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A Novel, IBS-Specific IgG ELISA-Based Elimination Diet in Irritable Bowel Syndrome: A Randomized, Sham-Controlled Trial

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BACKGROUND & AIMS: Personalized dietary therapies for irritable bowel syndrome (IBS) are needed and an immunoglobulin (Ig)G-antibody–based elimination diet presents a potential solution. However, existing studies have serious methodological limitations. This study aimed to assess the efficacy of an elimination diet by using a novel IBS-specific IgG assay. **METHODS:** We conducted a randomized, double-blind, sham-controlled trial enrolling subjects with IBS from 8 centers. Subjects positive for ≥1 food on an 18-food IgG assay and an average daily abdominal pain intensity score between 3.0 and 7.5 on an 11.0-point scale during a 2-week run-in period were randomized to either an experimental antibody-guided diet or sham diet for 8 weeks. The primary outcome was a ≥30% decrease in abdominal pain intensity for ≥2 of the last 4 weeks of the treatment period. **RESULTS:** Among 238 randomized subjects with IBS, 223 were included in the modified intention-to-treat analysis. A significantly greater proportion of subjects in the experimental diet group met the primary outcome than those in the sham diet group (59.6% vs 42.1%, $P = .02$). Subgroup analysis revealed that a higher proportion of subjects with constipation-predominant IBS and IBS with mixed bowel habits in the experimental diet group met the primary endpoint vs the sham group (67.1% vs 35.8% and 66% vs 29.5%, respectively). **CONCLUSIONS:** Subjects on an IgG-guided elimination diet were more likely to achieve the primary endpoint than those on a sham elimination diet. Subgroup analysis suggests a more robust benefit for subjects with constipation-predominant IBS and IBS with mixed bowel habits. This highlights the potential effectiveness of a personalized elimination diet based on a novel IBS-specific IgG assay. A larger study is warranted to validate these observations. (ClinicalTrials.gov, Number NCT03459482.)

Keywords: Functional Bowel Disorder; Precision Medicine; Bloating; IBS With Diarrhea; Bowel Habits; Disorders of Gut-Brain Interaction.

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction characterized by abdominal pain associated with altered bowel habits, affecting approximately 4% to 9% of the global population.[1] The considerable negative impact of IBS has been well documented, with 24% to 28% of patients with IBS reporting missing work due to their IBS symptoms, 82% to 87% recording decreased work productivity, and many reporting lower health-related quality of life.[2,3] More than 90% of patients with IBS state that they avoid certain foods and drinks and dietary modifications, either self-induced as well as provider-directed, are commonly used to manage IBS symptoms.[4]

Over the past decade, there has been considerable interest in dietary interventions for IBS, such as the low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet, which is effective at reducing abdominal pain and bloating.[5] Although the low-FODMAP diet is the most evidence-based elimination diet for IBS, it is restrictive; provides benefits to only 50% to 60% of IBS sufferers; and is cumbersome, time-consuming, and costly.[6–10] Furthermore, it is not currently possible to predict responders to a low-FODMAP diet before initiating the diet. Therefore, there is an unmet need to develop more personalized approaches to dietary therapies for IBS.

One promising approach involves an elimination diet based on elevated immunoglobulin G (IgG) antibodies to specific foods. It has been hypothesized that IgG antibodies are generated in response to exposure of the gut immune system to specific food antigens.[11] Previous studies have assessed the efficacy of IgG-based elimination diets in managing IBS symptoms, yielding conflicting results.[12–15] Most of these studies have suffered from methodological limitations including open-label design, lack of sham or control arms, single-center settings, and small sample sizes.

No major professional societies, such as the American Gastroenterological Association, the American College of Gastroenterology, the United European Gastroenterology, or

Abbreviations used in this paper: **API, abdominal pain intensity; BSS, Bristol Stool Scale; ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug Administration; FODMAP, fermentable oligosaccharides, monosaccharides, disaccharides, and polyols; IBS, irritable bowel syndrome; IBS-AR, IBS adequate relief; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-M, IBS with mixed bowel habits; IBS-GIS, IBS global improvement scale; IBS-SSS, IBS symptom severity score; IgG, immunoglobulin G; PP, per-protocol; RPSQ, Recent Physical Symptoms Questionnaire; SGA, subjective global assessment.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Immunoglobulin G-antibody–based elimination diet can provide a personalized approach to dietary therapy in irritable bowel syndrome but existing studies have serious methodological issues.

NEW FINDINGS

An elimination diet based on a novel irritable bowel syndrome–specific, immunoglobulin G assay was superior to a sham diet in patients with irritable bowel syndrome in improving abdominal pain.

LIMITATIONS

Although subgroup analysis showed that symptom improvement was more pronounced in patients with constipation-predominant irritable bowel syndrome and irritable bowel syndrome with mixed bowel habits, we were not adequately powered for this subgroup analysis. Adherence to the elimination diet was lower than the sham diet. Future studies should perform detailed adherence assessments using food diaries or recalls to delineate its impact on clinical outcomes.

CLINICAL RESEARCH RELEVANCE

A larger, adequately powered study to assess the efficacy of an elimination diet based on this novel immunoglobulin G assay in patients with constipation-predominant irritable bowel syndrome and irritable bowel syndrome with mixed bowel habits is required.

