Evaluate and compare the clinical efficacy of the Mediterranean diet to the low-FODMAP diet in treating Irritable Bowel Syndrome

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Specific aims

Irritable bowel syndrome (IBS) has a global prevalence of ~10% and up to 80% of patients with IBS report food as a trigger for their gastrointestinal symptoms.[1,2] A diet low in fermentable oligo-, di- and monosaccharides (LFD) has been shown to improve gastrointestinal symptoms in 50-60% of patients with IBS[3] and a recent network meta-analysis found it superior to other dietary approaches in improving abdominal pain and bloating in IBS.[4] However, the LFD is time-consuming, cumbersome, restrictive, and effective only in about 50% of patients.[5-7] Thus, there is a need for other dietary strategies that are effective in managing IBS symptoms.

The Mediterranean diet (MD), a time-honored diet rich in plant-based foods and monounsaturated fat, such as olive oil, but low in saturated fats, dairy, and meat,[8] has recently been considered a therapeutic dietary strategy for IBS. MD has been shown to have cardiovascular benefits in regard to both incidence and mortality,[9,10] along with other benefits such as the decreased risk of overall mortality, cognitive disorders, and diabetes.[11] It is hypothesized that it could also be beneficial in reducing bowel symptoms due to its positive impact on the gut microbiota[12,13] and microscopic inflammation,[14,15] lower intake of saturated fat, and regulation of the gastro-colonic reflex.[16] A population-based, cross-sectional study from Italy found the presence of IBS in the general population to be associated with low adherence to an MD.[17] Furthermore, lower adherence to the MD has been associated with more severe abdominal pain and flatulence in patients with IBS.[12] However, it is not clear whether the lower adherence to MD causes more IBS symptoms or whether patients with IBS are more likely to avoid the MD due to worsening symptoms on this diet. A small, open-label study compared the efficacy of three dietary interventions, LFD, gluten-free diet, and MD, in IBS.[18] Each patient followed the three diets for 4 weeks each. All three diets reduced symptom severity ($p<0.01$), abdominal bloating ($p<0.01$), and abdominal pain ($p<0.01$) when compared to baseline. Interestingly, 86% of patients preferred the Mediterranean diet ($p<0.01$). Limitations of the study include the small sample size, carry-over effects as well as lack of randomization, blinding, or assessment of adherence to the diet interventions. ***Despite this initial supportive evidence, no randomized controlled trial has investigated the efficacy of MD in IBS and MD is not routinely used in managing IBS symptoms.*** Therefore, there is a need to evaluate the efficacy of MD in managing IBS symptoms. *Our overall objective* is **to compare the clinical efficacy of the MD with the LFD in patients with IBS in a single-center, parallel-group, randomized controlled trial.**

In this study, **we hypothesize that:**

1. LFD and MD groups will achieve a similar improvement in abdominal pain
2. Both groups will achieve similar improvements in bloating, overall IBS symptom severity, and adequate relief

We plan to test our hypotheses and thereby, accomplish the objective of this application by pursuing the following 2 specific aims:

Aim 1: Compare the clinical effectiveness of MD vs. LFD by comparing the proportion of weekly responders to abdominal pain for at least 2 of the 4 weeks (measured using a decrease in the weekly average of worst abdominal pain in the past 24 hours score of at least 30% compared with baseline)

Aim 2: Compare the efficacy of MD vs. LFD on pre-specified clinical and disease-specific quality of life endpoints in patients with IBS

A positive result to the study will have a significant impact on the treatment of patients with IBS by expanding the armamentarium of evidence-based dietary interventions to include MD (the current quality of evidence is poor to make any recommendations about MD in IBS). If both the groups have similar clinical efficacy, MD could be less cumbersome, less restrictive, and a healthier dietary option for IBS compared to LFD. However, if the study shows MD is inferior to LFD in patients with IBS, this study will still be pertinent to patients with IBS and clinicians, given the increasing popularity of MD in the US.

