATMENT OF FUNCTIONAL BOWEL DISORDERS IN AN INTEGRATIVE MEDICINE CLINIC

ABSTRACT

Background Functional bowel disorders (FBDs), including irritable bowel syndrome (IBS) and others, are complex conditions that, as a result, are difficult to treat. Alternatives to medical interventions are ideal because IBS patients are a burden on physicians' time and healthcare spending. **Aim** The goal of this study was to determine the efficacy of alternative, lifestyle interventions for patients with FBDs. **Methods** Since integrative medicine (IM) specializes in alternative and lifestyle interventions, we performed a retrospective chart review in an IM clinic at an academic medical center to determine whether patients with FBDs had improvement in symptoms following IM interventions. We measured improvement using a medical symptoms questionnaire (MSQ) that is regularly used to measure symptom change in IM clinics. **Results** Digestive tract symptoms measured by the MSQ improved significantly in patients with FBDs following IM intervention. The mean pre-intervention MSQ Digestive Tract subtotal was 10.2 (s.d. 5.4) and the mean post-intervention score was 7.2 (s.d. 5.2). For FBD patients, the average digestive tract symptom score change was -3.0 ($p<0.0000001$). The majority of patients received nutrition-related interventions (specifically dietary supplements and elimination diet recommendations). **Conclusions** Patients in an IM clinic had improved digestive tract symptoms scores following IM intervention. Nutrition-based interventions were the primary intervention recommended by IM providers. Thus, nutrition-based interventions may be a viable intervention for primary care physicians and gastroenterologists who lack time for FBD patients. These providers can refer patients to Registered Dietitian-Nutritionists (RDNs) skilled in implementing elimination diets.

INTRODUCTION

Functional bowel disorders (FBDs) are a group of conditions that includes irritable bowel syndrome (IBS), functional bloating (FB), diarrhea (FD), functional constipation (FC), and unspecified functional bowel disorders (FBD-U) [61]. FBDs are not life-threatening conditions, but they negatively impact patients' quality of life [62]. FBDs are diagnosed based on patient-reported gastrointestinal (GI) symptoms despite a lack of physically identifiable etiology. IBS is the most common FBD. Patients with IBS report pain and their symptoms are related to defecation or a change in bowel habits. IBS symptoms are characterized by either constipation-dominance (IBS-C), diarrhea-dominance (IBS-D), mixed symptomatology (IBS-M), or are unclassified (IBS-U) [14]. IBS has both complex pathophysiology (also, not fully understood) and treatment [63]. Less common FBDs are FB, FD, and FC; these patients experience similar changes in bowel habits (constipation, diarrhea) or bloating but do not report pain (unlike IBS patients).

Internal medicine and family physicians refer about one third of their IBS patients to gastroenterology specialists [6]. Gastroenterologists report these patients are less ill than other GI patients but that IBS patients require more of their time [6], possibly reflecting some of the psychosocial effects of IBS. Thus, IBS patients pose a time burden on physicians who need to care for more critically ill patients, and alternative forms of care may be warranted.

Horrigan and colleagues [164] describe IM an approach to healthcare that "puts the patient at the center and addresses and environmental influences that affect a person's health" and combines therapies from conventional medicine and complementary and alternative medicine (CAM) [163]. The

Academic Consortium for Integrative Medicine and Health states that "Integrative medicine and health reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic and lifestyle approaches, healthcare professionals and disciplines to achieve optimal health and healing" [165]. One challenge to doctors treating patients with IBS is the importance of the therapeutic relationship between practitioner and patient [183], which is increasingly difficult to develop within the limited time providers have with patients. IM practitioners have significant time with patients to do clinical assessment and rapport-building, and IM healthcare providers can suggest and implement lifestyle interventions for FBD patients [166].

Most patients with IBS report stronger confidence that lifestyle recommendations would help them, but patients adhere more to medication recommendations [11]. Many IM interventions are based on lifestyle changes (e.g. diet, exercise, sleep), so an IM clinic is an appropriate population to study the impact of dietary interventions on persons with FBDs. Patients in an IM setting may be more willing to make lifestyle changes since these patients seek this additional healthcare and often pay out-of-pocket for their care. Thus, the IM clinic at an academic medical center (The University of Kansas (KU) Integrative Medicine) was the ideal setting to study the efficacy of lifestyle interventions in patients with FBDs. The aim of this study was to determine whether interventions for FBD patients at an IM clinic at an academic medical center were effective, based on symptom report and measurement.

METHODS

Patients

This was a retrospective chart review including 74 patients from an integrative medicine clinic at an academic medical center. Inclusion and exclusion criteria are found in Table 15. Patient charts were reviewed starting with May 1, 2016 and moving back in time until 85 subjects had been identified. Patients were included in the study if they were between the ages of 21 and 89 years old and diagnosed with a FBD (e.g. IBS, functional disorder of intestine, functional diarrhea, etc.). The patient must have attended at least 3 appointments at KU IM with a MD, APRN, PA or RDN. Finally, the time between initial completion of the medical symptoms questionnaire (MSQ) and follow up MSQ could not be longer than 18 months. Patients must have completed at least 2 MSQs to be included in the study.

Seventy-four patients fit study criteria, and 57 were included in the final analysis. Seventeen patients were excluded from the study for various reasons. The reasons included: 1) the patient's second MSQ completed at intervention visit, 2) the patient's first MSQ was completed after intervention visit, 3) the patient's second MSQ was blank or unfinished, and other reasons (see Table 16).

Symptom Measurement

To measure the effectiveness of the intervention, a symptom measurement tool was needed. At KU IM, patients are asked to complete a Medical Symptoms Questionnaire (MSQ) for each clinic visit to measure patient-reported symptoms. The MSQ is a clinical and research tool [171-173], organized by body system (e.g. head, nose, digestive tract, energy, emotions, etc.), and the MSQ is used to measure patient-reported symptoms. The MSQ asks patients to rate

symptoms on a scale from 0-4 (0 means the patient never or almost never has the symptom, and 4 means the patient experiences the symptom frequently and the symptom's effect is severe). Although the MSQ has not been validated, it has been used in other research to measure change in patient-reported symptoms over time [172 173]. Lerman and colleagues [172] used the MSQ to detect change over time in the joint/muscle sub-category to measure symptom change related to joint pain and arthritis. We used the MSQ to measure the change in digestive tract symptom severity from baseline to follow-up.

Table 15: Study inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• 21-89 years of age • Diagnosed with "functional bowel disorder" and/or "irritable bowel syndrome" and/or "functional dyspepsia" • Attended 3 or more appointments at KU Integrative Medicine with a "provider" (medical doctor, advanced practice registered nurse, physician assistant or registered dietitian) • Followed up within 18 months of intervention consultation • Third follow up on or before May 1, 2016 • Completed at least 2 Medical Symptoms Questionnaires (baseline and follow up after intervention)	• Only consultation at KU Medical Center was with a Registered Dietitian (likely no medical diagnoses in the chart) • Attended fewer than 3 appointments • Follow up longer than 18 months after intervention consultation • Patient completed fewer than 2 Medical Symptoms Questionnaires

Table 16: Rationale for excluding patient charts from final analysis*

Rationale
1. Patient's 2nd MSQ completed at intervention visit (n=6)
2. Patient's 1st MSQ was completed after intervention visit (n=3)
3. Patient's 2nd MSQ was blank/unfinished (n=1)
4. Time between MSQs was greater than 18 months (n=3)
5. No post-intervention MSQ completed (n=1)
6. MSQs not completed correctly (n=3)

*Total patient charts excluded from study (n=17)

Statistical Analysis

To determine the efficacy of IM treatment of FBDs, we compared the change in baseline MSQ digestive tract scores to post-intervention MSQ digestive tract scores. For normal data (IBS patient data), I performed a paired t-test to determine whether the difference between the baseline and post-intervention MSQ Digestive Tract scores were significantly different. For non-normal data (FB, FC, FD patients), I used a Wilcoxon Signed-Rank Test to determine whether the means for the pre- and post-intervention MSQ digestive scores were different.

RESULTS

Fifty-seven patients fit study criteria with an average age of 49.8 ± 13.7 years (range 22-80 years), and 84.2% (n=48) patients were women. Out of the 57 patients who fit study criteria and correctly completed at least 2 MSQs (pre-intervention and post-intervention), 43 (75.4%) of patients had improved digestive tract symptoms scores from baseline to post-intervention, 9 (15.8%) of the patient's symptoms worsened, and 5 (8.8%) patient's digestive tract symptoms remained unchanged.