BASIC RESEARCH RELEVANCE

Mechanisms of how immunoglobulin G-antibody response to food antigen generates symptoms in irritable bowel syndrome are not well understood. Delineating this might provide new insights into food-related irritable bowel syndrome pathophysiology.

the Asian Neurogastroenterology and Motility Association, recommend IgG-based testing to inform IBS management. In a previous double-blind, single-center, randomized controlled trial involving 150 patients with IBS, an IgG-based elimination diet demonstrated a 10% greater improvement in IBS symptom severity score (IBS-SSS) in comparison to a sham elimination diet.[15] Among fully compliant patients in this study, the therapeutic gain of the IgG-based elimination diet increased to 26% over placebo.[15] Although these results were promising, investigators did not provide a scientific rationale to explain the selection of foods included in the IgG assay that was used.[15] Furthermore, the cutoff used to determine a positive IgG test result for each food was not based on results from a healthy control population.[15] This is particularly important, as IgG responses to dietary antigens are not only elevated in patients with IBS but also in patients with other inflammatory conditions/diseases and the general population.[16] Given these limitations, there is a need for additional studies investigating the efficacy of IgG-based elimination diets using a rigorous, scientifically developed test.

The current study addresses these limitations using a novel IBS-specific IgG assay (inFoods IBS). This assay uses specific foods based on discriminatory *P* values between patients with IBS and healthy controls. Clinical cutoffs discriminate positive and negative results through statistical analysis of reference interval of healthy controls (95th percentiles of normal distribution). Here, we report the results from a clinical trial comparing the efficacy of an elimination diet using this novel IBS-specific IgG assay against a sham elimination diet.

Methods

Study Design and Procedures

We conducted a multicenter, randomized, double-blind, sham-controlled trial enrolling subjects from 8 centers in the United States from June 21, 2018, to December 31, 2021, to evaluate the efficacy of an experimental diet treatment that eliminated foods based on results of the inFoods IBS enzyme-linked immunosorbent assay (ELISA) (Biomerica, Irvine, CA). The trial was registered with clinicaltrial.gov (NCT03459482) and was approved by each institution's institutional review board. All authors had access to the study data and reviewed and approved the final manuscript.

Subjects with IBS were enrolled in a 10-week clinical trial. Subjects entered a 2-week run-in period followed by an 8-week treatment period during which they received either an antibody-guided experimental diet or a sham diet. During the screening visit, each subject disclosed any immunoglobulin E–based food allergies or intolerances, any current foods they eliminated from their diet, and the consumption rate of common foods. All subjects provided blood samples to be analyzed with the inFoods IBS ELISA (methods to develop the assay are described in the supplementary material). After the screening visit, each subject was enrolled in the run-in period (day −14 to day 0). During this period, they completed a 3-day diet diary and a daily survey of abdominal pain, stool consistency, and bloating. If subjects had missing values for ≥5 of the 14 days, they were given another 2 weeks to collect their baseline values. Subjects were excluded if they failed to collect their symptom information for ≥5 days.

At the end of the run-in period, eligible subjects were randomized to 1 of the 2 groups in a 1:1 allocation ratio to an experimental diet group that eliminated foods based on a positive result on the inFoods IBS ELISA assay or a sham elimination diet. The sham elimination diet contained the same number of foods removed as the number of positive food sensitivities but the foods eliminated in the sham diet tested negative on the IgG assay. Baseline food frequency questionnaires were reviewed and special care was taken to ensure, whenever possible, that the foods eliminated in the sham group were consumed at a similar rate as the foods to which subjects tested positive. In addition, efforts were made to match the eliminated foods in terms of belonging to the same food group (eg, vegetable, fruit, cereal). For example, if a sham diet subject tested IgG positive for corn and walnuts, and their baseline dietary diaries identified that alternative grains and nuts (eg, rice and almonds) were consumed at a similar frequency, then rice and almonds would be eliminated. In subjects in whom alternatives to foods with elevated IgG results were not found within the same food group, the most appropriate alternative from another food group would be eliminated. For example, if a

sham patient tested IgG positive for cow's milk and their baseline diaries indicated that they only consumed dairy products derived from cow's milk, then another source of animal protein such as turkey, chicken, or tofu would be eliminated, based on the frequency of consumption that matched cow's milk products. Thus, this approach aimed to achieve balance between the groups in the amount and type of foods that they consumed during the study period and was personalized to each subject.

Both true and sham diets were prepared for each subject. Once randomization was completed by the electronic data capture, the appropriate diet information sheet was uploaded to the electronic data capture system. This was customized for each participant with a separate information sheet for each food they needed to eliminate. Each subject received printed information that listed the foods they needed to eliminate and provided instructions on how to operationalize food elimination in their daily lives (eg, reading food labels, grocery shopping, common sources). The formatting of these information sheets was similar for the sham and intervention groups. An experienced study coordinator reviewed this information with each participant over 15 to 30 minutes (depending on the number of positive food items). Time spent per participant was similar between the 2 groups.

Two dietitians helped design the individualized sham diet using the principles described previously. They played a key role in developing, reviewing, and finalizing the diet information provided to the study participants (see previously). In addition, the dietitians developed a comprehensive guide for the research staff on how to counsel the participants to adhere to their assigned dietary protocols.

Study Population

Subjects 21 years and older with IBS (based on Rome IV criteria) were recruited for the study. In addition, subjects were required to have a 2-week average abdominal pain intensity (API) score between 3.0 and 7.5 measured during the run-in period. API is an 11-point Likert scale recording the worst abdominal pain in the past 24 hours. Subjects currently on medications for the treatment of IBS were allowed to continue these if they were on stable doses ($>$3 months) and no changes were planned or made in these medications for the duration of the study. All patients with IBS who met this inclusion criterion were screened further and patients with self-reported food intolerance/triggers were not specifically selected for the study.