Significance

Irritable bowel syndrome (IBS), characterized by abdominal pain in association with altered stool form or frequency, affects up to 10% of the general population worldwide.[1] The condition is a disorder of gut-brain interaction and is chronic with a relapsing and remitting natural history.[19] Costs to health services and society are substantial,[20,21] and the impact of symptoms on quality of life is considerable, with patients willing to accept a median 2% risk of sudden death with a hypothetical medication in return for a 98% chance of symptom cure.[22] However, the efficacy of most drugs is modest, and placebo response rates are high.[23] Even novel, more selectively targeted, therapies developed over the last 20 years produce a therapeutic gain over placebo of only 10%–15% and are expensive.[24] As a result, treatment satisfaction remains poor with the majority of both prescription and over-the-counter pharmacological options.[25]

Patients may, therefore, turn to other approaches. Over 80% of people with IBS report food-related symptoms,[2] and in one survey 92% of patients with IBS compared to 45% of controls reported dietary changes to manage their IBS.[26] Perhaps, as a result, there has been renewed interest in dietary therapies as a treatment for IBS. The LFD is the most rigorously studied diet in IBS and several randomized controlled trials have established its efficacy over habitual diet or other dietary advice such as those by the British Dietetic Association/National Institute for Health and Care Excellence (BDA/NICE). A recent network meta-analysis found it superior to these two diets in improving abdominal pain and bloating in IBS.[4] However, LFD is time-consuming, cumbersome, restrictive, and effective in only 50% of patients.[5-7] Furthermore, some data suggest that the LFD may be associated with reduced dietary intake of some micronutrients (e.g., iron and thiamine)[27] and may lead to a reduced fecal abundance of putatively beneficial bacteria such as Bifidobacteria.[28,29] Therefore, there is a need to develop additional evidence-based dietary strategies for IBS.

MD is the most recommended diet for general health by physicians. It has been consistently shown to reduce the risk of cardiovascular diseases and overall mortality. [9,10] However, its role in managing GI symptoms (if any) is not clear. MD is low in saturated fats and fatty food consumption has been shown to trigger IBS symptoms in IBS patients.[30] Fat ingestion has also been shown to slow intestinal gas transport, exaggerate gastrocolic response and decrease the threshold for visceral hypersensitivity.[16] Moreover, MD has been shown to increase the relative abundance of putative beneficial bacteria such as Bifidobacterium which are known to be reduced in IBS.[31,32] Furthermore, MD increases SCFA production[12,33] and reduces microscopic inflammation[14,15] in the gut which could improve colonic health in IBS. Despite the biological plausibility of MD improving IBS symptoms, data is limited on its efficacy in IBS.

A few observational cross-sectional studies suggest a higher likelihood of IBS symptoms with lower adherence to MD.[17,34] However, given the cross-sectional nature, the cause-effect relationship could not be established in these studies. In the only intervention study using MD in IBS, an open-label dietary intervention study was conducted on 28 IBS patients where each patient followed three different diets for 4 weeks each (MD, LFD, and gluten-free diet). MD was found to be as effective as LFD in improving IBS symptoms, and a significantly higher number of patients preferred MD over the other two diets.[18] However, this study had significant limitations including the small sample size, high likelihood of carry-over effects as well as lack of randomization, blinding, or assessment of adherence to the diet interventions. *To date, there are no randomized controlled studies evaluating the effect of MD on IBS. Thus, this proposal is significant* because it will provide pilot data comparing the efficacy of MD with LFM in IBS in a single-center, non-inferiority, parallel-group, randomized controlled trial.

Innovation:

Dietary therapies are commonly utilized by patients and providers to manage IBS symptoms. LFM is the most rigorously investigated dietary intervention in IBS but is effective in only 50% of the patients and is restrictive, time-consuming, expensive, and cumbersome.[5-7] Therefore, *there is an urgent need* for developing more evidence-based dietary therapies for patients with IBS. MD may be beneficial in reducing bowel symptoms due to lower intake of saturated fat, its positive impact on the gut microbiota,[12,13] SCFA production,[12,33] and, microscopic inflammation.[14,15] To date, no study has investigated the role of MD in a randomized controlled trial. This study is innovative by performing the first randomized controlled trial comparing the efficacy of MD with LFM in IBS.

