CME

A Randomized Controlled Trial Comparing the Low FODMAP Diet vs. Modified NICE Guidelines in US Adults with IBS-D

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OBJECTIVES: **There has been an increasing interest in the role of fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) in irritable bowel syndrome (IBS). We report results from the first randomized controlled trial of the low FODMAP diet in US adults with IBS and diarrhea (IBS-D). The objectives were to compare the efficacy of the low FODMAP diet vs. a diet based upon modified National Institute for Health and Care Excellence guidelines (mNICE) on overall and individual symptoms in IBS-D patients.**

METHODS: **This was a single-center, randomized-controlled trial of adult patients with IBS-D (Rome III) which compared 2 diet interventions. After a 2-week screening period, eligible patients were randomized to a low FODMAP or mNICE diet for 4 weeks. The primary end point was the proportion of patients reporting adequate relief of IBS-D symptoms ≥50% of intervention weeks 3–4. Secondary outcomes included a composite end point which required response in both abdominal pain (≥30% reduction in mean daily pain score compared with baseline) and stool consistency (decrease in mean daily Bristol Stool Form of ≥1 compared with baseline), abdominal pain and stool consistency responders, and other key individual IBS symptoms assessed using daily questionnaires.**

RESULTS: **After screening, 92 subjects (65 women, median age 42.6 years) were randomized. Eighty-four patients completed the study (45 low FODMAP, 39 mNICE). Baseline demographics, symptom severity, and nutrient intake were similar between groups. Fifty-two percent of the low FODMAP vs. 41% of the mNICE group reported adequate relief of their IBS-D symptoms (*P*=0.31). Though there was no significant difference in the proportion of composite end point responders (*P*=0.13), the low FODMAP diet resulted in a higher proportion of abdominal pain responders compared with the mNICE group (51% vs. 23%, *P*=0.008). Compared with baseline scores, the low FODMAP diet led to greater reductions in average daily scores of abdominal pain, bloating, consistency, frequency, and urgency than the mNICE diet.**

CONCLUSIONS: **In this US trial, 40–50% of patients reported adequate relief of their IBS-D symptoms with the low FODMAP diet or a diet based on modified NICE guidelines. The low FODMAP diet led to significantly greater improvement in individual IBS symptoms, particularly pain and bloating, compared with the mNICE diet.**

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) illness characterized by the presence of abdominal pain and altered bowel habits (1,2). Given the absence of reliable biomarkers, IBS is defined by the presence of typical symptoms rather than a specific physiologic abnormality. With prevalence estimates of 10–15% in the general population, IBS has been shown to negatively impact quality of life and is responsible for a substantial health resource and economic burden (3,4).

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Like the clinical phenotype, the pathogenesis of IBS is heterogeneous (5). This heterogeneity has created significant challenges in the development of effective medical treatments for IBS. However, up to 2/3 of IBS patients associate symptom onset or exacerbation with eating a meal (6). Because of this, patients often are interested in learning about potential dietary interventions for their IBS symptoms (7). Current dietary advice for IBS patients includes modification of dietary fiber intake, lactose elimination, avoidance of trigger foods, regularly scheduled meals, and minimizing consumption of caffeine and fat. Unfortunately, these standard dietary recommendations are not evidence-based and oftentimes prove ineffective for IBS patients (8–11).

Recently, a more comprehensive dietary approach has been developed as a treatment for IBS. This approach restricts the intake of foods that are high in fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) which may exacerbate the symptoms of IBS. FODMAPs are short-chain carbohydrates with common functional properties in that they are poorly absorbed, osmotically active (12), and rapidly fermented by bacteria (13). Fermentation of these substrates results in gas production and an increased fluid load with secondary luminal distension and resultant peristalsis involving the distal small bowel and proximal colon. It has been postulated that these physiological effects might underlie the symptoms of IBS in a subset of sufferers, though direct and indirect effects of FODMAPs on gut microbiota (14), immune function, and mucosal permeability could also affect IBS symptoms.

Initial studies provided support for the use of the low FODMAP diet in patients with IBS symptoms, though these studies were small and utilized non-validated end points (15–18). To date, no methodologically rigorous, randomized controlled trial has evaluated the low FODMAP diet in adult IBS patients from the United States. A more recent single-blind, randomized controlled trial from Sweden evaluated usual recommendations for IBS vs. the low FODMAP diet (19). Though both dietary interventions improved IBS symptoms compared with baseline, there was no statistically significant difference in the benefits yielded by the two interventions. Given the inconsistencies of the available data, further validation of the low FODMAP diet in different populations is warranted.

We hypothesized that a diet low in FODMAPs would improve overall and individual symptoms in a greater proportion of IBS patients than dietary recommendations for IBS based on modified guidance from the National Institute for Health and Care Excellence (mNICE). To test this hypothesis, we conducted a randomized controlled trial to assess the impact of the low FODMAP diet vs. mNICE recommendations in patients with IBS and diarrhea (IBS-D).