Exclusion criteria included subjects with a history of gastroparesis, uncontrolled gastroesophageal reflux disease, anorexia/bulimia, celiac disease, inflammatory bowel disease, abdominal cancers, malabsorption syndromes, prior gastrointestinal surgery (except cholecystectomy and appendectomy $>$6 months), psychosis, schizophrenia, mania, or major psychiatric illness requiring hospitalization within the previous 6 months. Those who received rifaximin in the past 3 months, those undergoing an alternative diet intervention such as a low-FODMAP diet or gluten-free diet, and those who were planning to change their medications for IBS were also excluded. Subjects with chronic pain from a non-IBS diagnosis and those with current or previous (within the past 3 months) narcotic medication use were also excluded. Finally, diabetic subjects on metformin and subjects with uncontrolled diabetes (HBA1c $>$7.5) were excluded from the study. All subjects provided written informed consent.

Study Measures

API and bloating were measured on an 11-point Likert scale from 0 to 10 based on the response to worst daily abdominal pain and bloating. Stool consistency was measured by the Bristol Stool Scale (BSS) and recorded for each bowel movement. Subjects also reported the number of bowel movements and whether they were associated with complete emptying (ie, CSBM). The IBS-SSS measures 5 items (severity of abdominal pain, number of days with abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and interference with quality of life), each on a 0 to 100 scale. IBS-SSS scores can range from 0 to 500, with higher scores indicating greater symptom severity. A decrease of 50 points is considered a clinically meaningful improvement in symptoms.[17] The IBS global improvement scale (IBS-GIS)[18] measures participants' global improvement in the past 7 days on a scale that ranges from 1 (substantially worse) to 7 (substantially improved). IBS adequate relief scale (IBS-AR)[19] is a single dichotomous question: "Have you had adequate relief of your IBS symptoms over the past week?" The Subject Global Assessment of Relief (SGA) measures relief of symptoms during the past week concerning overall well-being, symptoms of abdominal pain/discomfort, and bowel habits on a scale that ranges from 1 (completely relieved) to 5 (worse).

Study Outcomes

Subjects reported their daily API, bloating, stool consistency, and frequency. They also reported their compliance with the diet and medication use daily. IBS-AR and SGA were reported weekly. IBS-SSS and IBS-GIS were reported at randomization, week 4, and week 8.

The primary outcome was the Food and Drug Administration (FDA) responder definition for API (ie, a $\geq$30% reduction in mean daily abdominal pain score from baseline for $\geq$2 of the last 4 weeks of the treatment period). This was decided a priori after 3 meetings with the FDA team that recommended using a responder analysis (and not a continuous outcome) to ensure that the change in outcome was clinically meaningful and matched the rigor of previous registration trials of FDA-approved medications for patients with IBS. Given that this study planned to enroll all IBS subtypes, the responder analysis for change in API was deemed the most appropriate endpoint for the study.

Secondary outcomes included change from baseline in API, bloating, stool consistency, IBS-SSS, IBS-GIS, and SGA. For API and bloating, change from baseline (ie, average of the 2-week baseline period) to study completion (average of weeks 7 and 8) was calculated. For stool consistency, the number of days a subject had a normal bowel movement (BSS 3–5) was compared between the 2 groups. If a subject did not have a bowel movement that day it was recorded as if they had an abnormal bowel movement. IBS-SSS and GIS were compared between day 0 and the last visit (week 8). An SGA responder was defined as a response of "considerably relieved" or "better" for at least 4 of the 8 weeks. IBS-AR response was defined as reporting yes to having adequate relief for at least 50% of weekly assessments in the last month of the study. A responder

analysis using a 50-point reduction in IBS-SSS was also performed. Change in stool frequency was compared for IBS-D and IBS-C. Last, a subgroup analysis based on the 3 subtypes of IBS (IBS-C, IBS-M, and IBS-D) was performed.[20]

Compliance

A sensitivity analysis including those who were compliant with the diet was performed. Subjects were asked a yes or no question "Did you adhere to the diet today" every day of the 8-week treatment period. To be considered compliant with the diet, a subject had to respond to this question at least 70% of the days and answer "yes" for at least 80% of the responses (defined apriori).

Statistical Analysis

We performed a modified intent-to-treat analysis that consisted of all randomized subjects who received a study diet. For sensitivity analysis, a per-protocol (PP) analysis consisting of subjects who were compliant with the diet was performed.

Results were expressed as mean (SE) for continuous variables and count (%) for dichotomous variables. For the analysis, the least-squared mean was used for comparison. A multivariate model was used to assess the change from baseline at 8 weeks. For continuous outcomes, a general linear mixed model adjusted for treatment (experimental vs control), number of food sensitivities (<7, ≥ 7), IBS type (IBS-D, IBS-C, IBS-M), age, gender, site, baseline Recent Physical Symptoms Questionnaire (RPSQ), baseline IBS-SSS, time, and the time $\times$ treatment interaction was used. Random effects for subjects were used to account for the correlation among repeated measures in the same individuals.

For dichotomous outcomes, a generalized linear mixed model with a logit link adjusted for treatment (experimental vs control), the number of food sensitivities (<7, ≥ 7), IBS type, age, gender, site, and baseline RPSQ was used with an unstructured covariance structure. Efficacy results reported are based on the model-estimated values. The primary outcome considered individuals with a missing primary outcome as a non-responder.

