ORIGINAL RESEARCH

Gustavo G. Zarini, PhD, RD, Michael A. McLean, PhD, and Savina I. Delgado, BSc

Is Personalized Dietary Therapy Effective for Individuals With Irritable Bowel Syndrome?

Abstract: ***Introduction:*** *Adverse reactions to foods and food additives have a critical role in clinical manifestations of irritable bowel syndrome (IBS). Personalized dietary modifications conducted under the supervision of a qualified health practitioner could considerably impact the clinical care and course of the condition.* ***Objective:*** *To investigate the clinical effectiveness of the Lifestyle Eating and Performance (LEAP) program based on the Leukocyte Activation Assay-MRT (LAA-MRT®) results in improving IBS symptoms and quality of life.* ***Methods:*** *The retrospective study included de-identified client records (n = 146) from private group practices seen by registered dietitians. The eligibility criteria were adults aged > 18 years old with an established diagnosis of IBS.* ***Results:*** *Participants were 46.7 ± 12.6 years old and had a BMI of 26.7 ± 6.1 kg/m^2; the majority were female (87.0%) and followed-up by a registered dietitian for 10.1 ± 6.4 weeks. There was a significant reduction post-dietary intervention in overall Global Gastrointestinal Symptom Survey Scores (P < 0.001) and improvement in quality of life (P < 0.001).* ***Conclusion:*** *This study generates real-world evidence of an alternative treatment option for IBS using a personalized dietary approach. A more precise understanding of the effect of food intake reactions is vital for clinical improvements and enhancing health outcomes in IBS.*

> "This study generates real-world evidence of an alternative treatment option for IBS using a personalized dietary approach."

Keywords: Personalized diet; irritable bowel syndrome; lifestyle eating and performance program; leukocyte activation assay; quality of life

Introduction

Irritable bowel syndrome (IBS) is a common and chronic gastrointestinal disorder with a remitting-relapsing clinical course.[1,2] It is characterized by different abdominal discomfort patterns and pain, bloating, and coexisting abnormal bowel habits.[3,4] The reported prevalence of adults with IBS in the United States (US) is estimated to be 5–9.5%[5,6] and differs according to the diagnostic selection criteria (i.e., Rome III vs. Rome IV),[7,8] age, and sex.[6] IBS places a considerable burden on the healthcare system and negatively impacts an individual's quality of life.[9,11] Additionally, this condition increases workplace absenteeism and decreases work productivity.[12,13] Even though existing evidence does not allow for definitive conclusions about the etiology and pathophysiology of IBS, several possible

DOI: 10.1177/15598276221112309. Oxford Biomedical Technologies, Inc., Riviera Beach, FL, USA (GGZ, MAM, SID). Address correspondence to: Gustavo G. Zarini, PhD, RD, Oxford Biomedical Technologies, Inc., 3555 Fiscal Ct., Suite 9, Riviera Beach, FL 33404, USA; e-mail: Dr.GZarini@nowleap.com.

mechanisms have been explored.[14] Irritable bowel syndrome could be modulated and interrelated by abnormal gastrointestinal motility, inflammation, visceral hypersensitivity, adverse food reactions, enteric nervous system alterations, gut microbiome dysregulations, genetic and psychological factors.[4,14-17] Currently, there is no established cure for IBS. Treatment options are intended to reduce symptoms associated with this disorder and improve health outcomes and quality of life. Prior reports indicated that a small percentage of individuals with IBS notice long-term improvements with complete remission of symptoms with medications or standardized diet.[4,14,17] Additionally, the absence of pharmacological treatments with undoubted efficacy and side effects has led to the development of other complementary treatments for IBS management.[4] Medical nutrition therapy has long been recognized as a vital therapeutic intervention for IBS. Dietary modifications and food selection conducted methodically under the supervision of qualified health practitioners could considerably impact the clinical care and course of the condition. However, the absence of an in-depth understanding of the metabolic pathways and underlying causes has hindered the advancement and acceptance of effective nutritional therapeutic options.[18-21]

