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PART B
STUDY DESCRIPTION

Title of Protocol	**Effect of a low FODMAP diet on SIBO**
Principal Investigator	**Trisha Pasricha, MD, MPH**

B1. PURPOSE OF PROTOCOL

The primary objectives of this study are to evaluate the following in patients with SIBO:

1. The effect of LFD on bloating
2. The effect of LFD on hydrogen and methane levels in patients with bloating

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Bloating is the most common symptom associated with disorders of brain-gut interaction (i.e., functional bowel disorders) such as irritable bowel syndrome, a disorder characterized by abdominal pain and altered bowel habits which affects up to 11% of world population. A common cause of bloating is small intestinal bacterial overgrowth (SIBO), a condition defined by excessive and/or abnormal type of bacteria in the small bowel. The potential role of SIBO for irritable bowel syndrome (IBS) was initially proposed by Pimentel et al. Using lactulose breath tests (LBTs), 78% of patients with IBS were also diagnosed with SIBO. After antibiotic therapy, 48% of patients no longer met the Rome criteria for IBS. A recent systematic review and meta-analysis concluded that the prevalence of SIBO is increased in IBS.

Dietary factors are known triggers of IBS related symptoms up to 65% of IBS patients report symptoms attributed to food. In double-blind, randomized, placebo-controlled trials; fructose and fructans have been shown to induce IBS symptoms in a dose-dependent manner.[5] In fact, a diet low in fermentable, oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) is the most extensively investigated dietary intervention in IBS. A recent meta-analysis of seven randomized controlled trials comparing a low FODMAP diet (LFD) with various control interventions in 397 participants suggested a 31% greater likelihood in improvement of global IBS symptoms. In patients with diarrhea predominant IBS (IBS-D), Eswaran et al showed that those randomized to LFD had greater reductions in daily scores of abdominal pain, bloating, stool frequency, stool consistency, and urgency than the modified National Institute for Health and Care Excellence (NICE) diet. Others have also shown objective improvement in stool consistency of IBS-D patients with LFD using King's stool chart.

Despite the clinical efficacy of LFD in improving symptoms of IBS-D, its mechanism of action is not clear. Recently, Zhou et al have shown FODMAPs induce colonic tight junction dysfunction and visceral hypersensitivity in rat models, both of which are reversible when rats were fed an LFD. They further showed that this effect of FODMAPs is mediated by microbial dysbiosis and elevated fecal lipopolysaccharide level. However, studies evaluating the effect of LFD on colonic permeability of humans are lacking. Studies have shown significant differences in intra-individual luminal and mucosal microbiome of patients with functional gastrointestinal disorders as well as an increase in *Prevotella* abundance in IBS patients with SIBO as compared with IBS patients without SIBO. Thus, the exact effect of FODMAP on intestinal permeability and mucosal microbiome in humans is not clear and needs further evaluation.

Several studies have also shown increase in the number of mast cells in the colonic mucosa of IBS patients. Although diet is perceived as an important trigger for mucosal mast cell increase and activation reported in IBS-D, it has been poorly investigated. The above reported study by Zhou et al also reported increase in colonic mast cell in rats fed on high FODMAP diet.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design

Consenting patients fulfilling the inclusion and exclusion criteria will undergo a 7-day screening period to assess baseline symptoms and then go on a 3-week low FODMAP diet. The total study duration will be approximately 5 weeks with visits at screening and Day 21.

Screening Visit

- Informed consent will be obtained from the subjects.
- Medical history including IBS and SIBO history will be obtained from the subjects
- Blood samples will be obtained
- Glucose SIBO breath test
- Daily questionnaires. Subjects will be instructed on the online daily questionnaires (described below) to be completed for the duration of the study.
- 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 21.

Visit 2 (Start of Diet/Day 0)

- Subjects will start the low FODMAP diet. Subjects will be told to ingest only Epicured provided items (excluding water) and to avoid eating anything outside of Epicured provided items.
- Baseline stool sample will be returned

Final Visit (Day 21)

- Blood samples will be obtained
- Post-treatment stool sample will be returned
- Glucose SIBO breath test

Low FODMAP diet

Subjects who consent to participate in the study will have low FODMAP meals delivered to their home by Epicured. Epicured is a meal delivery service that provides ready-to-eat low FODMAP meals. Subjects will be required to provide their home address, name, phone number, and email address to Epicured. Epicured will provide meals and snacks to subjects for the duration of the 3-week low FODMAP period. Subjects will be told to only ingest Epicured provided items (excluding water).

Serological tests for intestinal permeability

The following serological markers for intestinal permeability will be assessed: serum lipopolysaccharide (LPS) activity measured with the Limulus Amebocyte Lysate assay (LAL, Hycult Biotechnology, the Netherlands) and serum zonulin levels (Catalog number 30-ZONSHU-E01; ALPCO, Salem, NH). This will be performed in our GI lab at BIDMC.

Serological tests for mast cell activation

Mast cell activation will be measured by tryptase level with the American Research Products assay (ARP, Waltham, MA)

Stool tests

Stool will be collected for 16S rRNA microbiome sequencing.

Concomitant Medications

Subjects will be allowed and advised to continue with their current IBS treatments (excluding rifaximin) as long as it was at a stable dose for 30 days prior to randomization.