Sample Size Estimation

We hypothesized that a parallel 2-group repeated-measures design with 2 measurements (summaries at week 4 and week 8) on each subject would be used to test whether the true diet proportion (P1) was different from the sham group proportion (P2) using a 1-sided, 2-sample time-averaged difference in logit proportions test (from a generalized linear mixed model formulation) assuming a type I error rate of 0.025 and power of 90%. Assuming the sham group proportion of 0.40, the true diet proportion of 0.60, a compound symmetry covariance structure for repeated observations on the same subject, and a correlation between observations on the same subject of 0.5, then 117 subjects per group would be needed. Assuming a 10% dropout rate, 260 subjects need to be randomized.[21]

Results

Subjects

Of the 556 subjects screened, 238 (42.8%) met the inclusion criteria and were randomized. This is slightly lower than the estimated sample size stated previously. Due to logistic and financial difficulties (eg, slow enrollment) during the COVID-19 pandemic, a decision was made to stop the trial before full enrollment. Fifteen subjects did not start the dietary intervention and were excluded; therefore 223 subjects were included in the modified intent-to-treat analysis. Of these, 118 subjects were randomized to the experimental diet group and 105 were randomized to the sham diet group. Baseline characteristics were similar between the 2 groups (Table 1). A total of 170 subjects (71.4 %) completed the study (Figure 1).

Table 1. Baseline Characteristics of the Study Population

Characteristics	Experimental diet (n = 118)	Sham diet (n = 105)
Age, mean (SD)	39.5 (14.6)	40.7 (15.2)
Sex, n (%)		
Female	90 (76.3)	85 (81.0)
Male	28 (23.7)	20 (19.0)
No. of sensitivities to food, n (%)		
0	0	0
1–6	101 (85.6)	86 (81.9)
7 or more	17 (14.4)	19 (18.1)
IBS type, n (%)		
IBS-C	43 (36.4)	37 (35.2)
IBS-D	38 (32.2)	36 (34.3)
IBS-M	37 (31.4)	32 (30.5)
Average scores[a]		
IBS-API	4.48 (1.22)	4.44 (1.07)
Bloating	4.60 (1.61)	4.81 (1.58)
IBS-SSS	289.5 (66.02)	294.0 (70.99)

[a]Mean scores with standard deviation.

Among those in the experimental diet group, the most commonly eliminated foods were egg, cow's milk, and wheat (Supplementary Table 1). Poultry (chicken/turkey), rice, and goat cheese were the most commonly eliminated foods in the sham group (Supplementary Table 2).

Primary Efficacy Endpoint

In multivariable analysis, a significantly greater proportion of subjects randomized to the experimental diet group met the primary outcome ($\geq$30% decrease in IBS-API for $\geq$2 of the last 4 weeks of the treatment period) compared with those in the sham diet group (59.6% vs 42.1%, $P = .02$) (Table 2). Site was included in the model to improve precision; whereas the overall site effect was statistically significant, the site-by-treatment interaction effect was not statistically significant.

Secondary Efficacy Endpoints

Changes from baseline in API, bloating, and IBS-SSS were numerically, but not statistically, greater in the experimental diet group compared with the sham diet group (Table 2).