Plans for future funding for the future project:

The overarching goal of our research team is to delineate the role of dietary factors in the pathophysiology of IBS and develop novel, evidence-based dietary therapies for IBS. I am currently funded by an NIH K23 CDA to delineate the role of FODMAPs in the pathophysiology of IBS-D. With my K23 grant, I have acquired the ability to use translational tools such as barrier function assessment, mast cell activation, and microbiome analysis to investigate how diet plays a role in generating IBS symptoms using *in vivo* and *in vitro* models. Delineating the mechanisms by which FODMAPs cause IBS pathophysiology is allowing me to identify novel predictors of response for LFM in IBS. I am also currently involved in additional diet-based clinical trials as a principal investigator or co-investigator. Furthermore, other co-investigators of the application (Dr. Eswaran and Dr. Chey) are world-renowned experts in the field of dietary therapies for IBS. Thus, our research team is the best-positioned research team to successfully complete this research proposal.

We will obtain data on the clinical efficacy of the MD in IBS through this pilot study. *In addition, we would be applying to GI societies (ACG, AGA, ANMS) for additional funding to support the analyses of stool and sera samples. However, we have enough discretionary funds to be able to analyze the stool and sera samples on our own (in case society funds are not granted).* Stool collected pre- and post-dietary interventions during this pilot study will be analyzed for microbiome analyses, fermentation indices (i.e., short-chain and branched-chain fatty acid profiles as markers of carbohydrate and protein fermentation), and bile acid profiles. Sera will be analyzed for markers of permeability (LPS, LBP, zonulin, etc.), mast cell activation, and inflammatory cytokines. Clinical data and biospecimens obtained through this pilot grant when coupled with the directed fecal microbiome and metabolite analyses performed using discretionary funds will position us very well to apply for ***an NIH-supported larger, multi-center, non-inferiority, parallel-group, RCT with the following aims:*** *1) comparing the efficacy of MD vs. LFM in IBS 2) define predictors of response to LFM vs. MD in IBS based on the fecal microbiome and metabolite profiles. 3) delineate mechanisms by which MD improves symptoms in a subset of IBS patients.*

Preliminary data

In the first and the largest US study to date, we conducted an RCT to evaluate the efficacy of an LFD with dietary recommendations based on the modified National Institute for Health and Care Excellence (mNICE).[25] In this study, 92 patients with IBS-D were randomized to either LFD or NICE dietary approaches for 4 weeks. We found that patients randomized to an LFD had greater reductions in daily scores of abdominal pain, bloating, stool frequency, stool consistency, and urgency than the group randomized to mNICE diet ($P<0.05$ for each). LFD also led to significantly greater improvements in health-related QOL, anxiety, and activity impairment in IBS-D compared with the mNICE diet. We have also conducted numerous other clinical trials evaluating diet therapies in patients with functional GI disorders.[35,36]

Recently, we aimed to determine whether it is the cumulative FODMAP consumption or the consumption of individual FODMAPs that drives response to the low FODMAP diet via a controlled reintroduction trial.[37] Patients with all IBS subtypes were invited to participate in a 12-week study to determine individual FODMAP sensitivities. Eligible patients underwent a 2-4 week open-label FODMAP elimination period under the direction of a research dietitian. If IBS symptoms improved (abdominal pain improved by ≥40% compared to baseline), participants were invited to continue to the 10-week reintroduction phase during which they remained on the elimination phase of the low FODMAP diet. FODMAP reintroduction (lactose, fructose, fructans, polyols, galactans) was achieved by providing subjects with a similar appearing and tasting daily supplement (low FODMAP brownie bite) which contained additional specific doses of supplemental FODMAPs prepared by research dieticians in a double-blind fashion for participants and investigators. Forty-five patients were enrolled in the study and 20 patients who improved with FODMAP elimination continued into the reintroduction phase. All patients who started the reintroduction phase completed the study. Using LME, abdominal pain was worse with fructan challenge ($P=0.007$), irrespective of the sequence of FODMAP reintroduced. When the analysis was restricted to the first reintroduction period, fructan challenge continued to be significantly associated with abdominal pain ($P=0.03$) as was galactan challenge ($P=0.04$). Bloating was worse with study period on LME

(P=0.002) but not with a specific FODMAP challenge. When we restricted the analysis to the first reintroduction period, galactan challenge was associated with the worsening of bloating (P=0.03).