Adverse reactions to foods and chemical food additives have a crucial role in the clinical manifestations of IBS.[22] Previous studies have shown that foods could generate and/or exacerbate the number and frequency of flare-ups and symptoms for IBS.[23,24] Identifying specific adverse reactions to foods or food additives through a series of oral food challenges is troublesome, time-consuming, and complicated for individuals with IBS and healthcare providers.[25-28] Furthermore, IBS clinical presentation poses significant challenges to planning an adequate dietary intervention. The application of diet therapy for IBS care is complex. Up to today, there is no single dietary approach accepted with robust evidence-based or cause-based treatment methods and consistency between study results.[4,29] Also, using a standardized dietary approach for clinical care is generally inappropriate for individuals with IBS. Personalized dietary modifications are a more reasonable strategy in managing IBS, as the specific foods and food chemicals that trigger symptoms vary from person to person. To the best of our knowledge, no research has examined the role of oral immunologic tolerance to food and chemical sensitivities from a diet using the Leukocyte Activation Assay-MRT (LAA-MRT®) nor implementing a personalized oligoantigenic eating program for IBS based upon the LAA-MRT® results. This study aimed to investigate the clinical effectiveness of the Lifestyle Eating and Performance (LEAP) program in improving IBS symptoms and quality of life.

Methods

Study Design

This retrospective study included de-identified client records (n = 146) from private group practices seen by registered dietitians. The eligibility criteria were adults aged > 18 years old with an established diagnosis of IBS. Since the follow-up time and number of visits to the registered dietitians varied according to the client's records availability, the analysis only included records if the subjects followed the LEAP program for at least three weeks. The data collected included age, height, weight, calculated body mass index (BMI), number of days on the LEAP program, LAA-MRT® results, Global Gastrointestinal Symptom Survey, and Short-Form Health Survey (SF-36) scores. The study protocol was reviewed and received approval from an independent Institutional Review Board (IRB).

Assessment of the Leukocyte Activation Assay-MRT (LAA-MRT®)

On the initial visit, standard venipuncture phlebotomy was used to collect blood from each subject in two 4.5 ml BD Vacutainer® tubes containing 3.2% buffered sodium citrate. The blood specimens were packaged and mailed overnight to Oxford Biomedical Technologies, Inc. (West Palm Beach, FL, USA). Oxford's CLIA-certified Clinical Laboratory performed the in vitro LAA-MRT® using Sony EC 800 Dual-Mode Flow Cytometry (FCM) Systems (Sony Biotechnology Inc., CA, USA). The LAA-MRT® laboratory testing procedure begins by diluting a specific volume of whole blood with buffered physiologic saline. An aliquot of the blood suspension was then pipetted into 150 reaction wells, each containing a single food, endogenous or exogenous chemical, followed by a predetermined incubation period at 37°C. After incubation, the reaction wells were loaded into the FCM, where dot plots were created from the neutrophils and Peripheral Blood Mononuclear Cells (PBMCs) reactivity to food and chemical antigens challenges. The dot plot displays each white blood cell data value based upon cell morphology and internal cell granularity and complexity using both forward scatter (FSC) and side scatter (SSC) single beam laser technology. The FCM is equipped with the LAA-MRT® software and is programmed with data acquisition and reduction,

which calculates and scales the degree of an adverse immune response after an antigenic challenge. The foods and endogenous or exogenous chemicals were then listed into color-coded categories based on the calculated and scaled reactivity levels: (a) non-reactive (green: 0.0–1.9), (b) moderately reactive (yellow: 2.0–2.9), and (c) reactive (red: >3.0) Supplemental appendix 1 (LAA-MRT® sample report).