After testing the data for normality (data normally distributed), we performed a paired t-test. The mean baseline digestive tract score was 10.2 (standard deviation 5.4) and the mean post-intervention score was 7.2 (standard deviation 5.2) (see Table 17). For all FBD patients, the average digestive tract symptom score decreased 3.0 points ($p<0.0000001$). See Figure 5 for graphical representation of overall average digestive tract MSQ score change for all FBD patients.

For patients with IBS (all sub-categories), the mean change in MSQ score was -3.66 (s.d.=4.0), and the change in MSQ scores for all IBS patients from pre- and post-intervention was statistically significant ($p<0.000001$) from a mean of 11.4 (s.d.=5.2) to 7.8 (s.d.=5.1). See Figure 6. Also, see Table 18 for p-values by category: 1) diagnosis, 2) IBS, and 3) dominant symptom. For symptom change by IBS sub-category, symptom improvement was statistically significant for patients with IBS-C ($p=0.005$), IBS-D ($p=0.0004$), and IBS-M ($p=0.02$), while symptom change (per MSQ score) for the other FBDs were not statistically significant. See Figure 9 (IBS-C), Figure 10 (IBS-D), and Figure 11 (IBS-M) for graphical representation of MSQ symptom score change. See Figures 12-14 for change in MSQ GI scores for FB, FD, FC.

Table 17: Mean pre- and post-intervention MSQ scores for all FBD pts

N=57	Pre-Intervention	Post-Intervention
Mean MSQ GI Score	10.2	7.2
Standard Deviation	5.4	5.2

MSQ, medical symptoms questionnaire.

Table 18: Statistical probability of symptom change by diagnosis, IBS and symptom

GI MSQ Score Symptom Change by Diagnosis and Symptom Type			
Diagnosis	Pre-intervention mean GI MSQ	Post-Intervention mean GI MSQ	p-value
FB (n=3)	7.7 ± 5.5	7 ± 9.5	0.75
FC (n=7)	5 ± 2.8	4.1 ± 2.4	0.33
FD (n=2)	6 ± 7.1	5 ±7.1	0.50
All IBS (n=45)	11.4 ± 5.2	7.8 ± 5.1	<0.000001
IBS-C (n=18)	11.4 ± 4.7	8.3 ± 3.5	0.005
IBS-D (n=16)	10.7 ± 5.8	6.0 ± 5.9	0.0004
IBS-M (n=11)	12.4 ± 5.4	9.5 ± 5.9	0.02
Predominant symptom			**p-value**
Diarrhea (n=18)	10.2 ± 5.9	5.9 ± 5.8	0.0003
Constipation (n=25)	9.6 ± 5.1	7.1 ± 3.7	0.004

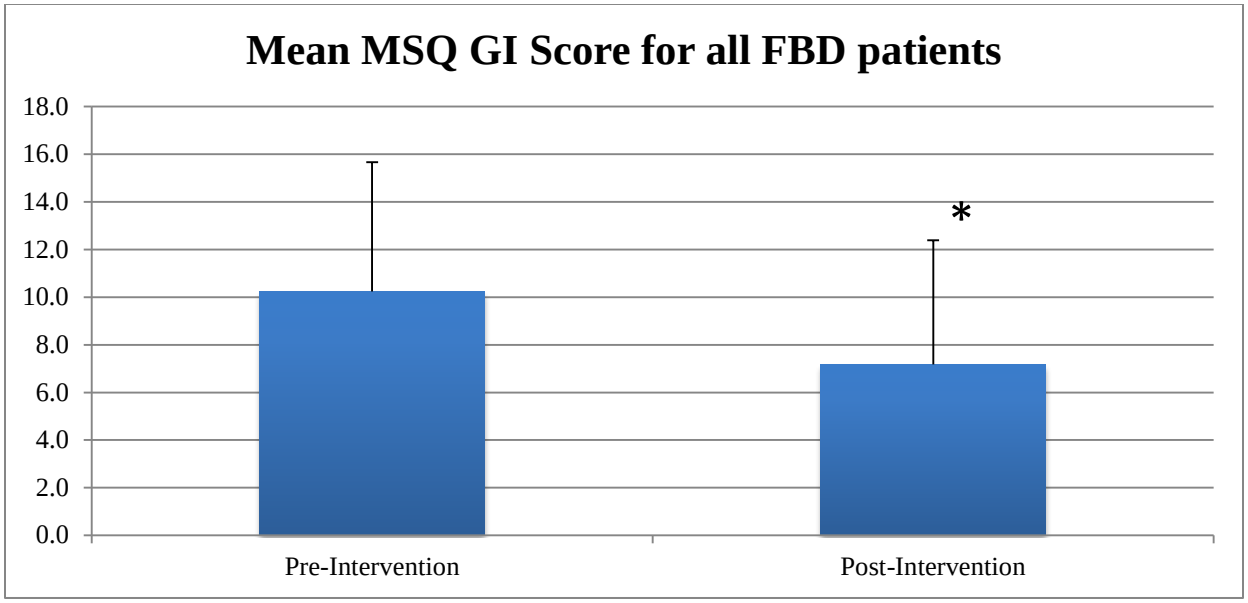

Figure 5: Mean pre- and post-intervention MSQ scores for all FBD patients with error bars. Mean baseline digestive tract score 10.2 (s.d. 5.4), mean post-intervention score 7.2 (sd 5.2). Mean post-intervention MSQ GI score was significantly different than baseline MSQ GI score ($p<0.0000001$). MSQ, medical symptoms questionnaire; GI, gastrointestinal; FBD, functional bowel disorder; Pts, patients.

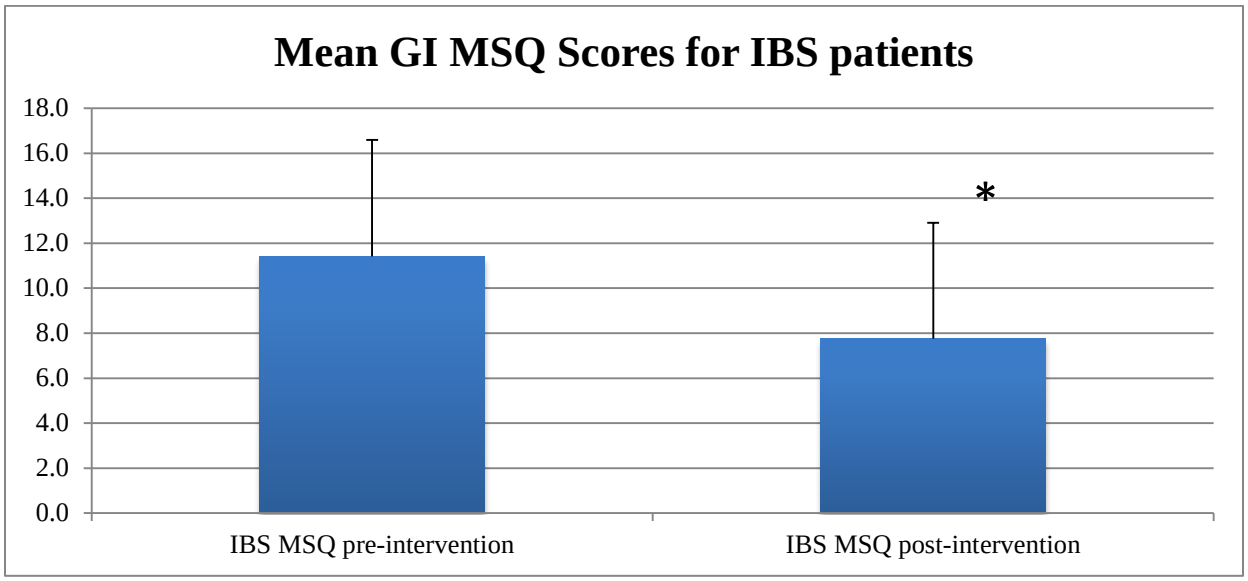

Figure 6: Mean pre- and post-intervention MSQ GI scores for IBS patients with error bars. Mean change in MSQ score was -3.66 (s.d.=4.0), and the change in MSQ scores for all IBS patients from pre- and post-intervention was statistically significant ($p<0.000001$). MSQ, medical symptoms questionnaire; GI, gastrointestinal; IBS, irritable bowel syndrome; Pts, patients.