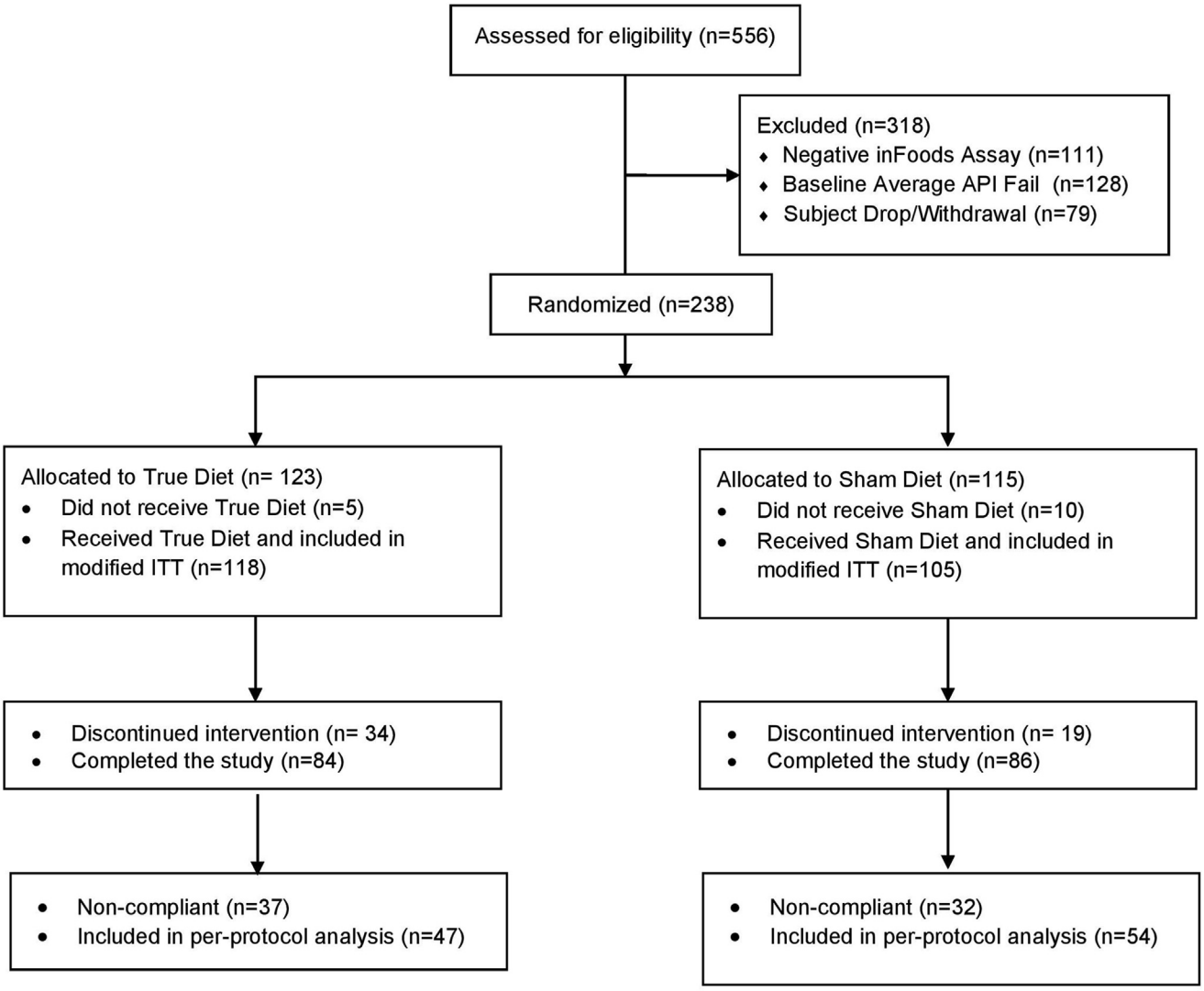

Figure 1. Consort flow diagram. ITT, intention to treat.

In addition, numerically more subjects in the experimental diet group reported IBS-AR at the end of the treatment period compared with the sham diet group (57.5% vs 46.8%). The experimental diet group reported a greater increase in IBS-GIS compared with the sham diet group (1.4 [0.20] vs 1.0 [0.19]). The number of days with normal bowel movements (BSS $\geq$3 and $\leq$5) was similar between the 2 groups (Table 2).

A numerically higher percentage of subjects in the experimental diet group were SGA responders compared with the sham diet group (18.1% vs 8.8%). The proportion of IBS-SSS responders (ie, $\geq$50-point decrease in IBS-SSS at week 8) was numerically higher in the experimental diet group compared with the sham diet group (62.9% vs 50.6%).

Subgroup Analysis

Several global and abdominal symptom (pain and bloating)–related measures numerically favored the experimental diet in subjects with IBS-C and IBS-M. In contrast, no such trend was seen for subjects with IBS-D (Supplementary Table 3).

Sensitivity Analysis

Of the experimental diet subjects and sham diet subjects, 18.2% and 13.6%, respectively, were noncompliant with the dietary diary (diary completed $<$70% of the days). Among those who were compliant with filling out daily diaries at least 70% of the time, 42% in the sham diet group were noncompliant with the prescribed diet and 35% in the experimental diet group were noncompliant. PP analysis was performed on subjects compliant with the diet (47 on the experimental diet and 54 on the sham diet). For the PP analysis, a numerically higher, although not statistically significantly different, proportion of subjects met the responder definition for API in the experimental diet compared with the sham diet groups (63.3% vs 45.7%). There were no differences in any other clinical outcomes between the 2 groups (Supplementary Table 4).

Table 2. Clinical Outcomes Between Experimental and Sham Diet Groups

Outcomes	Experimental diet (n = 118)	Sham diet (n = 105)	Δ	*P* value
Primary outcome				
30% reduction in API	70 (59.6%)	44 (42.1%)	17.5% (2.6, 32.5)	.02
Secondary outcomes				
IBS-API[a]	−1.3 (0.24)	−0.9 (0.23)	−0.4 (0.24) (−0.9, 0.0)	NA
Bloating[a]	−1.2 (0.25)	−0.8 (0.25)	−0.5 (0.26) (−1.0, 0.1)	NA
IBS-SSS[a]	−84.1 (13.72)	−64.5 (13.29)	−19.6 (12.21) (−43.7, 4.5)	NA
IBS-AR	68 (57.5%)	49 (46.8%)	10.7% (−0.5, 21.9)	NA
IBS-GIS[a]	1.4 (0.20)	1.0 (0.19)	0.4 (0.17) (0.0, 0.7)	NA
SGA responder	21 (18.1%)	9 (8.8%)	9.3% (−270.6%, 289.2%)	NA
50-point reduction in IBS-SSS	62.9%	50.6%	12.3% (−31.9%, 56.5%)	NA
100-point reduction in IBS-SSS	22.8%	18.2%	4.6% (−315.3%, 324.5%)	NA
Days with normal bowel movement per week (BSS ≥3 and ≤5)	63.9 (54.2%)	49 (47.0%)	7.20% (−8.5%, 23.0%)	NA

NOTE. Estimates are from repeated-measures models adjusted for treatment (experimental vs control), number of food sensitivities (<7, ≥7), IBS type (IBS-D, IBS-C, IBS-M), age, gender, site, baseline RPSQ, baseline IBS-SSS, time, and the time × treatment interaction was used. Random effects for subjects were used to account for the correlation among repeated measures in the same individuals.
NA, not applicable.
[a]Expressed as mean (SE). Other variables are presented as number of patients (percentage).