METHODS

This was a randomized controlled superiority trial with a parallel design conducted in a 1:1 fashion. The protocol was approved by the University of Michigan Hospital and Health Systems Institutional Review Board and registered with Clinicaltrials.gov.

Patient population

Adult patients meeting the Rome III criteria for IBS-D (1) (as assessed by a gastroenterologist) were consecutively recruited from the gastroenterology and primary care clinics at the University of Michigan and via local print and online advertising. Inclusion criteria included willingness to maintain a stable dosage of antidepressants during the study, documentation of normal colonoscopy or flexible sigmoidoscopy with normal colon biopsies within 5 years, normal thyroid stimulating hormone, complete blood count, electrolyte panel, and negative evaluation for celiac disease (either tissue transglutaminase immunoglobulin A, endomysial antibody, European Medicines Agency, and/or duodenal biopsy). Exclusion criteria included IBS with mixed or constipation subtype, comorbid medical problems affecting GI transit/motility (scleroderma, poorly controlled diabetes), inflammatory bowel disease, severe renal or hepatic disease, previous abdominal surgery (other than appendectomy, cholecystectomy (if >6 months before enrollment), and gynecologic/urologic surgery), and previous treatment with a low FODMAP diet. Pregnant patients and those patients currently taking probiotics, antibiotics, or narcotics were also excluded. Active participation in another form of dietary therapy at the time of enrollment (i.e., gluten-free, low carbohydrate, high protein) was not allowed.

Study protocol

Eligible patients were asked to participate in a study that would test the efficacy of 2 diets thought to help IBS symptoms. This was a diet trial; therefore the dietitians were not blinded, though the investigators analyzing the data were blinded to randomization. After informed consent was obtained, the potential subject entered into a 2 week screening period during which severity of symptoms was assessed daily (**Figure 1**). To be eligible for randomization, both an average daily abdominal pain score of 4 or higher on an 11 point numerical rating scale (0-no pain, 10-intolerable pain) and an average daily stool consistency, assessed by Bristol Stool Form Scale (BSFS), of ≥5 were required. IBS-D patients who fulfilled the entry criteria were randomized via computer generation in a 1:1 ratio to low FODMAP diet or mNICE guidelines for IBS.

Randomized patients met with a trained research dietitian at the Michigan Clinical Research Unit (MCRU) and were counseled on their allocated diet. Patients were informed that they were randomized to one of two diets thought to improve IBS symptoms: Diet 1 or Diet 2. Using standardized instructions, the mNICE group was instructed to eat small frequent meals, avoid trigger foods, and avoid excess alcohol and caffeine. Foods containing FODMAPs were not specifically excluded as part of the mNICE instructions provided to study participants. For the low FODMAP diet, instruction was administered in a standardized manner according to published materials from Monash University (20) and teaching materials created at the University of Michigan. Dietary compliance measures used in the counseling environment included prospectively recorded 3-day food diaries and a 24-hour dietary recall. A 3-day food diary is a validated dietary intake assessment method and when compared with either a 5-day food diary or 24-hour

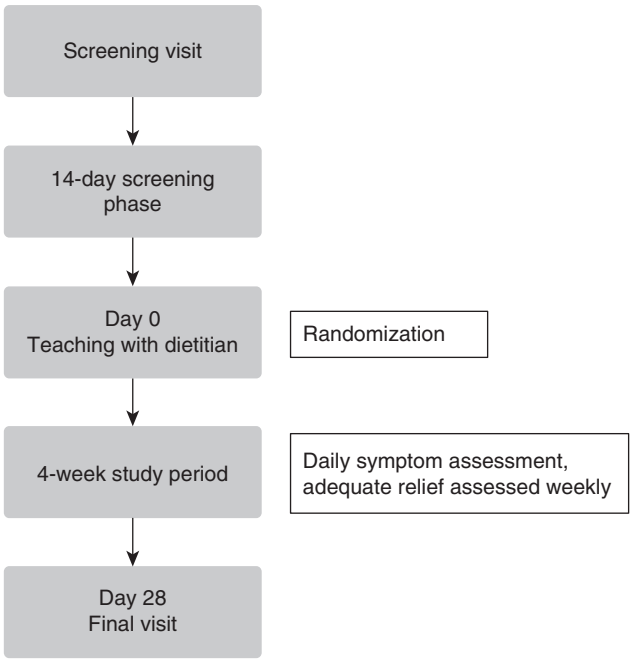

Figure 1. Schematic of study design.

dietary recall, is most accurate in validation studies (21). Food diaries were analyzed via the Nutrition Data System for Research (NDSR) computer program, measuring fructose, lactose, sucrose, pectins, sorbitol, and added sugars. At the completion of week 2, a 2nd visit was conducted to answer questions, assess adverse events, and obtain dietary information. At the completion of the 4-week study period, subjects met with the research dietitian to collect and assess the prospectively recorded 3-day food diaries and 24-hour dietary recall along with collection of clinical end points.