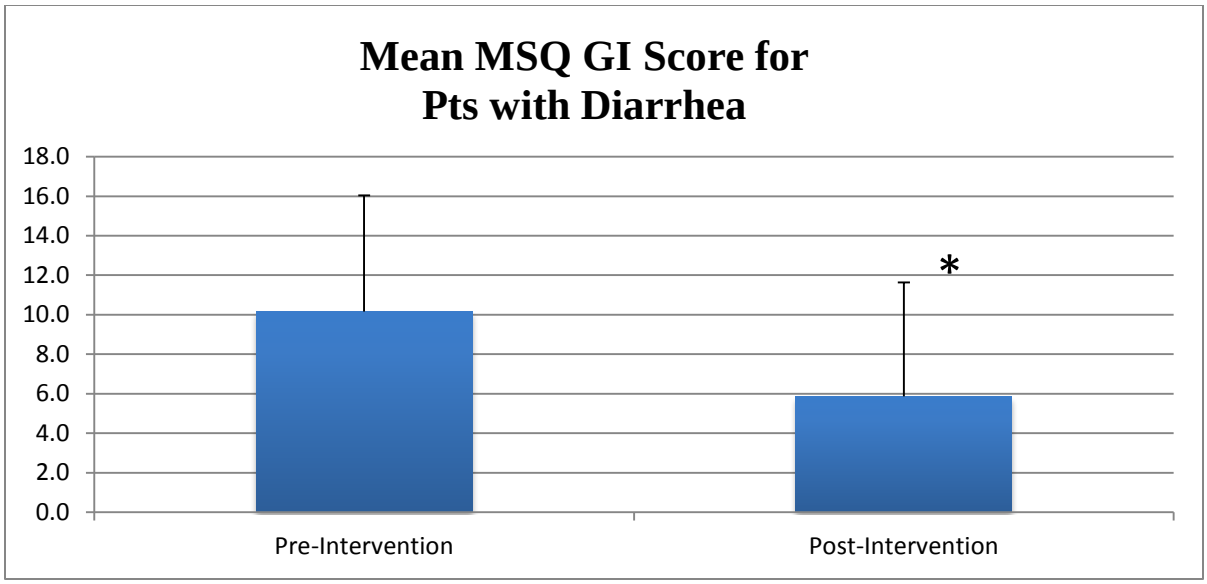

Figure 7: Mean pre- and post-intervention MSQ GI scores for patients with diarrhea with error bars. Mean change in MSQ score was -4.3 (p=0.0003). MSQ, medical symptoms questionnaire; GI, gastrointestinal; Pts, patients.

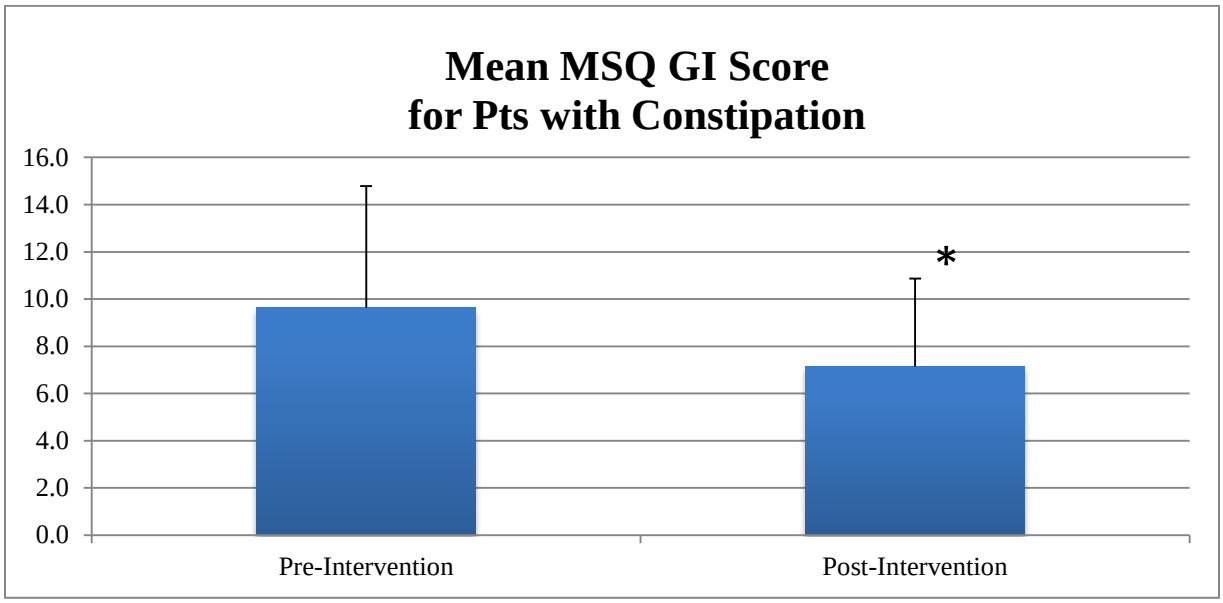

Figure 8: Mean MSQ GI Score for patients with constipation with error bars. Mean change in MSQ score was -2.5 (p=0.004). MSQ, medical symptoms questionnaire; GI, gastrointestinal; Pts, patients.

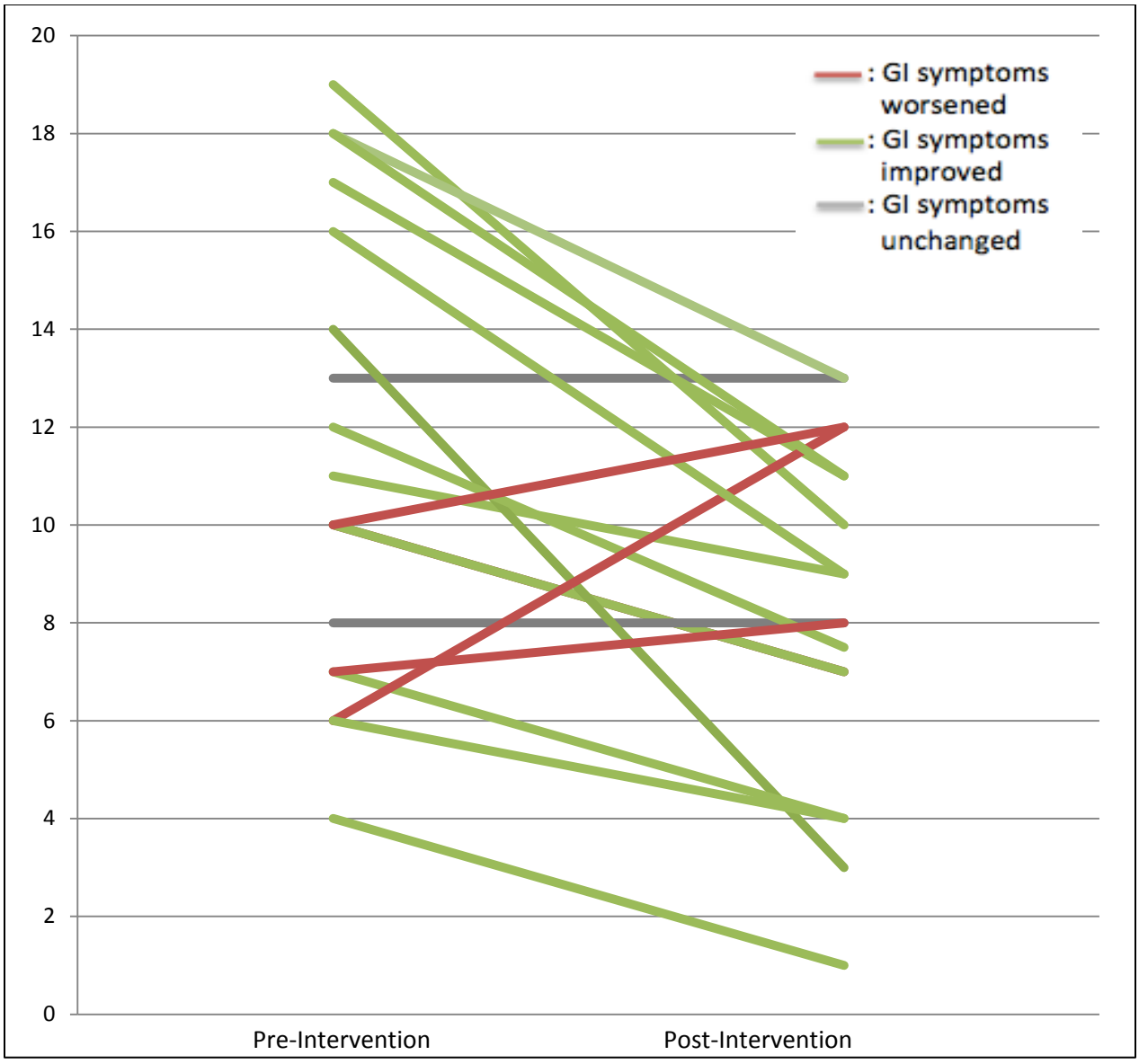

Figure 9: Symptom change of IBS-C patients from pre- to post-intervention MSQs (n=18). Red = symptoms worsened; Green = symptoms improved; Grey = symptoms did not change. IBS-C, constipation-dominant irritable bowel syndrome.