Safety Endpoints

There were 3 (2.5%) adverse events in the experimental group and 8 (7.6%) in the sham group (Table 3). None of the adverse events were considered related to the interventions by the investigators.

Discussion

A higher proportion of IBS subjects following an elimination diet based on an IBS-specific IgG assay met the primary efficacy endpoint of API responder compared with those randomized to a sham diet (59.6% vs 42.1%, $P = .02$). In addition, a numerically higher proportion of IBS subjects on the experimental diet met several global endpoints including improvement in IBS-GIS and SGA. On exploratory analyses, subjects with IBS-C and IBS-M reported more robust benefits from the experimental diet than subjects with IBS-D.

Table 3. Adverse Events in Experimental and Sham Diet Groups

Adverse events	Experimental diet (n = 118)	Sham diet (n = 105)
Total adverse events	3	8
Back pain	0	1
Eczema	1	0
Dizziness	0	1
Headcold	0	1
Seizure	1	0
Urinary tract infection	0	2
Postprandial stomach pain	0	1
COVID-19	1	0
Sinus headache	0	1
Sore arm	0	1

Our study has several notable advantages compared with the previous studies evaluating IgG-based dietary therapies for IBS. This is the largest study to investigate the efficacy of an IgG-based elimination diet in IBS and to use an IgG assay developed specifically for patients with IBS. Previous studies using IgG-based diets used assays developed without determining IBS trigger foods or establishing a 95% confidence interval–based cutoff using a healthy control comparison group. Atkinson et al[15] defined a cutoff for a positive IgG test as a level 3 times higher than the background signal obtained from the same patient. Because IgG-based antibodies to foods can be elevated in healthy controls, it is important to develop disease-specific assays.[16] The assay used in our study was developed specifically for patients with IBS and uses cutoff values derived from healthy controls (Supplementary Material). It is also important to note that the IgG response to a food antigen does not overlap with the IgE response to the same food antigen; the latter being associated with classic allergic reactions such as hives and/or anaphylaxis. In addition, we used a multicenter, randomized, double-blind, sham-

controlled study design with rigorous endpoints. Our study was double-blinded, and we also implemented stringent methods to ensure that the sham diet was as similar as possible to the experimental diet (described in detail in the Methods section). Given that IBS has a relatively high placebo rate of up to 37.5%, having a similar placebo group is imperative.[22]

We also found that in the experimental diet group, subjects with IBS-M and IBS-C had numerically higher responses for global endpoints and abdominal symptoms (pain and bloating) compared with the sham diet group. In contrast, no differences between the 2 groups were seen for these endpoints in subjects with IBS-D. Although the study was not powered for these exploratory analyses, findings from this phase 2 study will inform a future phase 3 study focusing on subjects with IBS-C and IBS-M. Validation of these results in a larger trial will have significant clinical implications, as currently there are few evidence-based dietary interventions for patients with IBS-C.[23] As there are no FDA-approved pharmacotherapies for IBS-M, dietary restriction based on IgG antibodies could represent a personalized therapeutic approach for this subset of patients.

The experimental diet in this study was well tolerated. Specifically, there were no adverse events attributed to the experimental diet. Therefore, this personalized dietary approach has the possible advantage of being less time-consuming and costly. We also found that symptom improvement between the experimental and sham diet groups began to separate at around 2 weeks, suggesting that the effect of the experimental diet is relatively rapid in onset, and continued for at least 8 weeks. The durability of response needs to be assessed in future studies and it is unclear if there is a role for repeat IgG testing to monitor treatment response. A higher percentage of patients in the experimental diet arm were noncompliant with their intervention than the sham diet arm. There are several possible explanations for this. It is possible that subjects found the experimental diet more difficult to comply with compared with the sham diet or that because the experimental diet was more likely to improve symptoms, dietary indiscretion may have been more common in this group (a phenomenon seen with other elimination diets such as gluten-free diet in celiac disease). A PP analysis generally overestimates the treatment effect; however, we did not find any significant difference between the 2 groups for any clinical outcome (including primary outcome) on PP analysis. This might be due to the small sample size included in the PP analysis cohort but could also reflect the quality of compliance measure and, therefore, the selection of participants for the PP analysis. To be included in PP analysis, a subject had to complete at least 70% of the daily compliance questions over 8 weeks and answer yes to this question at least 80% of the time. This would exclude those who may have occasionally ingested small quantities of an eliminated food and/or those who did not answer the compliance question at least 70% of the time. Future studies should use objective measurement of compliance (as measured by food diary or recall) to select the PP analysis group.

This study has some potential limitations. First, compliance was measured with a dichotomous outcome of yes or no and not by using a detailed food diary or recall. Without detailed dietary information, we do not have quantitative data on the effects of diet interventions on macronutrient or micronutrient intake. Second, we used a rigorous sham group in our study and whenever possible ensured the food eliminated in the sham group was of the same food group and consumed at a similar frequency as the food to which they tested positive. However, there may have been differences in FODMAP and fiber contents in the 2 groups as many of the most commonly eliminated food in the elimination arm were high FODMAP foods (eg, wheat and milk) for which other high FODMAP alternatives in the same food group consumed at the same frequency were limited. Third, although differences were detected in the efficacy of the experimental diet based on IBS subtypes, this study was not powered for this analysis so these results should be interpreted with caution. However, based on the promising results observed in this study, a larger study is justifiable, with $\geq$30% reduction in API as the primary outcome focusing on IBS-C and IBS-M patients. Finally, although we were slightly short of our estimated sample size (due to difficulty continuing the study during the COVID-19 pandemic), based on the observed results and group sizes, the post hoc power for the study was calculated as 83.6%, using a 5% 1-sided significance level.