Symptom assessment

During the 4-week study period, subjects reported stool frequency, BSFS, and individual symptom scores for abdominal pain, bloating, and urgency (all assessed by 11 point numerical rating scale) on a daily basis, recorded via interactive voice response systems and electronic applications. Once a week, over the 4 weeks, subjects were asked about improvement of their global symptoms with the following question, "In regard to all your IBS symptoms, as compared with the way you felt before you started the diet, have you, in the past seven days, had adequate relief of your IBS symptoms?"

Clinical end points

The primary end point for which the study was powered was "adequate relief of overall IBS symptoms" during 50% or more of the last 2 weeks of study period (weeks 3–4). The proportion of patients in each group reporting adequate relief of their IBS symptoms was compared. Secondary end points included the Food and Drug Administration (FDA) composite end point (a ≥30% reduction in mean daily abdominal pain score and a decrease in mean daily BSFS value of ≥1 compared with baseline for any 2 weeks of the 4 week study period), and the individual components of the composite end point (≥30% reduction in mean daily abdominal pain score for 2/4 weeks or a decrease in mean daily BSFS value of ≥1 compared with baseline for 2/4 weeks). Other pre-specified secondary end points included between group changes from baseline in abdominal pain score, bloating score, urgency score, stool consistency as measured by BSFS, and stool frequency, averaged over each treatment week.

Statistical analysis plan

From previously published literature we assumed a response rate of 40% with standard dietary advice and a response rate of 70% with the low FODMAP diet, yielding a difference of 30%. From this it was determined that to detect a difference of 30% with at least an 80% power and alpha of 0.05, 45 subjects were needed in each treatment arm. Anticipating a dropout rate of 10%, this equated to a sample size of 50 for each of the two treatment arms.

Differences in the response rates were assessed using the Fisher's and χ^2 tests for each of the following: the primary end point (adequate relief), composite end point, reduction in abdominal pain, and improvement in stool consistency. *T*-tests were used to compare the mean scores (as averaged over each treatment week) for daily stool frequency, abdominal pain, urgency, bloating, and consistency. *P* values of <0.05 were considered statistically significant. *F*-test was used to determine the normal variance. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC).

RESULTS

Of the 171 subjects enrolled and screened between October 2012 and November 2015, 92 subjects (65 women (71%), median age 42.6 years (range 19–75 years), 68 Caucasian (74%)) were deemed eligible and randomized (**Figure 2**). Eighty-four patients completed the study period (45 low FODMAP, 39 mNICE). Seventy-four percent of patients were recruited from University of Michigan gastroenterology clinics, 22% via advertisements, and 4% from primary care populations. There were more dropouts in the low FODMAP arm (five subjects) than the mNICE arm (two subjects). Demographics and baseline symptom severity were similar between groups (**Table 1**).

Nutritional data

Baseline energy, nutrient, and FODMAP intake were similar between groups (**Table 2**), but by the end of the study period, noticeable differences were observed in nutrient intake both within and between the two groups. Specifically, daily ingested total carbohydrates and measurable FODMAPs (fructose, lactose, monosaccharides, polyols) were significantly lower in the low FODMAP arm compared with the mNICE arm. There was no change from baseline in either group for any type of fiber intake. The mNICE group consumed less fat compared with baseline, as would be predicted based on the dietary advice administered, but this was not significantly different compared with the low FODMAP group. Both arms consumed fewer calories per day