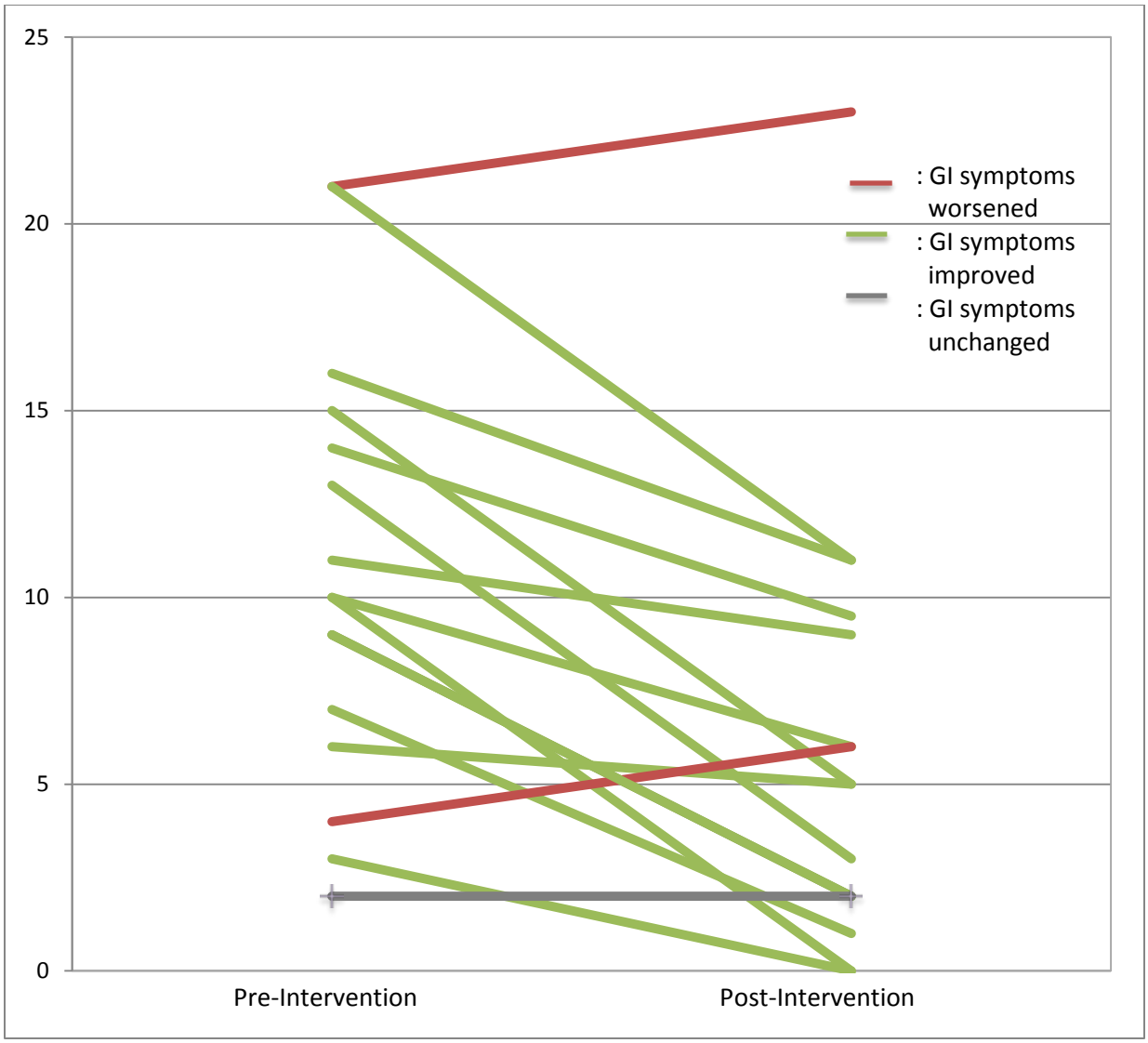

Figure 10: Symptom change of IBS-D patients from pre- to post-intervention MSQs (n=16). Red = symptoms worsened; Green = symptoms improved; Grey = symptoms did not change. IBS-D, diarrhea-dominant irritable bowel syndrome.

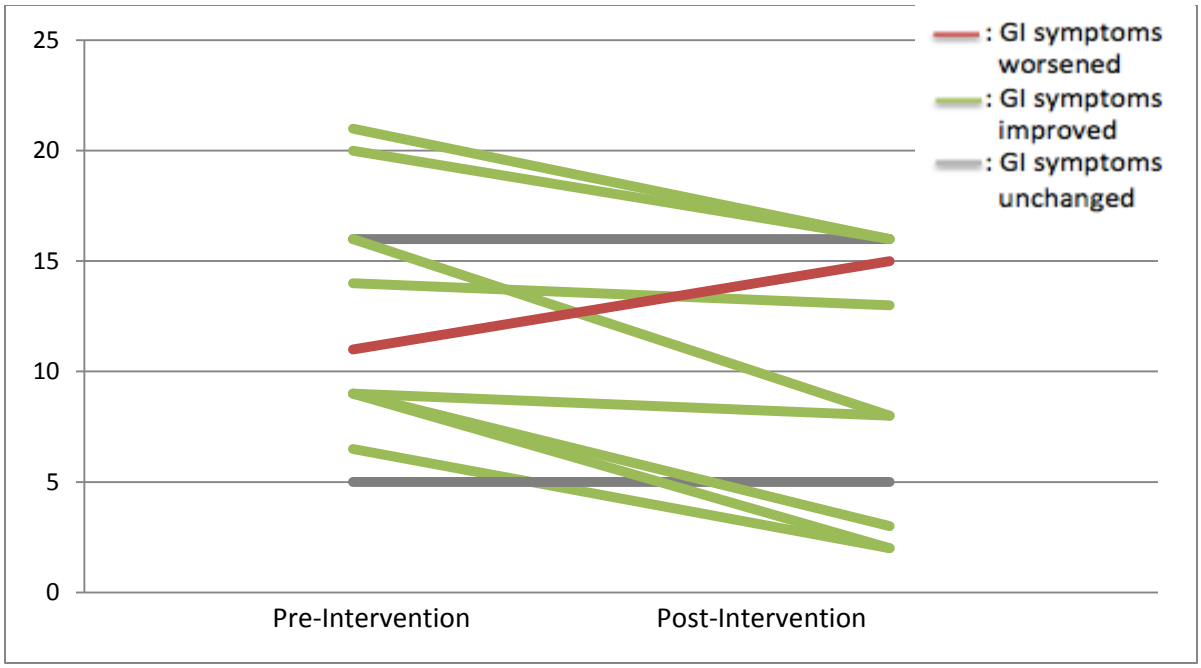

Figure 11: Symptom change of IBS-M patients from pre- to post-intervention MSQs (n=11).

Red = symptoms worsened; Green = symptoms improved; Grey = symptoms did not change. IBS-M, mixed type (alternating diarrhea and constipation) irritable bowel syndrome.

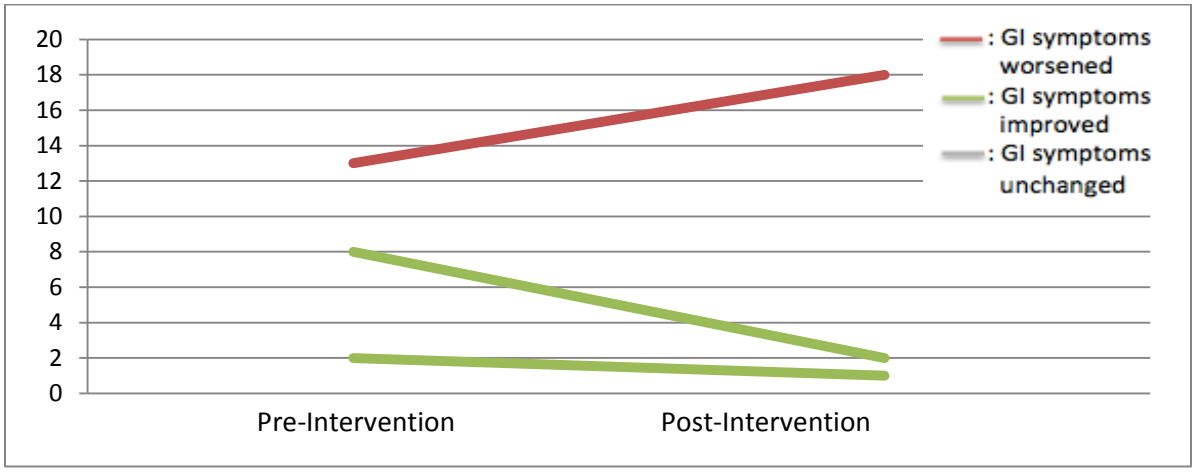

Figure 12: Symptom change of FB patients from pre- to post-intervention MSQs (n=3).