Intervention: Lifestyle Eating and Performance (LEAP) Program Protocol

The LEAP program is a personalized dietary approach based upon the proven principles of the oligoantigenic diet[30,31] and implemented by eliminating moderate- to high-immune-reactive foods and chemicals identified by the LAA-MRT® results. This is a novel approach in the clinical application of oligoantigenic diet therapy. Using a selection of foods based upon the use of dual-mode flow cytometry systems to characterize and quantify the morphologic changes in each assayed cell population after they are challenged and incubated with specific food antigens and chemicals, a patient-specific diet is constructed from the assay results. The LEAP program's objective included consuming only LAA-MRT® tested foods and ingredients which are deemed well-tolerated for a determined period in sequenced phases (Phase 1, 2, and 3) according to individuals' LAA-MRT® results and clinical response. Each phase ranges from 4–6 weeks and could vary due to specific clinical presentation, food patterns/habits, and the overall nutritional balance of the dietary approach. The goals of the LEAP program were to (a) reduce or eliminate the level of adverse immune food reactions and clinical symptoms; (b) through a series of serial open oral challenges, identify any additional dietary contributors to symptoms that may or may not be caused by adverse immunologic responses; (c) achieve an improvement in quality of life with reduced health-related risks associated with IBS. The initial phase (Phase 1): foods were chosen by the registered dietitian in consultation with the clients to build the personalized eating plan considering the specific goals of Phase 1: (a) consume only tested foods with the lowest immune response determined by the LAA-MRT® results; (b) determine current "normal" eating style and habits; (c) select foods that the client eats typically, or there are familiar foods to them; (d) take additional consideration of individuals' IBS diagnosis subtypes, past and current treatment outcomes, and other clinical factors which can influence food selection; (e) identify individuals' preferences, lifestyle factors, cooking skills, degree of commitment, and account for those when conducting lifestyle modification planning. The recommended structure of the LEAP program allowed flexibility in scheduling clients' progression. Progression was primarily based upon treatment outcomes and clients' response and tolerance to the dietary approach; this was not the estimated or projected scheduling deadlines for phase(s) duration, nor for the number of visits or interactions in any given phase.

The LEAP-trained registered dietitians exercised a significant degree of professional judgment within the phased design of eating only specific LAA-MRT® tested foods and ingredients under specific criteria for each of the 4–6-week periods (Phase 1, 2, and 3). Careful case assessment and clinical judgment based on history, diagnosis, and prior treatment were vital to these decisions. Improvement in GI symptoms was a critical prerequisite for progression to Phase 2 of the LEAP program. The primary purpose for Phase 2 is to begin expanding the diet and adding a wider variety of foods. This is achieved by conducting a serial open oral challenge of the remaining lesser immune reactive foods not introduced in Phase 1. The clients were instructed to keep eating from the Phase 1 food list; but, on each new day of Phase 2, they could incorporate one new food item into their diet on a schedule supervised by the LEAP-trained registered dietitians. If the clients were stable and satisfied with the degree of relief after immune-reactive foods were excluded from the diet, the clients were ready to begin challenging untested foods and progress to Phase 3. The focus of this final phase is to progressively expand and "normalize" the diet by serial open oral challenging of any remaining LAA-MRT® tested foods and monitoring for any adverse responses before moving forward. This is done by challenging one new untested food per day then assessing clients' clinical responses. It is important to note that the symptom surveys and food-symptom diary were vital tools for documenting challenges and symptoms when monitoring the progress of the LEAP program. Clients were asked and discussed their degree of adherence to the LEAP program with the LEAP-trained registered dietitians at each follow-up visit.

Measurements

Food-Symptom Diary. A food-symptom diary questionnaire was administered and supervised by the certified LEAP registered dietitians. From the first visit, all clients were instructed to record and maintain a dietary intake log (including the frequency and dose consumption of each food) and a symptom onset diary. The information recorded in the questionnaire was valuable to assist the clients and registered dietitians in identifying potential food triggers, symptomatic responses, and trends. There are many ways foods or

chemicals can cause adverse responses,[32] including (1) classic Immunoglobulin E (IgE) food allergies (2) other non-IgE mediated immunologic reactions (detectable with LAA-MRT®) (3) mixed IgE and non-IgE reactions, and (4) other non-immunologic mechanisms that are not detectable by the LAA-MRT® but which can be more easily unmasked by open oral challenge after the LAA-MRT® results have been isolated and removed. The questionnaire contains columns for writing the date and time, medications and supplements, foods and drinks consumed, the amount and complete description of the type of food(s) and preparation, and the symptoms—rating the symptom on a scale of 1–10 (1 meaning barely noticeable symptom and 10 meaning the most severe).

Global GI Symptom Survey

A global GI symptom survey was used to assess the frequency and severity of the gastrointestinal symptoms. The global GI symptom survey included nine domains: (1) heartburn/reflux; (2) stomach pains/cramps; (3) intestinal pains/cramps; (4) constipation; (5) diarrhea; (6) bloating sensation; (7) gas (of any kind); (8) nausea/vomiting; (9) painful elimination. The severity and frequency of symptoms were self-reported at each visit and rated based on a scale of 0–4 with a minimum score of 0 and a maximum of 36 points, with a higher score signifying adverse gastrointestinal outcomes.