There is a paucity of data evaluating the mechanism(s) that underlie the clinical benefits of an IgG-based elimination diet in patients with IBS. Some have argued that elevation in food-specific IgG could be an epiphenomenon and that IgG levels are elevated secondary to food exposure and reflect immune tolerance.[24] Many factors may contribute to intestinal barrier dysfunction, enabling the presentation of food antigens to the immune system, and perhaps leading to the production of serum IgG antibodies and a proinflammatory environment. Emerging data suggest that excess levels of IgG antibodies to food antigens may be associated with the activation of inflammatory pathways. Proteomic analysis has shown that wheat-specific IgG is associated with a decrease in complement factor H–related protein 3, a protein that helps regulate inflammation through the complement pathway.[25] In addition, IgG responses against food antigens were associated with C-reactive protein elevation in obese children.[26] This hypothesized proinflammatory cascade starts with increased intestinal permeability and because increased intestinal permeability is more often seen in IBS-D than IBS-C,[27] it would be reasonable to hypothesize that the benefits of this IBS-specific IgG assay should be greatest in those with IBS-D. However, this study refuted that hypothesis, and indeed, subjects with IBS-C and IBS-M experienced the greatest clinical benefit. The reason for this is unclear but may be due to several factors. First, it is possible, that a larger portion of patients in the IBS-D group had previously failed dietary interventions such as a low-FODMAP diet leading to a selection bias. Second, patients with IBS-D are more likely than other IBS subtypes to have bile acid malabsorption,

small intestinal bacterial overgrowth, disaccharidase deficiency, and so forth, which could also contribute to lack of efficacy with IBS-specific assay-guided elimination diet in this subgroup.

In conclusion, subjects on an elimination diet based on a novel IBS-specific IgG assay were more likely to meet the FDA-responder endpoint for API (ie, $\geq$30% reduction) compared with subjects randomized to a sham elimination diet. Other global endpoints and sensitivity analyses supported these findings and numerically favored the IBS-specific IgG assay intervention. Interestingly, subgroup analysis suggested greater benefit with the IgG-based elimination diet for subjects with IBS-C and IBS-M compared with those with IBS-D. Given, our promising results, a larger study, possibly focusing on IBS-C and IBS-M patients, should be considered.

Supplementary Materials

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2025.01.223.

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Supplementary Table 1. Most Commonly Eliminated Food in the Experimental Arm

Food	Number of subjects eliminating food in the experimental arm (N = 118)
Egg	55
Milk	44
Wheat	42
Grapefruit	38
Orange	31
Sugar	29
Lemon	27
Pineapple	27
Cabbage	23
Oat	23
Corn	22
Honey	20
Soybean	20
Cocoa	15
Black tea	14
Walnut	14
Rye	13
Yeast	13

Supplementary Table 2. Most Commonly Eliminated Food in the Sham Arm

Food	Number of subjects eliminating food in the sham arm (N = 105)
Poultry (chicken/turkey)	23
Honey	19
Oat	18
Orange	15
Pineapple	15
Goat cheese	14
Rice	14
Lemon	13
Corn	11
White potato	11
Cocoa	8
Maple syrup	8
Other natural sweeteners	8
Barley	7
Beans	7
Beef	7
Dark fatty fish	7
Grapefruit	7
Packaged food & beverages w/ artificial sweeteners	7
Quinoa	7
Rye	7
Sugar	7
Banana	6
Green tea	6
Peas	6
Shell fish	6
Stone fruit (apricot, nectarine, peach)	6
Apple	5
Cabbage	5
White fish	5

Supplementary Table 3. Subgroup Analysis Comparing the Efficacy of the Experimental Diet and the Sham Diet in IBS Subtypes