Red = symptoms worsened; Green = symptoms improved.

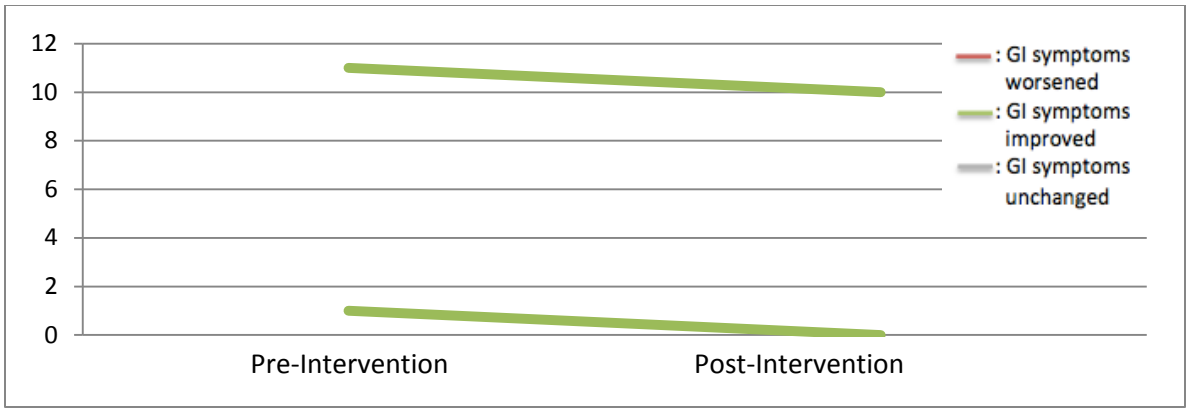

Figure 13: Symptom change of FD patients from pre- to post-intervention MSQs (n=2). Green = symptoms improved.

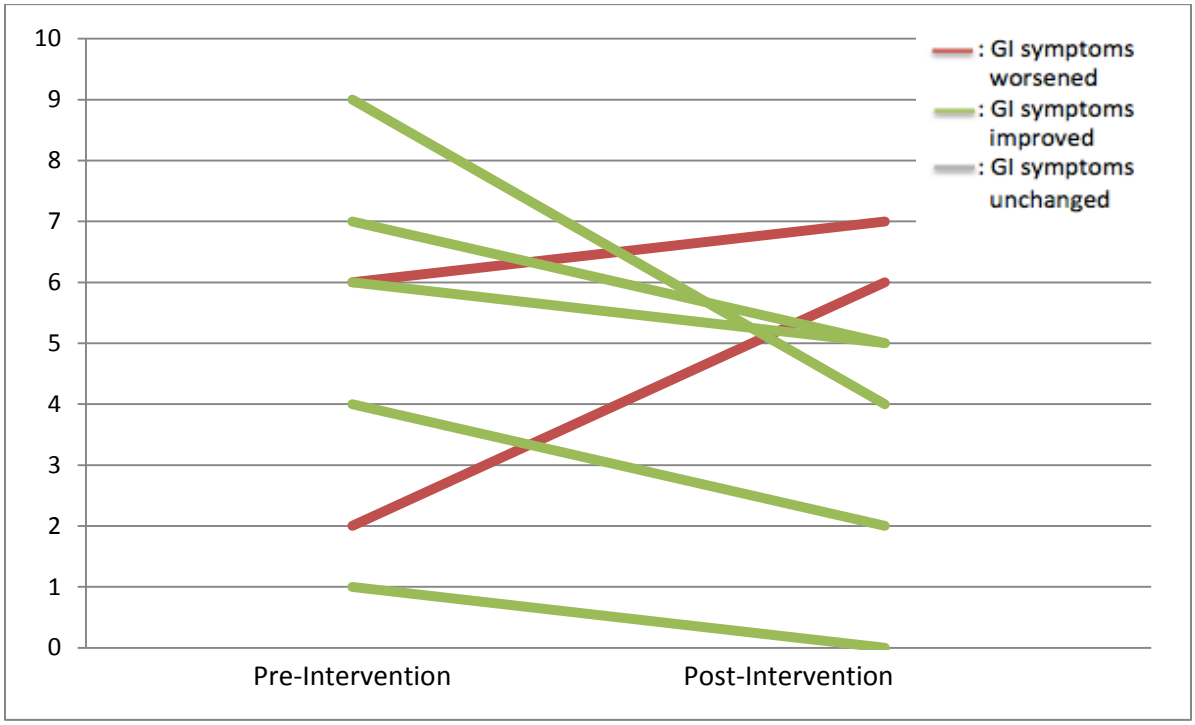

Figure 14: Symptom change of FC patients from pre- to post-intervention MSQs (n=7). Red = symptoms worsened; Green = symptoms improved.

DISCUSSION

Our study suggests that IM interventions for IBS are effective. Whether IM interventions work for other FBDs (FB, FC, FD) remains unknown, we found too few subjects with these

diagnoses to determine efficacy. One of the most common interventions was an elimination diet. The most common foods to be eliminated were (in descending order): gluten and/or grains, gluten (alone), dairy or casein, and "other foods" (e.g. beef, pork, caffeine, and others). Interestingly, few providers specifically recommended the low FODMAP diet, which is one of the more cited dietary interventions for IBS patients. Our data suggest that a less-strict elimination diet may be equally effective to the low FODMAP diet in patients with IBS. Others who have recommended elimination diets based on IgG food sensitivity testing have found benefits for their patients [91 180].

Since this study was retrospective in nature, we were able to assess the way that KU IM treats FBDs without manipulating the methods that practitioners would naturally use in their interventions. On the other hand, we were unable to control for variables including dietary interventions and completion of MSQs. We also had few patients with non-IBS FBDs (i.e. FB, FD, FC) so we cannot draw conclusions from non-IBS patient data.

Some possible explanations for patients with refractory symptoms include: a) patients with early life trauma are known to have increased IBS, b) patients not following recommended therapies, c) extensive nature of the interventions may have been overwhelming to the patient who ultimately does not follow any recommendations, d) expense of carrying out the recommended intervention(s) (although this explanation may be less likely since the patients in this clinic pay out-of-pocket for this care), and e) complications of IBS not understood such as psychosocial-related symptoms and "rectal perceptual thresholds" [184].

Spiller [41] suggests that the ideal length of any IBS clinical trial is longer than 12 weeks since the placebo effect diminishes at 12 weeks. Our results are compelling because the average

time between baseline MSQ and follow up MSQ was 8.75 months (about 35 weeks), which is well beyond the point that period of time [41].

Seventy-six percent of my study patients had improvement in their GI MSQ symptoms scores from pre- to post-intervention. The majority (87.8%) of patients received the recommendation to follow an elimination diet and an even greater number were told to take a vitamin or mineral supplement (94.6%).

For future research, I would use the IBS Satisfaction with Care (IBS-SAT) [162] questionnaire to determine whether patients' satisfaction differs between conventional and integrative IBS care.

Meta analyses suggest peppermint oil, Chinese herb preparations (specifically preparations made in the United States), soluble fiber, probiotics, mind-body therapies (cognitive behavioral therapy (CBT) and hypnosis), and variable evidence for acupuncture may be effective in treating IBS symptoms [175]. Additionally, a clinical review from the Journal of the American Medical Association [183] suggests that holistic, lifestyle interventions are appropriate for patients with IBS. Thus, studying the effectiveness of dietary interventions among a population of patients in an integrative medicine clinic is appropriate.

The effectiveness of interventions at KU IM may have been enhanced by defining "interventions" to include both recommendations from the diagnosing provider (MD, PA, APRN) and the RDN. It would be interesting to see the effect that additional psychological counseling would make on the efficacy of the interventions.

Our results suggest that integrative medical interventions for FBDs appear to be most effective at lowering GI-related symptoms for patients with IBS-D and general diarrhea-dominant symptoms (including both IBS-D and FD).

There were several limitations to this study. Patients were primarily Caucasian and able to afford healthcare outside of what is covered by Medicare, Medicaid and/or insurance. Thus, the results may not be generalizable. Secondly, we did not determine which patients became Rome IV criteria-negative after the intervention. Another limitation of the study is the degree to which we can be certain that the patients complied with the intervention. However, it would be reasonable to assume that the patients in this clinic might be more motivated to follow recommendations because they chose to pay for these services out-of-pocket. Another limitation is that the MSQ is not a validated tool and it is not specific to IBS patients. For future studies, I would suggest using the IBS quality of life (IBS-QOL) [185] to more accurately assess the impact on quality of life by these patients' conditions.