Quality of Life Measure - The 36-item Short-Form Health Survey (SF-36):

The 36-item Survey (SF-36) was used to assess the quality of life.[33] This questionnaire has been validated and widely used to measure the burden associated with IBS.[34,35] The SF-36 is a self-reported survey that contains eight health domains: (1) physical functioning (ten items); (2) bodily pain (two items); (3) role limitations due to physical health problems (four items); (4) role limitations due to personal or emotional problems (four items); (5) emotional well-being (five items); (6) social functioning (two items); (7) energy/fatigue (four items); and (8) general health perceptions (five items). Domain scores range from 0 to 100; a higher score described a more desirable health state.

Statistical Analysis

All data analyses for the study were conducted using the Statistical Package for the Social Sciences (SPSS) version 27 (IBM Corp., Armonk, NY). Data were examined for normal distribution of all continuous variables using the Shapiro–Wilk test. Descriptive statistics were created for all variables of interest included in the analysis and reported as mean with standard deviation. Linear mixed models were performed and reported as mean with standard error. All tests were analyzed two-sided, and a P-value at the alpha level of <0.05 was considered statistically significant.

Results

As shown in Table 1, participants (n = 146) in this study were 46.7 ± 12.6 years old and had a BMI of 26.7 ± 6.1 kg/m^2; the majority were female, 87.0% (127). Participants were counseled and followed-up by a registered dietitian for 10.1 ± 6.4 weeks. Linear mixed models indicated a significant reduction post-dietary intervention in overall global GI symptom survey scores (15.8 ± 0.6 vs. 5.4 ± 0.4, P<0.001) and each of the nine specific domains (P<0.001) Table 2. Measures of quality of life post-dietary intervention indicated a statistically significant improvement in all domains for the SF-36 Survey at (P<0.001) except for physical functioning (P = 0.001) and role emotional (P = 0.007) Table 3.

Discussion

Individuals suffering from IBS experience substantial healthcare utilization, high healthcare costs, and decreased functional capabilities and well-being.[9,36,37] There are considerable difficulties in planning an adequate diet intervention for IBS due to its clinical manifestations and the fact that there are no proven dietary interventions with a high level of evidence available at this time.[1,29] Our study evaluated the effectiveness of the LEAP program on gastrointestinal symptoms and quality of life for IBS. The marked improvements in gastrointestinal symptom scores and well-being at the end of the follow-up time signify the importance of a personalized dietary intervention to manage IBS. The LEAP program was found to be suitable and well-tolerated by all our study participants. The registered dietitians built the dietary approach from the least immune reactive foods indicated by the LAA-MRT® results, which provided a scale of relative oral tolerance for each client. This was accomplished through a progressive process where sources of provocation were eliminated, and low-inflammatory foods specific to that client were incorporated into the diet. Furthermore, the findings from this study are relevant as the LEAP program has the potential to improve IBS treatment outcomes and quality of life as a result of the adjustments in food selection.

People with IBS encountered development and exacerbation of symptoms after the intake of certain foods on an individual-specific basis.[24,38,39] Likewise, IBS patients were more predisposed to change their diet as compared to healthy controls.[40] In another study, 92% of

Table 1.

Baseline characteristics of participants with irritable bowel syndrome (IBS).

Characteristics	(n = 146)
Age (years)	46.7 ± 12.6
Sex	
Female	127 (87.0%)
Male	19 (13.0%)
BMI (kg/m^2)	26.7 ± 6.1
Time follow-up (weeks)	10.1 ± 6.4

Abbreviations: Body mass Index (BMI).

Table 2.

Measures of Global GI Symptom Survey Scores Pre- and Post-Dietary Intervention.

Participants with IBS (n = 146)					
Domain	Pre-LEAP intervention	Post-LEAP intervention	Mean Difference	95% CI	P-Value
Global GI symptom survey score	15.8 ± 0.6	5.4 ± 0.4	−10.4	−9.1 – −11.6	<0.001
Heartburn/reflux	1.4 ± 0.1	0.5 ± 0.1	−0.9	−0.7 – −1.1	<0.001
Stomach pains/cramps	1.8 ± 0.1	0.7 ± 0.1	−1.1	−0.8 – −1.3	<0.001
Intestinal pains/cramps	2.2 ± 0.1	0.7 ± 0.1	−1.4	−1.2 – −1.7	<0.001
Constipation	1.6 ± 0.1	0.6 ± 0.1	−1.0	−0.7 – −1.2	<0.001
Diarrhea	1.7 ± 0.1	0.5 ± 0.7	−1.2	−1.1 – −1.5	<0.001
Bloating sensation	2.5 ± 0.1	0.8 ± 0.1	−1.7	−1.1 – −1.9	<0.001
Gas (of any kind)	2.7 ± 0.1	1.2 ± 0.1	−1.5	−1.3 – −1.7	<0.001
Nausea/Vomiting	0.9 ± 0.1	0.3 ± 0.1	−0.6	−0.6 – −1.0	<0.001
Painful elimination	0.9 ± 0.1	0.1 ± 0.1	−0.8	−0.5 – −0.8	<0.001