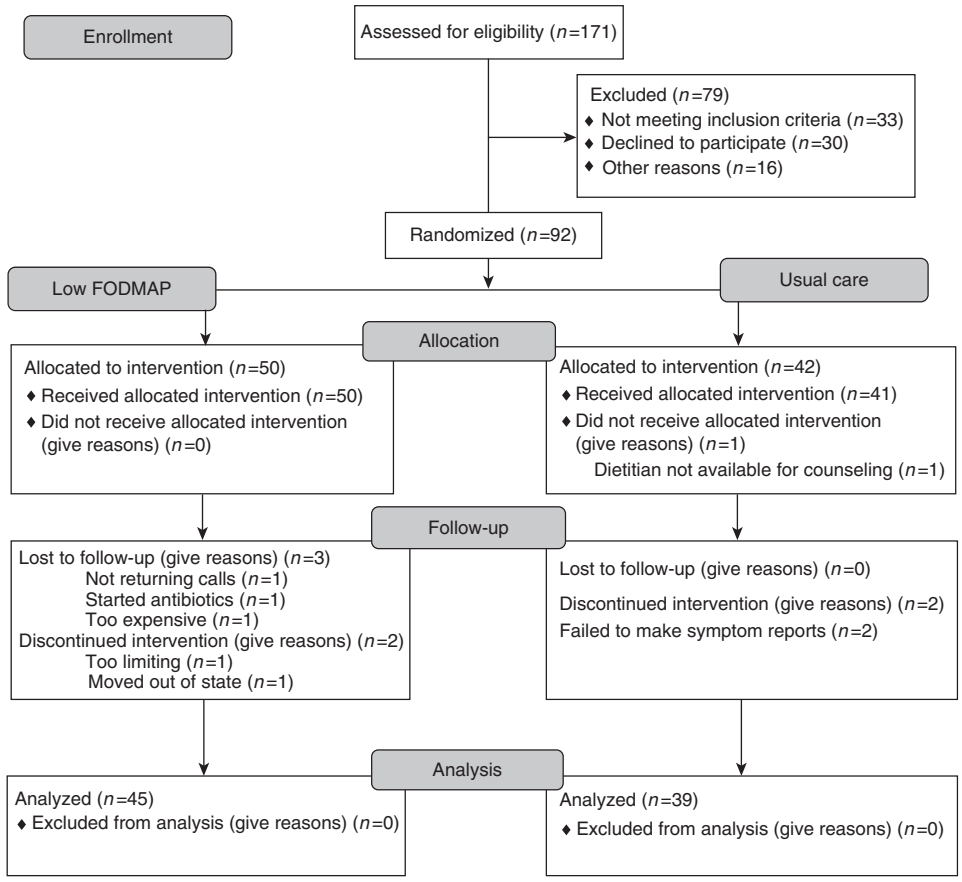

Figure 2. CONSORT flow diagram.

and fewer daily meals by 4 weeks compared with baseline. This was somewhat surprising as the only instructions for the mNICE group described smaller, more frequent meals as potentially beneficial for IBS. The amount of daily alcohol and protein was maintained in both arms throughout the intervention.

Adequate relief and composite end point

For the primary end point of adequate relief, 52% (23/44, 95% CI (0.37, 0.68)) of the low FODMAP group vs. 41% (16/39, 95% CI (0.26, 0.58)) of the mNICE group reported adequate relief of their IBS-D symptoms during at least 50% of the last 2 weeks (weeks 3–4) of the study period (P=0.31) (**Figure 3**). The proportion of patients reporting adequate relief for any 2 of 4 weeks was similar (data not shown). The low FODMAP diet led to a higher percentage of those achieving the composite end point in 2 of 4 weeks of the study period (27% (12/45, 95% CI (0.15, 0.42)) for the low FODMAP diet vs. 13% (5/39, 95% CI (0.04, 0.27)) for mNICE)), but this difference failed to reach statistical significance (P=0.13). However, more patients on a low FODMAP diet experienced ≥30% reduction in mean abdominal pain (51% (23/45, 95% CI (0.36, 0.66)) vs. 23% (9/39, 95% CI (0.11, 0.39)), P=0.008). Forty-two percent (19/45, 95% CI (0.28, 0.58)) of patients randomized to a low FODMAP diet reported improvement in stool consistency (a decrease in mean daily BSFS value of ≥1 compared with baseline for 2/4 treatment weeks) compared with 28% (11/39, 95% CI (0.15, 0.45)) of mNICE subjects (NS, P=0.18). When an intention-to-treat analysis was performed, the results were unchanged given the low number of drop-outs; the proportion of patients reporting adequate relief for both diets was the same as the per-protocol analysis (52% of low FODMAP subjects reporting adequate relief (24/46) compared with 41% for mNICE diet (16/39).

Individual symptoms

We compared two active interventions rather than an intervention with a placebo, therefore individual symptom scores of abdominal pain, bloating, and urgency were averaged by week and compared with baseline scores. Similar comparisons were made for stool consistency (BSFS) and stool frequency. Compared with baseline, the magnitude of improvement in abdominal pain (P=0.002), bloating (P=0.0008), stool consistency (P=0.02), stool frequency (P=0.0003), and urgency (P=0.0018) observed in the low FODMAP arm was significantly greater by 1 week, an effect which persisted through the duration of the study period (**Figure 4**; **Table 3**). In contrast, there was no significant improvement in abdominal pain, bloating, or stool frequency seen for subjects in the mNICE arm for any of the weeks during the study period. There were modest, but statistically significant improvements in stool consistency (by week 1, P=0.03) and urgency (by week 2,

Table 1. Demographics and baseline characteristics of patients

Characteristic	Low FODMAP *N*=50	mNICE *N*=42	*P* value
Average age (years)	41.6±14.70	43.8±15.2	*P*=0.4908
Average age–no. of patients (%)			*P*=0.4939
19–32 years	18 (36)	15 (35.7)	
33–49 years	18 (36)	11 (26.2)	
50–75 years	14 (28)	16 (38.1)	
Sex–no. of patients (%)			*P*=0.2850
Female	33 (66)	32 (76.2)	
Male	17 (34)	10 (23.8)	
Race–no. of patients (%)			*P*=0.3525
White	39 (78)	29 (69.1)	
Black	4 (8)	6 (14.3)	
Asian	0 (0)	3 (7.1)	
Latino	3 (6)	1 (2.4)	
Other	2 (4)	2 (4.8)	
Unknown	2 (4)	1 (2.4)	
Average BMI(kg/m^2)	27.2±6.12	31.7±7.96	*P*=0.0028
BMI–no. of patients (%)			*P*=0.1849
Underweight (≤18.5 kg/m^2)	1 (2)	0 (0)	
Healthy weight (18.6–24.9 kg/m^2)	18 (36)	10 (24.4)	
Overweight (25–29.9 kg/m^2)	16 (32)	10 (24.4)	
Obese (≥30 kg/m^2)	15 (30)	21 (51.2)	
Abdominal pain score	5.10±1.5	5.06±1.34	*P*=0.9051
Bloating score	4.87±1.83	5.01±2.07	*P*=0.7195
Bristol Stool Form	5.21±.60	5.25±.70	*P*=0.7710
Stool frequency	3.45±1.66	3.37±1.76	*P*=0.8204
Urgency score	4.98±1.93	5.39±2.1	*P*=0.3347