The low FODMAPs diet and a traditional IBS diet are both effective at alleviating IBS symptoms [124]. Although this randomized controlled trial by Böhn and colleagues [124] was only a 4-week intervention, this may have been a placebo effect. Our study adds to the evidence that dietary interventions can effectively alleviate IBS symptoms in most patients.

One strength of the study was that KU IM used mostly laboratory testing-based interventions to determine the specific elimination diet (instead of a broad spectrum of foods, like FODMAP foods). In clinics that do not use laboratory testing or in practitioners who do not have access to specialized testing, using a low FODMAP diet appears to be similarly efficacious [186].

CONCLUSIONS

IM interventions for patients with FBDs appear to be effective, especially among patients with IBS. The intervention appears to be most effective among patients with diarrhea-dominant symptoms. With this knowledge, primary care physicians and gastroenterologists should consider dietary interventions as a first-line therapy for patients with IBS. This would be an effective and timesaving approach for these healthcare providers who could refer IBS patients to RDNs to implement dietary interventions [6]. Along those lines, an interdisciplinary approach with multiple interventions over time may be worthwhile to help patients a) understand and follow the interventions and b) address the chronic nature of the condition over time.

CHAPTER 5

MICRONUTRIENT STATUS OF PATIENTS WITH FUNCTIONAL BOWEL DISORDERS IN AN INTEGRATIVE MEDICINE CLINIC

ABSTRACT

Background Patients with functional bowel disorders (FBDs), like patients with irritable bowel syndrome (IBS), may change their diets in attempt to alleviate gastrointestinal (GI) symptoms. In addition, FBD patients may be less able to absorb nutrients from foods due to fast GI motility. These dietary changes and symptoms could increase their risk for micronutrient deficiencies. **Aim** The aim of this study was to determine the status in FBD patients in an integrative medicine (IM) clinic of several micronutrients: vitamins B12, B6, D and minerals magnesium, zinc and copper. **Methods** In a retrospective chart review, we collected existing micronutrient data on FBD patients using various labs (Quest Lab, Lab Corp, and others). **Results** Patients with FBDs at this IM clinic appeared to have adequate micronutrient status except for vitamin D (23% deficient). The majority of patients' vitamin B6 levels were above the reference range, likely due to supplementation. Eighty-five percent of patients were taking nutritional supplements at their baseline visit to the IM clinic. **Conclusions** Patients with FBDs at this IM clinic had adequate micronutrient status and many had elevated vitamin B6 and B12 levels, likely secondary to supplementation prior to IM consultation.

INTRODUCTION

Functional bowel disorders (FBDs) are complex gastrointestinal (GI) conditions that are diagnosed based on patient-reported symptoms rather than physical abnormality. FBDs include several bowel disorders that negatively impact patients' quality of life. There are 6 categories of FBDs: irritable bowel syndrome (IBS), functional bloating, functional diarrhea, functional constipation, unspecified FBDs, and a new category, opioid-induced constipation [14]. IBS is the most common FBD and is defined by patient-reported pain and defecation-related symptoms.

The pathophysiology of FBDs is not fully understood, so FBDs remain relevant and widely studied conditions. Further, patients with FBDs, and especially IBS, may make dietary changes (e.g. eliminate trigger foods) since about two thirds of patients report their symptoms are related to food intake [187]. Specifically, IBS patients say that carbohydrate and fat-rich foods are the most common food-offenders [187].

Since IBS patients are likely to alter their diets, they may be vulnerable to micronutrient deficiencies. However, little is known about micronutrients status in persons with functional bowel disorders (FBDs). Since the primary cause of FBDs is unknown, investigating the micronutrient status of patients with FBDs is a reasonable next step to try to further characterize this population's biochemical make up and FBD pathophysiology.

The body requires micronutrients (vitamins and minerals) to perform countless physiological activities. One common evidence-based intervention for IBS is a diet low in fermentable carbohydrates (fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP)) or the low FODMAP diet (LFD) [125 186 188]. Although studies in the United Kingdom and Norway suggest that patients following an IBS diet are able to meet their macro- and micronutrient needs [189 190], elimination of these or other foods (i.e. elimination/exclusion diets) may contribute to nutritional deficiencies [191]. Additionally, frequent diarrhea, characteristic of diarrhea-dominant IBS (IBS-D) may also put IBS-D patients at higher risk for micronutrient deficiencies. Thus, it is reasonable to suspect micronutrient deficiencies in these patients since FBDs involve food-triggered symptoms, genetic factors, and abnormalities in neurological, immunological, microbiological, and inflammatory aspects of health [19 20 74].

Although little is known about micronutrient levels in relation to FBDs, new evidence suggests the severity of IBS symptoms is inversely related to vitamin D status in British IBS patients and that the majority of people with IBS may have vitamin D deficiency [153].

Magnesium status has not been measured in IBS, but magnesium supplementation may effectively alleviate symptoms of IBS [43]. Comorbidities of IBS have characteristics of magnesium deficiency, including anxiety [156], chronic headache [157], fibromyalgia [158]. It is reasonable to suggest that magnesium deficiency may play a role in patients with both IBS and anxiety. In a population of young (18-20 years old) Japanese women dietetic students (n = 3835), investigators found that water intake and magnesium intake were independently associated with chronic constipation [192]. Mg may be part of the pathophysiology of FBDs, but the mechanism of action remains unknown.

Additionally, magnesium deficiency alters gut microbiota and contributes to anxiety in mice [155]. Magnesium-deficient mice have abnormalities in the hypothalamus pituitary adrenal (HPA) axis, leading to increased anxiety-related behaviors [156]. Since the majority of patients with IBS have anxiety or depression [68], magnesium assessment is justified in patients with FBDs.

Other nutrients may be implicated in the pathogenesis of IBS. In zinc metabolism, specifically, IBS pathogenesis may follow a different course depending on the patient's blood levels of zinc or the amount of fecal zinc excretion [159].

A Swedish study [189] found that IBS patients and the general population both met micronutrient needs, however patients with IBS had significantly higher intake of vitamins E and C, folate, iron and dietary fiber but lower intake of vitamin A, riboflavin, calcium and potassium.

In a study done in Norway, low intake of vitamin B6 was related to severity of IBS symptoms [154]. Patients in the United States with IBS may or may not have similar dietary intakes compared to the general population. The aim of this study was to measure micronutrient levels (vitamins D, B6, B12, and minerals zinc, copper and magnesium) in FBD patients in an integrative medicine clinic at an academic medical center.

METHODS

This study was a retrospective chart review from an integrative medicine clinic at an academic medical center. Patients' charts were selected if the patient had been diagnosed with a functional bowel disorder and fit study criteria. Patients included in the study were between 21 and 89 years old, diagnosed with a FBD, and attended at least 3 appointments at KU IM. See Table 19 for inclusion and exclusion criteria.

Table 19: Study inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• 21-89 years of age • Diagnosed with a FBD (e.g. IBS, functional diarrhea, functional constipation, functional disorder of intestine, and/or functional bowel abnormality) • Has attended 3 or more appointments at KU Integrative Medicine with a "provider" (medical doctor, advanced practice registered nurse, physician assistant or registered dietitian) • Third follow up on or before May 1, 2016	• Only consultation at KU Medical Center was with a Registered Dietitian unless they had been previously diagnosed with a FBD by a diagnosing healthcare provider (i.e. medical doctor, advanced practice registered nurse, physician assistant) • Patient has attended fewer than 3 appointments

FBD, functional bowel disorder; IBS, irritable bowel syndrome; KU, University of Kansas.

Patients/Chart Review

After screening 547 charts for study inclusion and exclusion criteria, 75 patient charts fit study criteria. Subsequently, a board certified gastroenterologist reviewed the records, assessed patient-reported symptoms and used Rome IV diagnostic criteria and determined that one patient did not fit study criteria. That patient was excluded from analysis. The remaining 74 patients were diagnosed with IBS-C (n=23), IBS-D (n=19), IBS-M (n=14), FC (n=11), FB (n=4) or FD (n=3).

Micronutrient analysis

All patients in the study had labs analyzed by one of several different laboratories, including Quest Diagnostics Lab (Quest Lab) (n=26), MedTox Laboratories (n=23), Lab Corp (n=16), NMS Laboratories (n=7), and one of two other local hospital labs (n=2). Micronutrient data from patients included plasma or serum zinc, serum copper, red blood cell (RBC) magnesium, serum vitamin D (25-hydroxy (OH)), plasma vitamin B6, and plasma or serum vitamin B12. Micronutrient values reported using different units of measure were converted so all patients' labs were reported comparably. Patients' baseline micronutrient status was used because it was common for practitioners to recommend supplementation as an intervention.