Data is reported as Mean ± SE. P is considered significant at <0.05.

people with IBS refrain from eating certain foods to avoid or alleviate their gastrointestinal symptoms.[40] Böhn et al. (2013) found that gastrointestinal symptoms were attributed to at least one of the 56 foods and food additives examined.[41] Hence, adverse reactions to foods in IBS individuals remain a significant and established concern for health care providers. The identification of foods and chemicals that may have an impact on IBS symptoms and subsequently on quality of life is essential for the proper management of this condition. A clearer understanding of the effect of food intake reactions is vital to individuals with IBS seeking to reduce their symptoms and improve their nutritional status.

Research on the therapeutic value of personalized dietary approaches is limited. Studies available on nutritional management for IBS lack robust and consistent evidence.[29] The use of a restrictive elimination diet where only a few foods are included are not recommended for long-term use because they can lead to nutritional deficiencies, especially in individuals with IBS.[42] The key

Table 3.

Measures Quality of Life measures using SF-36 Survey Pre- and Post-Dietary Intervention.

Participants with IBS (n = 61)					
Domain	**Pre-LEAP intervention**	**Post-LEAP intervention**	**Mean Difference**	**95% CI**	**P-Value**
Physical functioning	76.9 ± 3.1	86.4 ± 2.6	9.5	3.9 – 15.1	0.001
Role physical	45.1 ± 4.9	72.1 ± 4.7	27.0	17.7 – 36.4	<0.001
Role emotional	59.0 ± 5.8	74.9 ± 4.8	15.8	4.4 – 27.2	0.007
Vitality	38.2 ± 2.9	57.4 ± 3.0	19.2	13.1 – 25.4	<0.001
Bodily pain	59.5 ± 2.9	72.7 ± 2.7	13.1	6.3 – 19.8	<0.001
Social functioning	62.3 ± 3.4	75.2 ± 3.0	12.9	6.9 – 18.9	<0.001
Emotional well-being	60.4 ± 2.4	76.1 ± 2.0	15.7	11.7 – 19.7	<0.001
General health	55.4 ± 3.0	67.6 ± 2.6	12.2	8.0 – 16.4	<0.001

Data is reported as Mean ± SE. P is considered significant at <0.05.

aspect of the LEAP program is that it is a nutritionally balanced dietary approach guided by an in vitro assay that prevents the exclusion of foods at random. In addition to the restrictive elimination diets, investigations have been conducted to eliminate foods based on Immunoglobulin G (IgG) antibody titers. The evidence available for dietary approaches based on selecting foods based on IgG tests is controversial and contradictory, indicating an absence of consensus on the efficacy of this antibody test.[29,43-45]