Our group is also interested in understanding the mechanisms of how diet mediates IBS pathophysiology. Using rodent models, we have recently shown that a high fodmap diet causes gram-negative dysbiosis mediated mast cell activation which in turn leads to barrier dysfunction.[38] Furthermore, we have also validated that an LFD improves mast cell activation and barrier dysfunction in IBS-D patients.

In summary, our group, which includes expert gastroenterologists and specially trained research dietitians, is widely considered a leader in conducting clinical trials evaluating diet interventions in patients with FGIDs. We have successfully conducted various diet-based clinical trials and also utilized translational tools to understand the role of diet in the pathophysiology of IBS and biomarkers for response.

Research plan:

Patient population
Patients with IBS diagnosed using ROME IV criteria will be consecutively recruited from outpatient gastroenterology and primary care clinics at Michigan Medicine and via online advertisement.

Eligibility Criteria
Inclusion criteria

1. Patients with IBS-D (diarrhea-predominant IBS) or IBS-M (IBS with mixed subtype) diagnosed per Rome IV questionnaire and without any unexplained alarm features (rectal bleeding, weight loss, nocturnal symptoms, personal history of celiac disease, microscopic colitis, inflammatory bowel disease)
2. Aged 18-70 years at the time of screening
3. Weekly average of worst daily (in the past 24 hours) abdominal pain score of ≥3.0 on a 0-to-10-point scale
4. At least 80% compliance in daily questionnaire entries during the 7-day screening period

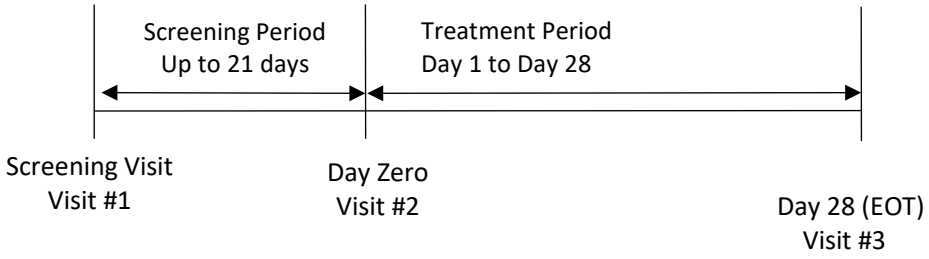
Exclusion criteria

1. Subjects adhering to any dietary IBS treatment such as the low-fat diet, LFD, or gluten-free diet, MD currently or within the past 6 months
2. Subjects with a known food allergy to eggs, seafood, peanuts, tree nuts or milk (subjects with lactose intolerance who are experiencing IBS symptoms while on a lactose-free diet will not be excluded from the study).
3. Subjects with a history of poorly controlled insulin-dependent or non-insulin-dependent diabetes
4. Subjects with a known history of organic GI disease (i.e., celiac disease, inflammatory bowel disease or microscopic colitis)
5. Subjects with a history of an eating disorder requiring medical or behavioral treatment within the past 10 years.
6. Subjects with prior small bowel or colonic surgery (excluding appendectomy or cholecystectomy if over 6 months since these 2 procedures)
7. Oral antibiotic use in the past 3 months
8. Any planned significant changes in dietary or exercise regimen within 30 days prior to Screening or during the study.
9. Currently pregnant or breastfeeding.

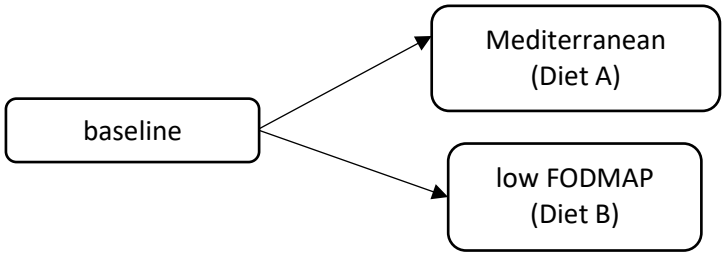
Concomitant Medications
Subjects will be allowed to remain on their current IBS medications, provided a stable dose in the past 30 days and they fulfill entry criteria for symptom frequency and severity.