Laboratory analysis for micronutrients was based on Quest Lab's validated methodology and reference ranges since Quest Lab analyzed most patients' labs (n=26). Quest Labs' reference ranges were also used but were similar to Lab Corp and Mayo Clinic reference ranges. For plasma vitamin B6 (or pyridoxal-5-phosphate or "P5P"), Quest Lab used liquid chromatography/tandem mass spectrometry (LC/MS/MS), and the reference range for adults 18 or older was 2.1-21.7 ng/mL. Quest Lab measured vitamin B12 (cobalamin) via immunoassay,

and the reference range for adults was 200-1100 pg/mL. Vitamin D (25-hydroxy-vitamin D_2 + 25-hydroxy-vitamin D_3 or "25-OH-D") was measured using Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS). The reference ranges for 25-OH-D for adults were 30-100 ng/mL. Zinc was measured via inductively coupled plasma/mass spectrometry (ICP/MS), and the reference range for adults was 60-130 μg/dL. Copper was measured the same way as zinc (ICP/MS) and the reference range was 70-175 μg /dL. Finally, RBC magnesium was measured via ICP/MS with a reference range between 4.0-6.4 mg/dL.

RESULTS

The average age of patients in this study was 50.8 years (std. dev. 12.8 years) with a range between 22-80 years. The majority of patients were women (n=63 or 85.1%). At baseline, 85% of patients (n=63) were taking at least one dietary supplement, 10.8% (n=8) were not taking any dietary supplements, and we were unable to find data on baseline supplementation for 4.1% of patients (n=3).

Out of the 74 patients who fit study criteria, serum zinc and vitamin B12 levels were measured in 74 patients (100%). Copper, RBC magnesium, and vitamin D levels were available in 73 patients (98.6%), and vitamin B6 levels were measured in 71 patients (95.9%).

The mean RBC magnesium level of patients with FBDs at KU Integrative Medicine was 4.9 mg/dL. The mean zinc and copper levels were 79.6 ug/dL and 119 ug/dL respectively. Mean 25-OH vitamin D level was 43.8 ng/mL (median 37.4 ng/mL). The mean vitamin B6 level was 42.2 ug/L (median 22 μg /L) and B12 was 691.1 pg/mL (median 508 pg/mL). See Table 20.

Table 20: Micronutrient blood levels for copper, zinc, vitamin B6, red blood cell magnesium, vitamin B12, and vitamin D.

	Patients, n (%)	Mean level	Standard Deviation	Range	Reference range (Quest Lab)	Mid range
Copper (μg/dL)	73 (98.6%)	**119**	32.0	68-221	70-175 μg/dL	122.5 μg/dL
Zinc (μg/dL)	74 (100%)	**79.6**	15.6	48-144	60-130 μg/dL	95 μg/dL
Vitamin B6 (P5P) (μg/L)	71 (95.9%)	**42.2***	45.5	2.4-250	2.1-21.7 μg/L	11.9 μg/L
Magnesium (mg/dL)	73 (98.6%)	**4.9**	0.9	3.2-8.5	4.0-6.4 mg/dL	5.2 mg/dL
Vitamin B12 (pg/mL)	74 (100%)	**691.1**	429.7	172-2000	200-1100 pg/mL	650 pg/mL
Vitamin D (ng/mL)	73 (98.6%)	**43.8***	20.6	14-112	30-100 ng/mL	65 ng/mL

*median vitamin B6 was 22 μg/L; median vitamin D was 37.4 ng/mL

Most of the patients (between 74 and 94.6%) were within the Quest Lab reference range for each micronutrient measured except for vitamin B6 (49.3%). The percentage of patients within the reference range for vitamin B6 (2.1-21.7 μg/L) was 49.3% (n=35) while 50.7% (n=36) were above the reference range and none were below the reference range. Similarly, 11 patients (14.9%) had vitamin B12 levels above the reference range while only 1 patient was deficient. See Table 21.

Table 21: Micronutrient reference ranges (per Quest Lab) with number and percentage of patients within the reference range, above the reference range and below the reference range.

	Reference Range	Within Reference Range n (%)	> Ref. Range	< Ref. Range	Patients with Micronutrient lab results (n)
Copper	70-175 µg/dL	66 (90.4%)	6 (8.2%)	1 (1.4%)	73
Zinc	60-130 µg/dL	70 (94.6%)	1 (1.4%)	3 (4.1%)	74
Vitamin B6	2.1-21.7 µg/L	35 (49.3%)	36 (50.7%)	0	71
RBC Magnesium	4.0-6.4 mg/dL	67 (91.8%)	2 (2.7%)	4 (5.5%)	73
Vitamin B12	200-1100 pg/mL	62 (83.8%)	11 (14.9%)	1 (1.4%)	74
Vitamin D	30-100 ng/mL	54 (74.0%)	2 (2.7%)	17 (23.3%)	73

DISCUSSION

Results of micronutrient status of patients with FBDs have not been reported previously outside of Tazzyman [153] reporting vitamin D status in IBS patients. Our results suggest that micronutrient deficiency is an unlikely explanation for IBS pathophysiology with the exception of vitamin D deficiency as a possible component [153].

That over half of the patients with vitamin B6 levels above the reference range is likely related to the majority of patients (85%) of KU IM taking dietary supplements before receiving an intervention. With elevated levels of vitamin B6, patients would be told by KU IM providers to decrease vitamin B6 via supplements. The micronutrient with the most overt deficiencies measured was vitamin D_3, which is unsurprising given wide prevalence vitamin D deficiency among Americans [193]. However, our population of IM patients had a lower prevalence of vitamin D deficiency than the general US population (23.3% compared to 41.6%) [193].

Although few of the patients' micronutrient status was deficient, IM clinicians would less likely depend on deficiency (formally outside of reference range) to intervene using supplementation; IM clinicians would likely recommend supplementation when patients' levels were in the lower part of the reference range. Alternatively, measuring micronutrient status in patients at a general primary care or gastroenterology clinics may show different micronutrient results. Micronutrient lab testing is less common in these practices, likely due to unlikely insurance coverage and the practitioners' limited experience with nutritional lab testing and subsequent interventions.

There are several limitations of this study. First, this study was retrospective, so the conclusions we can draw from our findings are limited since we were unable to control for variables, retrospectively. Similarly, the providers in this study did not administer a standard diet. Most providers used laboratory testing to inform the dietary intervention. We did not measure the dietary intake pre- and post-intervention. Thus, our measurement of micronutrient adequacy was exclusively based on micronutrient levels per blood tests.

CONCLUSIONS

Patients with FBDs in this IM clinic predominantly had adequate micronutrient status (within the Quest Lab reference ranges). However, most patients' vitamin B6 levels and several patients' vitamin B12 levels were above the reference range, most likely reflecting that most patients at this clinic were already taking dietary supplements. Several patients were also below the reference range for Vitamin D, but fewer were deficient compared to the general U.S. population. The majority of patients visiting this IM clinic took dietary supplements, which may suggest that these patients would be at lower risk for nutritional deficiency than the general

population. A reasonable next step would be to measure micronutrient status in patients with FBDs who are seen in primary care and/or gastroenterology clinics.

CHAPTER 6

DISCUSSION AND CONCLUSIONS

I. Summary of findings, discussion and conclusions

Treatment of FBDs at KU IM is primarily diet and nutrition-based. The most common intervention for FBD patients by IM practitioners was to recommend that patients take a vitamin or mineral supplement (94.6%) and then to follow an elimination diet (87.8%). Patients were most often suggested to avoid gluten-containing foods and ingredients (92.3%), and when added to suggesting a patient avoid gluten and/or grains, nearly all patients were told to avoid gluten (98.5%). These nutrition-based interventions seemed to contribute to improvement in GI related symptoms. About 75% of FBD patients reported improvement in GI symptoms using the MSQ.

IM interventions appeared to be most effective for diarrhea-predominant FBDs. However, the IM interventions for the any of the FBDs did not appear to differ. This suggests that dietary intervention may be more effective in patients with IBS-D or FD compared to patients with IBS-C, FC, or FB.

Since IBS is a complex condition with various pathophysiological mechanisms, the effectiveness of IM interventions for IBS may be due to the holistic nature of IM. Patients have appointments with providers that often last an hour, so they are able to develop a strong relationship with providers. Additionally, the patient feels their symptoms and experience is validated, and they feel listened to and like the provider believes them. This may have a therapeutic effect, as well. Patients also feel like they have some control over their health, and they can take ownership of the treatment by changing their diet. IM patients are also likely to be patients who would be more skeptical of conventional medical treatment, and they would have a stronger belief in the idea that IM therapies would be more effective.