BMI, body mass index; FODMAP, fermentable oligo-, di-, and monosaccharides and polyol; mNICE, modified National Institute for Health and Care Excellence guidelines.

P=0.01). Differences in the magnitude of response yielded by the low FODMAP and mNICE diets at week 4 compared with baseline were significantly greater for abdominal pain (*P*=0.0049), bloating (*P*=0.0019), stool consistency (*P*=0.0092), stool frequency (*P*=0.0003), and urgency (*P*=0.0419) (**Table 3**).

Predictors of response

There were no significant differences in race, BMI, gender, or baseline symptom severity for abdominal pain, bloating, or stool consistency amongst responders and nonresponders for either adequate relief or a ≥30% reduction in abdominal pain. Baseline psychological distress as measured by Hospital Anxiety Depression Scale did not influence the response rates to either dietary intervention. Detailed psychometric and quality of life data will be reported elsewhere.

Adverse events and patient follow-up

Both interventions were generally well tolerated. While patients did not report any significant adverse events throughout the study or at the follow-up visits, more patients in the low FODMAP arm dropped out of the study (**Figure 2**). Reasons for dropout included failing to make symptom reports (mNICE) and not returning phone calls, initiating of antibiotics, added expense of the diet, moving out of state, and the diet being too restrictive (low FODMAP).

DISCUSSION

We report data from a randomized controlled trial comparing the low FODMAP diet vs. dietary recommendations based upon modified NICE guidelines in IBS patients with diarrhea. Our study, the largest randomized controlled trial (RCT) to date and the only one conducted in the US, yielded a mixed message regarding the efficacy of the low FODMAP diet when compared with the mNICE diet, demonstrating that both dietician-taught interventions led to adequate relief of IBS symptoms in 40–50% of patients. For the pre-specified primary end point of adequate relief of overall IBS symptoms, there was no statistically significant difference in benefit offered by the low FODMAP diet vs. the mNICE diet. In addition, for a composite end point similar to that endorsed by the US Food & Drug Administration, which requires benefits for abdominal pain and stool consistency, we did not identify a statistically significant difference between interventions. It is interesting that for both of these end points, there was an absolute benefit offered by the low FODMAP diet over the mNICE diet that did not reach statistical significance. The therapeutic gains of 11% for the adequate relief end point and 14% for the composite end point yielded by the low FODMAP diet are similar to other currently available medical therapies (rifaxmin, alosetron, eluxadoline) for IBS with diarrhea (22–26). As we powered the study for a difference in diet interventions of 30% for adequate relief, it is very likely that a type II error may have confounded our ability to demonstrate statistically significant differences between the low FODMAP and mNICE diets.

A careful assessment of the individual symptom data from our study yields some powerful messages regarding the efficacy of the low FODMAP when compared with the mNICE diet. Patients randomized to the low FODMAP diet experienced a robust benefit in abdominal pain and bloating when compared with the mNICE diet. Whether this end point was evaluated as a ≥30% reduction in abdominal pain scores compared with baseline or the mean between group differences in abdominal pain or bloating scores at week 4 compared with baseline, there were statistically significant differences favoring the low FODMAP diet. The low FODMAP diet also led to a greater magnitude of benefit at week 4 when compared with baseline for stool consistency, stool frequency as well as urgency compared with the mNICE diet. It is notable that the low FODMAP diet led to a

Table 2. Daily nutritional intake as measured by NDSR for each dietary intervention, comparisons made per protocol (mean±s.d.)