Study Design

This pilot study is designed to assess the comparative effectiveness of MD with LFD. Approximately 20 subjects will undergo a seven-day baseline screening period during which symptoms will be recorded. If a subject doesn't meet all eligibility criteria in the first seven days of the baseline screening period, the screening period can be extended up to 21 days. Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to receive either the MD or the LFD for a four-week period.



Diet interventions and delivery: Patients randomized into the LFD cohort will receive meals and snacks that are low in all FODMAP groups (lactose, fructose, polyols, etc.). The diet for the LFD cohort is essentially a re-creation of the clinically used restriction phase of the low-FODMAP diet. Patients randomized into the MD will receive meals and snacks that are consistent with an MD (plant-based foods, olive oil, etc.). We and others have shown that among the FODMAPs, fructans are the most likely culprit for IBS patients.[37,39] To ensure the MD group was not receiving very high amounts of fructans, we decided to limit the fructan content in the MD group to 4 grams/day, the average daily fructan consumption in the general US population.[40] This will ensure MD diet these patients are receiving is not low in fructan but is not very high either and is close to the US general population. Meal Delivery: Three meals and 2 snacks per day (approximate 2000 kcal/day) will be shipped several times per week by ModifyHealth. ModifyHealth has agreed to provide us with all the meals for every patient for the entire study duration without any cost (beyond this they will not have any role in data collection, analysis, and interpretation). Subjects will be instructed not to eat outside of the food provided and extra food shipment for emergency use will be provided at the beginning of the study. Meals for both groups will be packaged identically.



Blinding: To best ensure the validity of the data collected, as well as the ability to evaluate the efficacy of the MD, participants will be blinded to the mechanics and specifics of the diets provided. Participants will know that both diets (the Mediterranean and low FODMAP) may help improve their IBS symptoms but will not know that these specific diets are being compared. Instead, participants will be told that the study is investigating two different diets for IBS, and they will be receiving either Diet A or Diet B, differing in the types and amounts of specific foods provided. Furthermore, study coordinators and investigators from the site will be blinded to which diet the participant receives.

Screening Visit (Visit #1)

- Informed consent will be obtained from the subjects.
- Medical history including IBS history will be obtained from the subjects.
- Blood samples will be obtained.
- Vitals, weight and height will be obtained
- Pregnancy test will be obtained in women of childbearing age if no reliable method of contraception is being utilized (e.g. IUD, OCP,implant)
- Subjects will be given two stool collection kits for at-home collection. One stool sample will be collected prior to beginning the treatment period. One stool sample will be collected on Day 28 (-1 day).
- Subjects will be instructed on the online questionaries according to Chart A (described below) which will assess periodic symptoms and diet compliance to be completed for the duration of the study.

- Subjects will be instructed on the 3-day food diary to assess for nutritional content to be completed at the start and end of the study.
- A detailed dietary history will be obtained.

Screening Period

- Subjects will complete a 3-day food diary which will be analyzed for nutritional content.
  Subjects will complete a daily online questionnaire to assess symptoms
- For subjects who don't meet all eligibility criteria in the first seven days of the screening period, this period can be extended up to 21 days

Day 0 Visit (Visit #2)

- Patients who fulfill the inclusion and exclusion will be randomized to either the Mediterranean or low FODMAP cohorts (Diets A and B)
- Vitals will be obtained including height and weight at visit 2

Treatment Period

- Subjects will fill out a daily online questionnaire to assess symptoms and diet compliance according to Chart A throughout the treatment period.

Day 28 (End-of-treatment) Visit

- Subjects will complete a 3-day food diary which will be analyzed for nutritional content and compliance
- Adverse events and concomitant medications will be reviewed.
- Blood samples will be obtained.
- Post-treatment stool samples will be collected.
- Subjects will finish the last set of questionnaires

Clinical Outcome Measures

Online questionnaire entries will include the following measures, to be assessed on a frequency according to Chart A.