In addition to the seeming effectiveness of dietary intervention, it is possible that IM patients have improvement in FBD symptoms due to the additional time spent by IM providers. This idea is supported by the fact that patients IBS patients' negative emotions are related to their symptoms and the feeling that their healthcare providers do not believe the reality of their symptoms [161]. One way to address the patients' needs would be that physicians validate the patients' experience and subsequently refer the patient to a RDN who is skilled in administering dietary approaches for FBDs or to an IM clinic that has more time to listen to the patients' stories. There may be a therapeutic nature of listening to the patient.

Although Spiller and colleagues [41] suggest that the placebo effect diminishes after 12 weeks, this is the only suggestion in the literature of the placebo effect in IBS patients. Thus, it is possible that the IM patients' symptoms may have improved due to a placebo effect.

IM patients with FBDs did not appear to have micronutrient deficiencies except for vitamin D deficiency, which was less common than among the general population. That patients had adequate micronutrient status may be due to patients taking nutritional supplements prior to their IM consultation. Although these IM patients were not deficient in micronutrients based on clinical lab reference ranges, providers in an IM clinic would likely intervene with dietary or supplemental recommendations when patients' micronutrient levels were in the lower part of the reference range. If patients are above the reference range, as in the case of vitamin B6, then they would be encouraged to decrease vitamin B6 via supplementation.

Based on the evidence presented in this study, clinicians may feel more confident that dietary interventions may be warranted for FBD patients, and especially for IBS patients. Since

pharmaceutical interventions lack efficacy, are expensive and may come with side effects, dietary interventions are feasible, effective, and safe for these patients.

The clinical significance of micronutrient testing is lacking. Our evidence suggests that micronutrient deficiency is an unlikely explanation for IBS or FBD pathophysiology with the exception of vitamin D as a possible factor [153]. More research may help determine reference and optimal ranges of blood micronutrient levels.

Ideally, both primary care providers and gastroenterologists who see patients with IBS would first validate the patients' experience of their symptoms. Next, since they have limited time, the physician can refer to a RDN who could a) spend time listening to the patients' story and b) lead the patient through an elimination diet or the low FODMAP diet. This would make the most of the relationship between physician and patient and also allow the patient to take an active role in their treatment.

II. Limitations

The proposed study is limited in the conclusions that can be made. Since it was a retrospective chart review (RCR), many limitations are inherent in such a research design. I tried to address as many of the 10 common mistakes of RCRs as published by Vassar and Holzmann [194]. To address these common mistakes, I created well-defined research questions, calculated power to determine the number of charts to review, operationalized as many variables as possible, developed inclusion/exclusion criteria, and addressed ethical considerations of reviewing clinical charts by being reviewed by the human subjects committee at The University of Kansas Medical Center. Limitations that were not addressed in this study are intrerrater

reliability, as I was the only person abstracting data. A nursing student helped with data entry into excel database. I also did not perform a pilot test.

There are other limitations of this RCR. Since all patients in this study were from KU IM, the study population had a self-selection bias. Additionally, the fact that I am a clinician at KU Integrative Medicine poses a research bias. Ideally, a person who is blinded to the study questions would objectively collect data based on an objective procedural manual. Also, the MSQ is not a validated symptom measurement tool; therefore the conclusions that can be drawn from this study are limited.

Patients in an IM clinic are often seeking care because they either have had unsatisfactory outcomes from conventional medical treatment or they hope to find solutions without medical treatment. These patients would more likely be motivated to make dietary and other lifestyle changes than those patients who might seek conventional medical are. Thus, results from this study are not generalizable to the population. However, the results suggest the efficacy of lifestyle interventions for IBS.

III. Future directions

From this investigation, I will begin to describe the current treatment of FBDs in an integrative medical setting and identify key areas to improve practice. I can use the KU Integrative Medicine FBD Care Algorithm to inform future research and methods.

A possible next step would be to look at the microbiota of patients with FBDs and especially those who had worsening or unchanged GI symptoms. Since evidence suggests that IBS patients have altered microbiota compared to people without IBS [195 196] it would be important to investigate.

Another possible research direction would be to consider the combined impact of food elimination with other interventions, like acupuncture, psychotherapy, and supplementation like peppermint oil, medications, or other therapies. We might also investigate which foods are most effective at alleviating FBD-related symptoms, that when eliminated we would continue to meet the patient's nutritional needs.

In a recent Lancet review, Holtmann and colleagues [2] make clear the importance to further characterize the pathophysiology of IBS. Clarification of pathophysiology will allow a transition away from symptom-based approaches to IBS. Mounting evidence for pathophysiology (suggesting organic disease) demonstrates abnormalities in patients' microbiota, serotonin metabolism, bile salt metabolism, post-infectious and chronic infection-related symptoms, diet-induced symptoms, inflammation, and others [2]. When we approach IBS solely based on symptoms (diarrhea, constipation, bloating), we may group and treat patients similarly who actually have heterogeneous pathophysiology. By addressing the physically measurable abnormalities in these patients, we might get closer to a curative versus treatment approach. Measuring the microbiota, food sensitivities, and other nutrition or diet-related aspects of a patient's health may inch us closer to curing IBS instead of merely treating its symptoms.

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APPENDIX

Appendix A: Medical Symptoms Questionnaire (MSQ)

THE UNIVERSITY OF KANSAS PHYSICIANS
3901 Rainbow Boulevard
Kansas City, Kansas 66160
INTEGRATIVE MEDICINE
Medical Symptoms Questionnaire (MSQ)

Do not write in this box

Name:_____

DOB:_____

MR#_____

Date:

Rate each of the following symptoms based upon your typical health profile for: ☐ Past 30 days ☐ Past 48 hours

Point Scale

0 – Never or almost never have the symptom
1 – Occasionally have it, effect is not severe
2 – Occasionally have it, effect is severe
3 – Frequently have it, effect is not severe
4 – Frequently have it, effect is severe

Head
____ Headaches
____ Faintness
____ Dizziness
____ Insomnia
____ **Total**

Eyes
____ Watery or itchy eyes
____ Swollen, reddened/sticky eyelids
____ Bags, dark circles
____ Blurred or tunnel vision (does not include near or far-sightedness)
____ **Total**

Ears
____ Itchy ears
____ Earaches, ear infections
____ Drainage from ear
____ Ringing /hearing loss
____ **Total**

Nose
____ Stuffy Nose
____ Sinus problems
____ Hay fever
____ Sneezing attacks
____ Excessive mucous
____ **Total**

Mouth/Throat
____ Chronic coughing
____ Gagging/throat clearing
____ Sore throat, hoarseness
____ Swollen/discolored tongue, gums, lips
____ Canker sores
____ **Total**

Skin
____ Acne
____ Hives, rashes, dry skin
____ Hair loss
____ Flushing, hot flashes
____ Excessive sweating
____ **Total**

Heart
____ Irregular /skipped beats
____ Rapid/pounding beats
____ Chest pain
____ **Total**

Lungs
____ Chest congestion
____ Asthma, bronchitis
____ Shortness of breath
____ Difficulty breathing
____ **Total**

Digestive Tract
____ Nausea, vomiting
____ Diarrhea
____ Constipation
____ Bloated feeling
____ Belching, passing gas
____ Heartburn
____ Intestinal/stomach pain
____ **Total**

Joints/Muscle
____ Pain or aches in joints
____ Arthritis
____ Stiffness/limited movement
____ Pain or aches in muscles
____ Feeling of weakness or tiredness
____ **Total**

Weight
____ Binge eating/drinking
____ Craving certain foods
____ Excessive weight
____ Compulsive eating
____ Water retention
____ Underweight
____ **Total**

Energy/Activity
____ Fatigue/sluggishness
____ Apathy, lethargy
____ Hyperactivity
____ Restless leg
____ Jetlag
____ **Total**

Mind
____ Poor memory
____ Confusion, poor comprehension
____ Poor concentration
____ Poor physical coordination
____ Difficulty making decisions
____ Stuttering or stammering
____ Slurred speech
____ Learning disabilities
____ **Total**

Emotions
____ Mood swings
____ Anxiety, fear, nervousness
____ Anger, irritability, aggressiveness
____ Depression
____ **Total**

Other
____ Frequent illness
____ Frequent or urgent urination
____ Genital itch or discharge
____ Bone pain
____ **Total**

MSQ Total _____

Reviewed by_____ **Date/Time**_____

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Medical Symptoms Questionnaire (MSQ)

Appendix B: KU Integrative Medicine FBD Care Algorithm