Clinical variables
Data will be collected and stored via Research Electronic Data Capture (REDCap). Patients will be automatically emailed a link daily (via REDCap) with a REDCap link to the questionnaires listed below. Patients do not need access to WiFi, but do need Internet access (can be wired). If subjects do not have access to the Internet, they will not be eligible for participation.

- Rome IV Functional Bloating
  Patients will be asked to compete a modified version of the Rome IV bloating questionnaire specific to the past 24 hours.

- IBS-SSS
  Patients will be asked to record IBS-SSS and most common stool consistency of the day (measured using Bristol stool form scale).

- Diet compliance: Patients will also be asked to record their day's food and drink intake and record whether they were compliant with the FODMAP diet.

In addition, the following questionnaires will be administered at the end of the baseline period as well as the end of the 3-week LFD.

- Patient Reported Outcomes Measurement Information System (PROMIS)
  The Patient Reported Outcomes Measurement Information System (PROMIS) is a National Institutes of Health (NIH) set of tools used to provide information on patient outcomes in a variety of fields.

- Gastrointestinal PROMIS scales: PROMIS scales of belly pain, constipation and diarrhea will be administered to assess the severity of belly pain and diarrhea in our patients. PROMIS Belly pain questionnaire and PROMIS diarrhea questionnaire have five and six questions, respectively, which assess symptom severity on a 5 point Likert scale. Higher T-scores on these questionnaires refer to more severe gastrointestinal symptoms.
  - PROMIS belly pain asks how often did you have belly pain, severity of belly pain, interference with activities, bothersomeness and discomfort.
  - PROMIS diarrhea asks how many days did you have loose stools, interference with activities, bothersomeness, and how often you experience urgency.
  - PROMIS constipation asks how often did you experience hard stools, straining and incomplete evacuation.

<u>Blood Collection</u>
Any blood that is remaining after the analysis is completed will be stored frozen indefinitely at BIMDC for use in future studies. The sample will remain de-identified, but be labeled with the unique subject code. Information related to the subject's diagnosis, treatment, and study results will be retained and possibly used in future analysis and more information becomes identified regarding functional bowel disorders. PHI related to the stored samples will not be used in the future analysis and will be kept on BIDMC's secure server. Any samples that may be shared with collaborators will contain the subject code, but will not have any identifiable information or PHI.

B. Statistical Considerations

Sample Size Justification:

This study aims to recruit 30 subjects until 20 subjects are enrolled.

Data 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 chi-square test or fisher exact test as appropriate. Since we anticipate that most of our tests will involve continuous data that is normally distributed, we based our power analysis on pre-post comparisons using paired t-tests. Assuming two-tailed tests, with alpha set at 5%, a sample size of 20 will provide 80% power to detect a medium effect size (i.e., Cohen's d=.5) when the pre-post correlation is r=.7.

C. Subject Selection

Patients with functional bloating diagnosed per Rome IV questionnaire and without any alarm features (rectal bleeding, weight loss, nocturnal symptoms, family history of inflammatory bowel disease or celiac disease) will be considered for the study if they had:

i) Aged 18-65 years at the time of screening

Exclusion criteria

i) individuals already on a LFD or other dietary restriction such as gluten free diet within the past 6 months
ii) individuals with peanut, soy, or seafood allergies or insulin-dependent diabetes
iii) known history of celiac disease, inflammatory bowel disease or microscopic colitis
iv) prior small bowel or colonic surgery or cholecystectomy
v) pregnant patients
vi) antibiotics, excluding topical, in the past 3 months

B4. POSSIBLE BENEFITS

Subjects may experience improvement in their bloating symptoms.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Blood Drawing

The risks and discomforts of blood drawing from a vein include the possibility of pain or bruising at the site of the blood draw; occasional feeling of lightheadedness; and rarely, infection at the site of the blood draw.

There is a possible risk of loss of confidentiality, however every effort will be made to ensure patient confidentiality which includes but is not limited to only discussing medical information in a private clinical setting and collecting information necessary to accomplish the research purpose. Physical data will be kept in a locked room that only the research team have access to. Electronic data will be kept on the secure server with access granted only to the individuals on the research staff.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Patients will be identified in the following ways:

- Clinical practice of the Center for Functional Bowel Disorders and GI Motility at BIDMC
- GI referrals from BIDMC
- Review of medical records, data repositories, and appointment logs
- Clinical Query 2
- Advertisements

Recruitment letters or postcards with opt-in information will be mailed to potential study participants identified through Clinical Query 2, GI referrals, and review of medical records, databases, and appointment logs. A study coordinator will also be present in the motility lab where the breath tests are conducted to recruit any potential study participants.

Participants who are recruited through the means listed above will then be contacted by phone and a brief phone screening will be initiated to assess the subject's eligibility before scheduling the office visit.

Consent

During the screening visit the Investigator will fully explain the purpose of the study to the patient and all questions and concerns regarding the study will be addressed as well (informed consent process) in a private area in the Division of Gastroenterology.

B7. STUDY LOCATION

Privacy

Every effort will be made to ensure the patient's privacy which includes but is not limited to only discussing medical information in a private clinical setting and collecting information necessary to accomplish the research purpose.

Physical Setting

Study visits will be conducted in the Division of Gastroenterology

B8. DATA SECURITY

Physical data will be kept in a locked room that only the research team has access to. Electronic data will be kept on BIDMC server.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

B10 Dissemination of Research Results

Subjects will be thanked for their participation following their participation in the study and informed of the possibility of future publications.