Variable	Low FODMAP			mNICE			*P* value between groups: baseline	*P* value between groups: week 4
	Baseline (*n*=43)	Week 4 (*n*=41)	*P* value within group	Baseline (*n*=39)	Week 4 (*n*=37)	*P* value within group		
Kilocalories	2020±661	1691±600.7	*P*=0.0023	2006±502.5	1835±714.1	*P*=0.0416	*P*=0.9166	*P*=0.3370
Average number of daily meals	5.43±1.7	4.92±1.5	*P*=0.0119	5.52±1.7	4.80±1.4	*P*=0.0040	*P*=0.8070	*P*=0.7259
Protein (g)	76.53±28.6	72.7±36.7	*P*=0.3959	74.14±21.9	77.27±36.1	*P*=0.4959	*P*=0.6743	*P*=0.5790
Fat (g)	79.26±32.9	75.05±37.9	*P*=0.3580	80.97±25.6	69.90±36.3	*P*=0.0116	*P*=0.7954	*P*=0.5425
Alcohol (g)	8.60±16.4	5.91±12.4	*P*=0.3580	5.74±9.3	7.14±13.5	*P*=0.6179	*P*=0.3311	*P*=0.6754
Carbohydrates (g)	244.59±87.7	180.31±55.5	*P*<0.0001	244.07±70.6	219.39±84.3	*P*=0.0450	*P*=0.9767	*P*=0.0220
Monosaccharides (g)	43.59±33	25.96±14.1	*P*=0.0013	39.47±28	37.3±30.5	*P*=0.6686	*P*=0.5457	*P*=0.0448
Fructose (g)	20.97±17.2	10.44±7.1	*P*=0.0004	19.62±14.6	17.79±14.3	*P*=0.4920	*P*=0.7051	*P*=0.0075
Total dietary fiber (g)	18.67±8.4	17.76±7.2	*P*=0.4336	19.14±8.1	18.68±9.1	*P*=0.8972	*P*=0.7992	*P*=0.6173
Insoluble dietary fiber (g)	12.68±6.8	12.04±5.5	*P*=0.4744	12.73±6.3	12.22±6.7	*P*=0.9720	*P*=0.9682	*P*=0.8929
Soluble dietary fiber (g)	5.86±2.3	5.43±2.2	*P*=0.2114	6.32±2.5	6.27±3.0	*P*=0.9802	*P*=0.3905	*P*=0.1744
Lactose (g)	9.95±9.9	2.10±2.7	*P*<0.0001	9.30±8.8	7.32±6.9	*P*=0.1927	*P*=0.7543	*P*=0.0001
Polyols (g)	0.98±1.3	0.68±1.4	*P*=0.3173	0.57±0.6	0.84±1.1	*P*=0.0872	*P*=0.0746	*P*=0.5901

FODMAP, fermentable oligo-, di-, and monosaccharides and polyol; mNICE, modified National Institute for Health and Care Excellence guidelines.

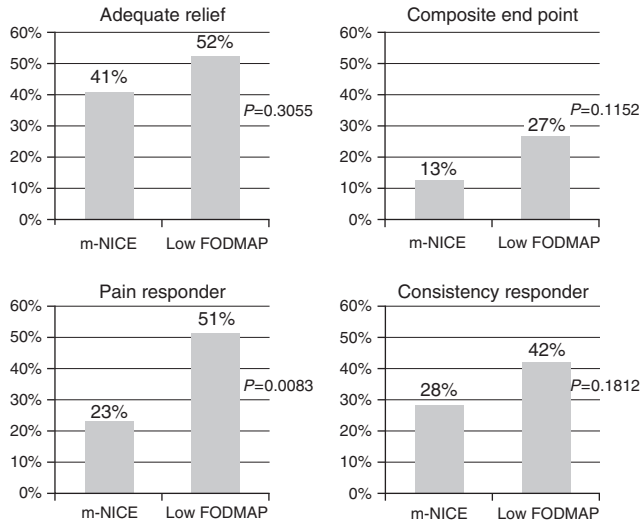

Figure 3. The proportion of subjects meeting the primary end point (adequate relief) for at least 50% of the last 2 weeks of the study period and the secondary end points over 2/4 weeks (FDA composite end point, 30% reduction in mean daily abdominal pain score, and decrease in mean daily BSFS value of ≥1 compared with baseline).

greater magnitude of improvement and shorter time to benefit for abdominal symptoms, including pain and bloating, than for bowel related end points, including stool consistency, stool form and urgency. This observation, along with the fact that both interventions were delivered by trained dietitians, may provide possible explanations for our inability to show a statistically significant benefit of the low FODMAP diet for the adequate relief or composite end points. These results may also serve to inform the selection of the most appropriate primary and secondary end points for future research addressing the low FODMAP diet. For example, our study makes clear that the most robust benefits yielded by the low FODMAP diet are for abdominal pain and bloating and thus, these symptoms may be better choices than adequate relief for the primary outcome of future studies.