The latest American College of Gastroenterology (ACG) guidelines for managing IBS showed a weak level of evidence to recommend the use of the low Fermentable Oligo-, Di-, and Mono-saccharides, and Polyols (FODMAPs) diet for improvements in IBS symptoms.[1,29] On the other hand, the ACG guidelines published results of a dietary therapy for IBS based upon leukocyte activation testing[46] were intriguing with potential interest for IBS treatment.[29] To that end, this line of investigation and confirmatory evidence is being conducted in our study. Subjects in our study were included if a dietitian provided initial consultation, treatment planning, and followed-up on results for at least three weeks with a mean follow-up time of 10.1 ± 6.4 weeks. Two meta-analyses[1,47] that used randomized controlled trials on low FODMAPs diets in IBS showed a duration of no longer than six weeks where reintroduction and maintenance of FODMAPs were not evaluated throughout the study. This is a considerable medical nutrition therapy difference between the FODMAPs diet and LEAP program; the reintroduction of eliminated foods was assessed during follow-up. There were no significant differences between the proportions of adequate relief of their overall IBS symptoms between two effectiveness studies that compared a low FODMAPs diet vs. a standardized diet guided by dietitians.[48,49] Additionally, the low FODMAPs diet could adversely influence gut microbiota in adult subjects with gastrointestinal conditions.[50] While individuals with IBS will often experience pain, bloating, diarrhea, and other GI symptoms associated with the foods included in the FODMAPs diet, the root of these symptoms is not only improper digestion itself. IBS is a condition characterized by an inflammatory process where[18,51] individuals with IBS have been reported to have higher blood levels of pro-inflammatory cytokines than healthy controls.[52-54] Therefore, appropriate nutritional choices may mitigate diet-induced inflammation and the mechanisms of IBS progression. As noted by the ACG clinical guidelines, more research is warranted to further clarify metabolic implications of the leukocyte activation testing and the clinical relevance of diet-induced inflammation that could explain changes in biomarkers for IBS and improved treatment outcomes.

Limitations

Limitations of this study included the retrospective design and use of a self-reported survey to assess gastrointestinal symptoms and quality of life. There were more charts

available from women than men; however, women are found to have a higher prevalence of IBS as compared to men.[6] The present study did not include inflammatory markers such as pro-inflammatory cytokines prior reported in individuals with IBS.[52] We have not differentiated between the subclasses of IBS: IBS-D and IBS-D and IBS-M and unclassified (IBS-U). We analyzed a subsample for the SF-36 questionnaire (n = 61) for those whose data was available. Finally, gut microbiota was not assessed in this study.

Strengths

Trained registered dietitians administrated the LEAP program with experience in gastrointestinal conditions and the use of food diaries to better understand clients' dietary eating patterns and compliance. The LEAP protocol was flexible to the individuals' needs and preferences, leading to improved adherence and treatment outcomes. Implications of this research provide scientific evidence for clinical practice. The findings from the study could potentially facilitate the implementation of the LAA-MRT® and LEAP program into a broad clinical application. At the same time, the LAA-MRT® blood test results are essential to identify reactive foods and chemicals to plan a personalized diet plan to improve clinical endpoints of IBS.

Conclusion

Irritable bowel syndrome features different clinical manifestations that present significant challenges for individuals and healthcare providers to plan an appropriate nutritional intervention. This study generates real-world evidence of an alternative treatment option for IBS using a personalized dietary approach. We found clinical improvements post-LEAP program intervention in gastrointestinal symptoms and quality of life underlying the need for IBS personalized and comprehensive management processes. As the basis for future investigations, the study contributes to the scientific knowledge and application into practice necessary to reduce adverse outcomes related to IBS. Lastly, future research into the relationship between inflammatory markers and diet may assist in developing more effective therapeutic strategies for IBS.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: GGZ works at Oxford Biomedical Technologies as the Director of Clinical and Scientific Research. MAM works at Oxford Biomedical Technologies as the Director of Laboratory and Technology. SID works as a research assistant at Oxford Biomedical Technologies, Inc.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Publication fees are sponsored by Oxford Biomedical Technologies.