- Abdominal Pain Intensity: The abdominal pain score is a single-question, 11-point numeric rating scale in which 0 represents no abdominal pain and 10 represents the worst possible abdominal pain. Once per day, subjects will report their worst daily (in the past 24 hours) abdominal pain.
- Abdominal Discomfort Intensity: The abdominal discomfort score is a single-question, 11-point numeric rating scale in which 0 represents no abdominal discomfort and 10 represents the worst possible abdominal discomfort. Once per day, subjects will report their worst daily (in the past 24 hours) abdominal discomfort.
- Abdominal Bloating: The abdominal bloating score is a single-question, 11-point numeric rating scale in which 0 represents no abdominal bloating and 10 represents the worst possible abdominal bloating. Once per day, subjects will report their worst daily (in the past 24 hours) abdominal bloating
- Stool Frequency: Subjects will report the number of bowel movements over the previous 24 hours.
- Stool Form: Subjects will use the Bristol Stool Scale (BSS) to report the form of each bowel movement over the previous 24 hours.
- IBS Medication: Subjects will be asked whether they used an IBS medication over the previous 24 hours that is not typically taken daily (i.e., prn antispasmodic, loperamide or laxative).
- IBS-Adequate Relief: Subjects will provide a binary (yes or no) response to rate the adequacy of relief of global IBS symptoms at the start of the study and weekly thereafter.
- Quality of Life: Subjects will report quality of life measures specific to IBS using a validated 34-point questionnaire at the start and end of the study.
- IBS-SSS: Subjects will complete the IBS Symptom Severity Score questionaries at the start of the study and weekly thereafter
- Non-GI symptoms: non-GI symptoms often associated with IBS including fatigue, "brain fog", and quality of sleep will be assessed at the start and end of the study. Fatigue and brain fog will be scored using an 11-point numeric rating scale. Sleep quality will specifically be assessed with the PROMIS Sleep questionnaire.
- Anxiety: Anxiety will be assessed via GAD-7 score at the start and end of the study.

- Diet compliance: Patients will fill out the Mediterranean Diet Adherence Screener (MEDAS), described below, to assess their adherence to the Mediterranean diet at the start and end of the study. Given there are no high-quality, validated questionnaires to assess LFD adherence, a 3-day diet recall will be obtained at baseline and at the end of the study which will eventually be reviewed by a registered dietitian to confirm adherence to the LFD in the LFD group.

Chart A

	Day 0	Daily	Weekly	Day 28
Abdominal Pain		X		
Abdominal Discomfort		X		
Abdominal Bloating		X		
Stool Frequency		X		
Stool Form		X		
IBS Medications		X		
IBS Adequate Relief	X		X	X
Quality of Life	X			X
IBS-SSS	X		X	X
Non-GI Symptoms	X			X
Anxiety	X			X
Diet Compliance and 3-day food diary	X			X
Daily food log/diary		X		

Food diary/log

Participants will fill out a daily food diary where they will record breakfast, lunch, dinner, and snacks every day for the duration of the study. If they ate the food provided, they would record the food provided. If the meal consisted of items not provided by us, a detailed log of quantity and ingredients will be obtained.

3-Day diet recall

Given there are no high-quality, validated questionnaires to assess LFD adherence, a 3-day diet recall will be obtained at baseline and at the end of the study which will eventually be reviewed by a registered dietitian to confirm adherence to the dietary interventions to the allocated arms. 3-day or 24-hour diet recalls are routinely done in clinical practice to confirm adherence to LFD.

Mediterranean Diet Compliance Assessment

The Mediterranean Diet Adherence Screener (MEDAS) is a 14-question adherence tool that has been well validated.[41-44] The final MEDAS score can range between 0 and 14. For categorization of the adherence to the Mediterranean diet, we applied the following criteria: weak adherence, ≤5; moderate to fair adherence, 6–9; good or very good adherence ≥10. Participants will be asked to fill out MEDAS at the beginning of the study and again at the end of the study.