Our results are in line with a number of previously published retrospective, non-randomized (13,16,17,27,28) and randomized clinical trials (15,19), which have reported clinical benefits of the low FODMAP diet in IBS patients, particularly for abdominal pain and bloating. Our results differ from one recent RCT from Sweden with a similar study design, which reported no differences in clinical outcomes yielded by the low FODMAP diet compared with a diet based upon the NICE guidelines (19). The explanation for the different findings between the Swedish trial and our study is likely multifactorial. First, questions about whether some FODMAP containing foods may have been excluded from the mNICE diet in the Swedish trial have been raised. In our study, we modified the NICE guidelines so as not to instruct subjects to avoid FODMAP containing foods. Other potential issues which could have contributed to the discordant results between the Swedish study and ours include differences in sample size, efficacy

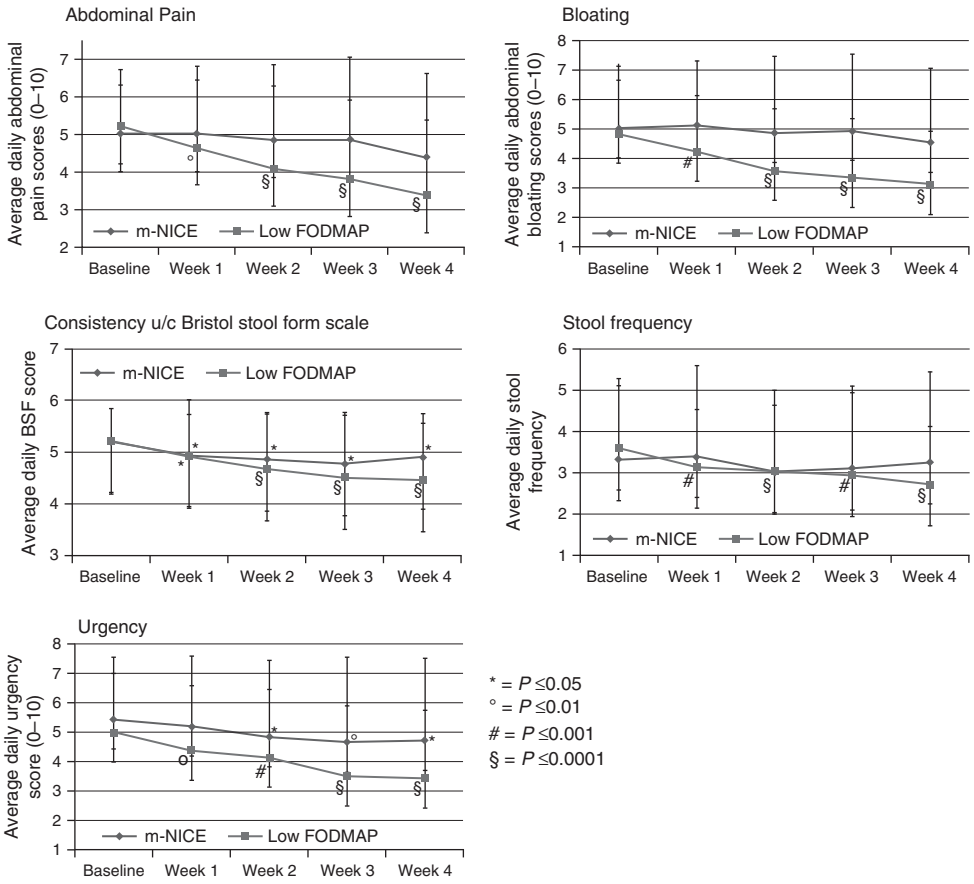

Figure 4. Comparison of daily scores averaged by week for abdominal pain score, bloating score, BSFS, stool frequency, and urgency score to baseline for each treatment group. *P* values refer to the change within group comparing specified week with baseline score.

Table 3. The effect of dietary intervention on individual IBS symptoms

Variable	Low FODMAP (*n*=43)				mNICE (*n*=39)				*P* value between groups
	Baseline	Week 4	Difference	*P* value within group	Baseline	Week 4	Difference	*P* value within group	
Abdominal pain, mean±s.d.	5.22±1.5	3.38±2.0	1.8	*P*=<0.0001	5.01±1.3	4.41±2.2	0.6	*P*=0.0574	*P*=0.0049
Bloating, mean±s.d.	4.84±1.8	3.11±1.8	1.7	*P*=<0.001	5.02±2.1	4.54±2.5	0.49	*P*=0.0557	*P*=0.0019
Stool consistency, mean±s.d.	5.22±.62	4.46±1.1	0.76	*P*=<0.0001	5.19±.66	4.90±.85	0.28	*P*=0.0174	*P*=0.0092
Stool frequency, mean±s.d.	3.59±1.7	2.72±1.4	0.86	*P*=<0.0001	3.32±1.8	3.25±2.2	0.07	*P*=0.6634	*P*=0.0003
Urgency, mean±s.d.	4.99±1.9	3.43±2.3	1.5	*P*=<0.0001	5.43±2.1	4.71±2.8	0.71	*P*=0.0215	*P*=0.0419

FODMAP, fermentable oligo-, di-, and monosaccharides and polyol; mNICE, modified National Institute for Health and Care Excellence guidelines.
Between group *P* values refer to the change from baseline between groups at week 4 for low FODMAP and control subjects.

end points, how the diets were administered, and the subtypes of IBS patients included. It is also quite possible that intrinsic differences in genetics, microbiome, diet, and cultural issues between the study populations could have contributed to the differences in results reported by the two studies. Despite the differences in the two trials, it is interesting that each reported that roughly half of IBS patients experience symptom improvement with the low FODMAP diet.