ORCID iD

Gustavo G. Zarini https://orcid.org/0000-0003-3130-3568

Supplemental Material

Supplemental material for this article is available online. AJLM

References

1. Ford AC, Moayyedi P, Chey WD, et al. ACG Task Force on Management of Irritable Bowel Syndrome. American college of gastroenterology monograph on management of irritable bowel syndrome. *Am J Gastroenterol*. 2018;113(suppl 2): 1-18.
2. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. *N Engl J Med*. 2017; 29376(26):2566-2578.
3. Lacy BE, Mearin F, Chang L, et al. Bowel Disorders. *Gastroenterology*. 2016;18(16):S0016-S5085.
4. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA*. 2015;3313(9): 949-958.
5. Palsson OS, Whitehead W, Törnblom H, Sperber AD, Simren M. Prevalence of Rome IV Functional Bowel Disorders Among Adults in the United States, Canada, and the United Kingdom. *Gastroenterology*. 2020; 158(5):1262-1273. e3.
6. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of rome foundation global study. *Gastroenterology*. 2021; 160(1):99-114.
7. Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2020;5(10):908-917.
8. Black CJ, Craig O, Gracie DJ, Ford AC. Comparison of the Rome IV criteria with the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. *Gut*. 2021;70(6): 1110-1116.
9. Creed F, Ratcliffe J, Fernandez L, et al. Health-related quality of life and health care costs in severe, refractory irritable bowel syndrome. *Ann Intern Med*. 2001;1134(9 Pt 2): 860-868.
10. Addante R, Naliboff B, Shih W, et al. Predictors of health-related quality of life in irritable bowel syndrome patients compared with healthy individuals. *J Clin Gastroenterol*. 2019; 53(4):e142-e149.
11. Amouretti M, Le Pen C, Gaudin AF, et al. Impact of irritable bowel syndrome (IBS) on health-related quality of life (HRQOL). *Gastroenterol Clin Biol*. 2006;30(2): 241-246.
12. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nat Rev Dis Primers*. 2016;24(2):16014.
13. Dean BB, Aguilar D, Barghout V, et al. Impairment in work productivity and health-related quality of life in patients with IBS. *Am J Manag Care*. 2005;11(1 suppl l):S17-S26.
14. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. *Lancet*. 2020;396:1675-1688.