	IBS-C		IBS-M		IBS-D		Non-IBS-D (IBS-C and IBS-M)	
Outcomes	Experimental diet (n = 43)	Sham diet (n = 37)	Experimental diet (n = 37)	Sham diet (n = 32)	Experimental diet (n = 38)	Sham diet (n = 36)	Experimental diet (n = 80)	Sham diet (n = 69)
IBS-API mean (SE)	−2.1 (0.38)	−1.2 (0.35)	−1.1 (0.51)	−0.2 (0.53)	−1.1 (0.41)	−1.1 (0.39)	−1.5 (0.30)	−0.7 (0.30)
Delta (SE) 95% CI	−0.9 (0.39) (−1.7 to −0.1)		−0.9 (0.56) (−2.0 to 0.2)		0.1 (0.44) (−0.8 to 0.9)		−0.8 (0.31) (−1.4 to −0.2)	
IBS-SSS mean (SE)	−88.4 (24.98)	−61.5 (22.48)	−71.0 (22.50)	−49.5 (25.30)	−103.4 (26.64)	−89.2 (24.03)	−80.9 (17.03)	−58.6 (16.60)
Delta (SE) 95% CI	−26.9 (22.29) (−71.6 to 17.9)		−21.5 (23.52) (−68.8 to 25.7)		−14.2 (21.72) (−57.7 to 29.4)		−22.3 (15.19) (−52.4 to 7.8)	
Bloating mean (SE)	−2.3 (0.43)	−1.6 (0.40)	−0.9 (0.47)	0.1 (0.49)	-0.6 (0.44)	-0.5 (0.41)	−1.6 (0.31)	−0.9 (0.31)
Delta (SE) 95% CI	−0.7 (0.43) (−1.5 to 0.2)		−0.9 (0.53) (−2.0 to 0.1)		−0.1 (0.46) (−1.0 to 0.8)		−0.7 (0.32) (−1.4 to −0.1)	
GIS mean (SE)	2.0 (0.33)	1.2 (0.30)	1.5 (0.29)	1.0 (0.30)	1.3 (0.40)	1.4 (0.36)	1.8 (0.23)	1.1 (0.22)
Delta (SE) 95% CI	0.8 (0.31) (0.2 to 1.5)		0.4 (0.27) (−0.1 to 1.0)		0.0 (0.34) (−0.7 to 0.7)		0.6 (0.20) (0.2 to 1.0)	
SGA mean (SE)	2.6 (0.22)	3.2 (0.21)	3.3 (0.22)	3.8 (0.23)	2.9 (0.22)	2.9 (0.20)	2.8 (0.15)	3.3 (0.16)
Delta (SE) 95% CI	−0.6 (0.23) (−1.0 to −0.1)		−0.5 (0.22) (−1.0 to −0.1)		0.0 (0.21) (−0.4 to 0.4)		−0.5 (0.15) (−0.8 to −0.2)	
IBS-AR %Yes	66.0	56.1	58.4	39.9	66.0	49.9	58.2	46.3
Difference 95% CI	9.9 (−36.9 to 56.8)		18.5 (−3.2 to 40.3)		16.2 (−33.4 to 65.8)		11.8 (−2.1 to 25.7)	
30% reduction in API %Yes	67.1	35.8	66.0	29.5	52.0	54.7	64.8	34.3
Difference 95% CI	31.3 (5.8 to 56.8)		−2.7 (−29.1 to 23.7)		−2.7 (−29.1 to 23.7)		31.3 (5.8 to 56.8)	
50-point reduction in IBS-SSS %Yes	61.8	41.8	66.0	47.7	69.4	60.6	67.0	47.2
Difference 95% CI	20.1 (−13.2 to 53.3)		18.4 (−69.7 to 106.5)		8.8 (−31.6 to 49.2)		19.8 (−38.4 to 78.0)	
100-point reduction in IBS-SSS %Yes	38.4	21.0	17.3	13.5	20.0	27.4	29.0	16.2

Supplementary Table 3. Continued

Outcomes	IBS-C		IBS-M		IBS-D		Non-IBS-D (IBS-C and IBS-M)	
	Experimental diet (n = 43)	Sham diet (n = 37)	Experimental diet (n = 37)	Sham diet (n = 32)	Experimental diet (n = 38)	Sham diet (n = 36)	Experimental diet (n = 80)	Sham diet (n = 69)
Difference 95% CI	17.4 (−187.4 to 222.3)		3.8 (−96.9 to 104.5)		−7.4 (−138.1 to 123.3)		12.8 (−255.3 to 280.9)	
Days with normal bowel movement (BSS ≥3 and ≤5) %Yes	48.7	43.5	62.1	55.1	58.1	42.4	53.1	50.0
Difference 95% CI	5.2 (−22.3 to 32.7)		7.0 (−21.7 to 35.7)		15.7 (−12.2 to 43.5)		3.0 (−16.4 to 22.5)	

NOTE. Estimates are from repeated measures models adjusted for the treatment arm, number of food sensitivities (<7 vs ≥7), gender, and site as fixed effects; as well as age, baseline RPSQ, and baseline IBS-SSS as continuous measures. Week and the week-by-treatment interaction are also included in the model, where week is a fixed effect.

Supplementary Table 4. PP Analysis Between the 2 Groups

Outcomes	Experimental diet (n = 47)	Sham diet (n = 54)	Δ (SE) (95% CI)
IBS-API mean[a]	−1.6 (0.31)	−1.2 (0.28)	−0.4 (0.31) (−1.0 to 0.2)
Bloating[a]	−1.6 (0.34)	−1.2 (0.31)	−0.4 (0.35) (−1.1 to 0.3)
IBS-SSS[a]	−103.6 (18.13)	−95.6 (16.5)	−8.0 (16.42) (−40.6 to 24.7)
IBS-AR	28 (60.4%)	29 (54.5%)	5.9% (−19.0 to 30.9)
IBS-GIS[a]	1.9 (0.26)	1.6 (0.13)	0.3 (0.24) (−0.2 to 0.8)
SGA	11 (22.6%)	8 (13.9%)	8.7% (−173.1 to 190.5)
30% reduction in API	63.3%	45.7%	17.6% (−3.5 to 38.7)
50-point reduction in IBS-SSS	65.7%	62.4%	3.2% (−22.8 to 29.2)
100-point reduction in IBS-SSS	28.4%	22.2%	6.2% (−121.8 to 134.2)
Days with normal bowel movement per week (BSS ≥3 and ≤5)	25 (54.2%)	23 (42.1%)	12.1% (−9.3 to 33.4)

NOTE. Estimates are from repeated measures models adjusted for treatment (experimental vs control), the number of food sensitivities (<7, ≥7), IBS type (IBS-D, IBS-C, IBS-M), age, gender, site, baseline RPSQ, baseline IBS-SSS, time, and the time × treatment interaction was used. Random effects for subjects were used to account for the correlation among repeated measures in the same individuals.

[a]Expressed as mean (SE).