There are a number of limitations which should be considered when interpreting the results of our trial. First, dietitians and patients could not be blinded to the diet interventions utilized in this trial. As such, it is possible that bias could have been interjected by either of these parties. When we began this trial in 2012, very few patients had any awareness of the low FODMAP diet or the NICE guidelines. Though awareness has increased over time, the low FODMAP diet remains relatively unrecognized in Michigan. We were careful to tell patients that they were to be randomized to one of two diet therapies for IBS and to avoid any discussion of efficacy or research conducted regarding either intervention. Another limitation of our study was that research meals were not provided to study participants. Thus, it is possible that patient's diets could have been contaminated by foods which did not adhere to the assigned diet interventions. We tried to limit this possibility by conducting a 2-week study visit and by having study participants complete sequential food diaries. The food diaries collected as part of this trial suggested that study participants did a remarkably good job adhering to their assigned study diet. In addition, we would argue that our study provides "real world" results which are likely to be representative of what a clinician might expect when recommending the low FODMAP diet. As has already been mentioned, though our study is the largest RCT reported in the literature to date, it was underpowered to detect modest differences in clinical benefit yielded by the low FODMAP and mNICE diets for our primary end point.

The inclusion of only patients fulfilling criteria for IBS-D was deliberate; we hypothesized that FODMAPs increase colonic fermentation and the production of fermentation byproducts such as short-chain fatty acids which through their osmotic effects can cause diarrhea. Thus, we surmised that a low FODMAP diet might be most beneficial for IBS-D patients. Our results actually suggest otherwise; that the greatest benefits of the diet are for abdominal symptoms including pain and bloating with less impressive benefits for bowel symptoms.

Though the randomization code was computer generated, there was an imbalance in the number of mNICE subjects at the end of the trial. In retrospect, this may have occurred because the computer generated randomization strategy we employed did not include blocking. This allocation discrepancy was exacerbated by our decision to terminate the study before full enrollment, which was based on lagging enrollment due to both GI practitioners' and patients' increased desire to refer directly to our dieticians for low FODMAP teaching rather than to a randomized controlled trial. Though we regret not fully enrolling the mNICE arm of the study, the reality is that enrolling another 10 patients would not have significantly influenced our primary outcome of adequate relief. In order to demonstrate a statistically significant between-group difference for this end point (based upon a therapeutic gain of 11%), we retrospectively calculated that a sample size of over 500 IBS-D patients would be required.

As expected, the low FODMAP diet resulted in substantially reduced intake of measurable FODMAPs. However, we did not expect that both dietary interventions would result in decreased overall caloric intake. A similar reduction in caloric intake was also reported by Bohn *et al.* (19) A decrease in intake can occur from changed dietary behavior caused by keeping a food diary or underreporting. It is well established in the nutrition literature that measuring human dietary intake is difficult and at this time, there is no method which yields flawless results. Rather, completing a 3-day food diary has proven to be the best validated tool (validated against actual observed intake) available to measure actual intake (29–31). The full low FODMAP diet is not intended to be maintained indefinitely, thus long-term adverse effects on health from reduced caloric intake should not be a significant concern. Future studies to address the durability of response and important safety issues, particularly pertaining to nutrition and effects of the diet on the gut microbiome, are strongly encouraged.

In summary, this US RCT showed that the low FODMAP diet and a diet focused on modified NICE guidelines led to adequate relief of overall symptoms in 40–50% of patients with IBS and diarrhea. The low FODMAP diet led to significantly greater benefits for individual IBS symptoms, particularly abdominal pain and bloating, than the mNICE diet. Thus, our data support a role for the low FODMAP diet in the management of patients with IBS and diarrhea. It is important to note that the low FODMAP diet is not intended as a long-term solution for IBS patients. Uncertainties about the long-term efficacy and safety of the low FODMAP diet should encourage providers to recommend a structured reintroduction of FODMAP containing foods to responders to the full low FODMAP diet. This exercise allows IBS patients to diversify the types and quantity of foods they can consume while maintaining symptom remission.

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CONFLICT OF INTEREST

Guarantor of the article: Shanti L. Eswaran, MD.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Dietary fermentable carbohydrates (FODMAPs) may exacerbate gastrointestinal (GI) symptoms in irritable bowel syndrome (IBS).
- ✓ Evidence that FODMAP restriction improves IBS symptoms is conflicting.

WHAT IS NEW HERE

- ✓ A low FODMAP diet and a diet based upon modified National Institute for Health and Care Excellence (NICE) guidelines led to adequate relief of overall IBS symptoms in 40–50% of IBS and diarrhea (IBS-D) patients.
- ✓ The low FODMAP diet led to significantly greater improvements in individual IBS symptoms, particularly pain and bloating, compared with the mNICE diet.
- ✓ This study supports a role for FODMAP restriction when treating IBS with diarrhea.

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