15. Farah DA, Calder I, Benson L, MacKenzie JF. Specific food intolerance: its place as a cause of gastrointestinal symptoms. *Gut*. 1985;26(2):164-168.
16. Petitpierre M, Gumowski P, Girard JP. Irritable bowel syndrome and hypersensitivity to food. *Ann Allergy*. 1985;54(6):538-540.
17. Camilleri M. Diagnosis and Treatment of Irritable Bowel Syndrome: A Review. *JAMA*. 2021;325(9):865-877.
18. Ohman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol*. 2010;7(3): 163-173.
19. Moayyedi P, Simrén M, Bercik P. Evidence-based and mechanistic insights into exclusion diets for IBS. *Nat Rev Gastroenterol Hepatol*. 2020; 17(7):406-413.
20. Hayes PA, Fraher MH, Quigley EM. Irritable bowel syndrome: the role of food in pathogenesis and management. *Gastroenterol Hepatol (N Y)*. 2014;10(3):164-174.
21. Simrén M, Törnblom H, Palsson OS, Whitehead WE. Management of the multiple symptoms of irritable bowel syndrome. *Lancet Gastroenterol Hepatol*. 2017;2(2):112-122.
22. Niec AM, Frankum B, Talley NJ. Are adverse food reactions linked to irritable bowel syndrome? *Am J Gastroenterol*. 1998;93(11):2184-2190.
23. Monsbakken KW, Vandvik PO, Farup PG. Perceived food intolerance in subjects with irritable bowel syndrome– etiology, prevalence and consequences. *Eur J Clin Nutr*. 2006; 60(5):667-672.
24. Simrén M, Månsson A, Langkilde AM, et al. Food-related gastrointestinal symptoms in the irritable bowel syndrome. *Digestion*. 2001;63(2): 108-115.
25. Versluis A, Knulst AC, van Erp FC, et al. Reintroduction failure after negative food challenges in adults is common and mainly due to atypical symptoms. *Clin Exp Allergy*. 2020;50(4):479-486.
26. Eigenmann PA, Caubet JC, Zamora SA. Continuing food-avoidance diets after negative food challenges. *Pediatr Allergy Immunol*. 2006;17(8): 601-605.
27. Zwetchkenbaum J, Burakoff R. The irritable bowel syndrome and food hypersensitivity. *Ann Allergy*. 1998; 61(1):47-49.
28. Plaut M. New directions in food allergy research. *J Allergy Clin Immunol*. 1997; 100(1):7-10.
29. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. *Am J Gastroenterol*. 2021; 116(1):17-44.
30. Carroccio A, Mansueto P, Morfino G, et al. Oligo-antigenic diet in the treatment of chronic anal fissures. Evidence for a relationship between food hypersensitivity and anal fissures. *Am J Gastroenterol*. 2013;108(5): 825-832.
31. Egger J. Food allergy and the central nervous system. In: Vevey SE, ed., *Food Allergy. Nestle Nutrition Workshop Series* 17. Vevey, Switzerland: Nestec Ltd.; 1988:159-175.
32. Anvari S, Miller J, Yeh CY, Davis CM. IgE-Mediated Food Allergy. *Clin Rev Allergy Immunol*. 2019;57(2):244-260.
33. Ware JE, Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.
34. Sierżantowicz R, Lewko J, Jurkowska G. The Impact of an Individual Educational Program on the Quality of Life and Severity of Symptoms of Patients with Irritable Bowel Syndrome. *Int J Environ Res Public Health*. 2020;1317(12):4230.
35. Han BY, Shao QF, Cong Y, et al. Transcutaneous electric nerve stimulation over acupoints for patients with diarrhea-predominant irritable bowel syndrome: Protocol for systematic review and meta-analysis. *Medicine (Baltimore)*. 2018;97(51): e13267.
36. Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. *Gastroenterology*. 2019;156(1):254-272.
37. Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2014;40(9): 1023-1034.
38. Böhn L, Störsrud S, Simrén M. Nutrient intake in patients with irritable bowel syndrome compared with the general population. *Neurogastroenterol Motil*. 2013;25(1):23-30.
39. Posserud I, Strid H, Störsrud S, et al. Symptom pattern following a meal challenge test in patients with irritable bowel syndrome and healthy controls. *United European Gastroenterol J*. 2013; 1(5):358-367.
40. Hayes P, Corish C, O'Mahony E, Quigley EM. A dietary survey of patients with irritable bowel syndrome. *J Hum Nutr Diet*. 2014;27(suppl 2): 36-47.
41. Böhn L, Störsrud S, Törnblom H, Bengtsson U, Simrén M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. *Am J Gastroenterol*. 2013;108(5):634-641.
42. Parker TJ, Naylor SJ, Riordan AM, Hunter JO. Management of patients with food intolerance in irritable bowel syndrome: the development and use of an exclusion diet. *Journal of Human Nutrition and Dietetics*. 1995;8: 159-166.
43. Stapel SO, Asero R, Ballmer-Weber BK, et al. EAACI Task Force. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. *Allergy*. 2008;63(7):793-796.
44. Hunter JO. Food elimination in IBS: the case for IgG testing remains doubtful. *Gut*. 2005;54(8):1203.
45. Zwetchkenbaum J, Burakoff R. The irritable bowel syndrome and food hypersensitivity. *Ann Allergy*. 1988; 61(1):47-49.
46. Ali A, Weiss TR, McKee D, et al. Efficacy of individualised diets in patients with irritable bowel syndrome: a randomised controlled trial. *BMJ Open Gastroenterol*. 2017;4(1): e000164.
47. Krogsgaard LR, Lyngesen M, Bytzer P. Systematic review: quality of trials on the symptomatic effects of the low FODMAP diet for irritable bowel syndrome. *Aliment Pharmacol Ther*. 2017;45(12):1506-1513.
48. Eswaran S, Dolan RD, Ball SC, Jackson K, Chey W. The Impact of a 4-Week Low-FODMAP and mNICE Diet on Nutrient Intake in a Sample of US Adults with Irritable Bowel Syndrome with Diarrhea. *J Acad Nutr Diet*. 2020; 120(4):641-649.
49. Staudacher HM, Ralph FSE, Irving PM, Whelan K, Lomer MCE. Nutrient Intake, Diet Quality, and Diet Diversity in Irritable Bowel Syndrome and the Impact of the Low FODMAP Diet. *J Acad Nutr Diet*. 2020;120(4):535-547.
50. Hill P, Muir JG, Gibson PR. Controversies and Recent

Developments of the Low-FODMAP Diet. *Gastroenterol Hepatol (N Y)*. 2017;13(1):36-45.

51. Akiho H, Ihara E, Nakamura K. Low-grade inflammation plays a pivotal role in gastrointestinal dysfunction in irritable bowel syndrome. *World J Gastrointest Pathophysiol*. 2010; 151(3):97-105.
52. Liebregts T, Adam B, Bredack C, et al. Immune activation in patients with irritable bowel syndrome. *Gastroenterology*. 2007;132(3): 913-920.
53. Bennet SM, Polster A, Törnblom H, et al. Global Cytokine Profiles and Association wiith Clinical Characteristics in Patients with Irritable Bowel Syndrome. *Am J Gastroenterol*. 2016;111(8): 1165-1176.
54. Bashashati M, Rezaei N, Shafieyoun A, et al. Cytokine imbalance in irritable bowel syndrome: a systematic review and meta-analysis. *Neurogastroenterol Motil*. 2014;26(7): 1036-1048.