Breath gas

Participants will use a portable breath test device (MedAIRE 2®, FoodMarble Digestive Health Ltd. - https://foodmarble.com/GI) and app to measure exhaled breath hydrogen and methane content. Participants will take readings before the first (morning) and last (evening) meal of each day for the duration of the study. Breath reading results will not be made available to participants. All data will be anonymized and encrypted to

ensure participant confidentiality and data security. Patients will not record any identifiers (name, email etc.) in the app and this will not be shared with foodmarble. Unique IDs(generated and maintained in secured location by study team) will be utilized by patient to login into the app and record breath test.

Endpoints

Primary Endpoint

- Abdominal pain intensity – Proportion of patients who would be weekly responders to abdominal pain for at least 2 of the 4 weeks. A weekly responder is defined as a decrease in the weekly average of worst abdominal pain in the past 24 hours score of at least 30% compared with baseline.

Secondary Endpoints

- Adequate relief - Proportion of patients who would be weekly responders to adequate relief symptom assessment for at least 2 of the 4 weeks. A weekly responder is defined as adequate relief in symptoms in at least 2 out of 4 weeks of the treatment period.
- IBS-SSS - Proportion of weekly responders for at least 2 of the 4 weeks. A weekly responder is defined as a decrease in the weekly IBS-SSS score of at least 50 points compared with baseline.
- Bloating - Proportion of patients who would be weekly responders to bloating for at least 2 of the 4 weeks. A weekly responder is defined as a decrease in the weekly average of worst bloating in the past 24 hours score of at least 30% compared with baseline.
- Stool consistency: Proportion of patients who would be weekly responders to stool consistency assessment for at least 2 of the 4 weeks. A stool consistency weekly responder will be defined as a 50% or greater reduction in the number of days per week with at least one abnormal stool (defined as BSS 1 or 2 or 6 or 7)

Exploratory endpoints:

- Mean changes in stool frequency, abdominal discomfort, IBS-QoL, anxiety, fatigue, brain fog, and sleep quality will be measured before and after the study.

- Stool and sera will be collected during the study and stored for future analyses. The stool will be stored for microbiome analysis, fermentation indices (short-chain and branched-chain fatty acid profiles), and bile acid profile and serum will be stored for analysis of the effect of diets on permeability using serological markers such as LPS, LBP, Zonulin, and inflammatory cytokines.

- Changes in breath hydrogen and methane pattern with the dietary interventions

Statistical Analysis

All continuous variables will be tested for normality using the Shapiro-Wilk test. Normally distributed continuous data will be presented as mean (+/- SD) and will be compared pre-and post-dietary interventions using paired Student's t-test. Continuous data which are not normally distributed will be presented as median (range) and compared using Wilcoxon signed-rank test. Proportions will be expressed as percentages and compared using a chi-square test or fisher exact test as appropriate. As this is a pilot feasibility study, a sample size of 20 patients will allow us to get data on the outcomes and non-inferiority margin needed to power the larger Phase III multi-centered trial.

Potential difficulties

One of the potential difficulties might be the difficulty in patient recruitment for the study. Our group has successfully completed several pharmacological and diet-based RCTs in this patient population and has been able to recruit a much larger sample size for previous studies. However, to ensure we can recruit the required sample size, we will assign a study coordinator who will dedicate a significant proportion of her/his time to

recruiting patients from our functional and general GI clinics. Online and on-site advertisements will also be utilized to recruit patients from general gastroenterology and primary care clinics. We will further utilize a novel digital recruiting tool called “My GI Health” which will identify potential study subjects through social media platforms. We feel that this study will be attractive as we will be providing meals for the duration of the study. In addition, the lack of a placebo group will ensure that all participants will receive a potentially beneficial diet intervention. Other potential difficulties include patients being non-compliant with the diet. We are providing meals to all participants to minimize this and will obtain a daily food log, 3-day recall as well as MEDAS (Mediterranean Diet Adherence Scale) to ensure that our patients are compliant with their allocated diet arm.

Limitations

Despite our best effort (i.e. providing the meals and not disclosing the two dietary interventions being compared), there is a chance that patients realize what diet they are on. However, this risk cannot be completely eliminated in a dietary intervention study. The other limitation is the small sample size of the study. However, this is designed to be a pilot (and not a definitive study) which will be utilized to derive the non-inferiority margin and preliminary efficacy data for a larger multi-centered study.

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