

Fructose Reintroduction in Irritable Bowel Syndrome Patients Successfully Treated with a low FODMAP diet

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Background and Aims

- Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal cramping, bloating, and altered bowel habits which may be due to abnormalities in motility, visceral sensation, mucosal and immune function, gut microbiota, and central nervous system (CNS) processing.
- The low FODMAP (fermentable oligo-, di-, monosaccharides and polyols) diet (LFD) eliminates high FODMAP foods and has been shown to improve symptoms in controlled clinical trials for IBS-D and –M.
- FODMAPs are not fully metabolized in the small intestine, leading to increased small bowel water content, perhaps leading to bloating and abdominal pain. When they reach the colon, these sugars are fermented by bacteria, causing further bloating and flatulence.
- The LFD is used during an elimination phase after which patients reintroduce FODMAPs in a stepwise manner to better understand their individual tolerances for each.
- This project focused on the reintroduction phase to understand how patients with IBS-D and IBS-M respond to a 3-day fructose or fructose in excess of glucose challenge after following a low FODMAP diet for 4 weeks.
- We also explored how a low FODMAP diet affects the intestinal microbiome (analysis is ongoing).

Methods

Subjects: n = 38 patients (30 LFD “Responders”, 8 “Non-responders”)

Data collection:

- Screening visit** – eligibility and baseline values were collected for: IBS Severity Scoring System (IBS-SSS), HAD, Bowel Symptom Questionnaire (BSQ), PHQ-15, Visceral sensitivity index (VSI), 100 MM VAS for symptoms (Overall; Abdominal Pain; Bloating), and diet-type checklist. Subjects received LFD counseling with Registered Dietician. Thirty-two subjects provided stool samples at this visit.
- Post-LFD visit** – subjects completed IBS-SSS, HAD, VSI, PHQ-15, medication list, and modified BSQ. Twenty-four subjects provided second stool samples at this visit. Eligible subjects (“Responders”) completed the VAS scale. “Responders” answered “Yes” to the question, “Have you had adequate relief of your IBS symptoms in the past 7 days?”
- Thirty Responders were randomly assigned to one of three solution groups (n = 10 per group): 1) 100% fructose, 2) 100% glucose or 3) ~56% fructose/~44% glucose. Total sugar amount per solution sets were 2.5 g, 5 g, 10 g, and 15g.
- Patients drank one solution first thing in the morning, either alone or with a low-FODMAP meal or beverage for three days straight, with a 3-day washout period between solution sets.
- VAS scores were recorded daily on both solution and washout days. When a difference of 20 mm was reached compared to baseline, subjects met their tolerance “threshold” and stopped taking solutions.

Data Analysis:

- Group differences in demographic characteristics were assessed using t tests, fisher tests, and ANOVA analyses. Generalized linear model was used to evaluate differences in symptom measurements. Mixed model analyses were used to assess the effect of solution group and time on symptom severity scores. A p-value of <0.05 was considered significant. All statistical analyses were performed using R version 4.1.0 and were two-tailed.
- Stool microbiomes will be analyzed using shotgun metagenomics.

Results

Table 1. Patient demographics at Pre-LFD Visit

Characteristic	Non-Responders	Responders	P-value
Age (years) avg (sd)	40.13 (17.72)	32.13 (6.52)	0.25
Sex - male count (% of group)	4 (50%)	15 (50%)	1.00
Education avg (sd)	5 (0.8)	5.2 (0.8)	0.52
Income avg (sd)	6 (2.9)	7.2 (2.8)	0.33
BMI (kg/m ²) avg (sd)	25.07 (4.94)	25.32 (5.27)	0.91
Bowel Habit count (% of group)			0.19
IBS-D	6 (75%)	28 (93%)	
IBS-M	2 (25%)	2 (7%)	
Race number (percent of group)			0.42
White	5 (62.5%)	23 (77%)	
Black	0 (0%)	1 (3%)	
Asian	2 (25%)	2 (7%)	
American Indian /Multiracial	1 (12.5%)	2 (7%)	
Declined to Specify	0 (0%)	2 (7%)	
Ethnicity - Hispanic	0 (0%)	4 (13%)	0.56

Pre-Low FODMAP Diet

- 30 (79%) LFD “Responders” vs. 8 “Non-responders”
- No significant differences in baseline demographic or clinical characteristics between the Responder and Non-Responder groups (Table 1), or between the three Solution groups

Table 2. Symptom Scores in Solution groups at Pre-LFD, Post-LDF, and Post-Solution Visits.

Values reported as mean (standard deviation). BSQ scale : 1 – 20.

Solution	PRE-LFD				POST-LFD/PRE-REINTRODUCTION				POST-REINTRODUCTION			
	Fructose	Excess Fructose	Glucose	P-value (ANOVA)	Fructose	Excess Fructose	Glucose	P-value (ANOVA)	Fructose	Excess Fructose	Glucose	P-value (ANOVA)
Overall Severity (BSQ)	13.6 (3.0)	13.6 (2.6)	11.2 (3.2)	0.13	4.4 (4.3)	5.5 (3.5)	4.1 (2.4)	0.66	6.4 (3.4)	5.9 (4.0)	6.2 (5.4)	0.96
Abdominal pain (BSQ)	10.7 (5.3)	12.4 (3.6)	9.8 (4.3)	0.43	3.2 (2.8)	5.2 (4.4)	4.2 (2.8)	0.44	5.2 (4.2)	5.4 (4.2)	5.1 (5.3)	0.99
Bloating (BSQ)	11 (5.9)	12 (5.1)	10.4 (4.6)	0.80	4.4 (5.1)	6.1 (5.6)	5 (4.1)	0.74	6.3 (4.2)	6.0 (6.0)	4.8 (4.8)	0.79

Reintroduction Phase

No significant difference in:

- Overall GI symptom severity, pain, or bloating between the three different solution groups at each visit (Table 2)
- the CHANGE in overall GI symptom severity, pain, or bloating between the three solution groups, between pre-reintroduction and post-reintroduction visits (P-values)

Change in symptoms between solution groups

- Overall GI symptom severity (BSQ): P = 0.91
- Abdominal pain (BSQ): P = 0.91
- Bloating (BSQ): 0.78

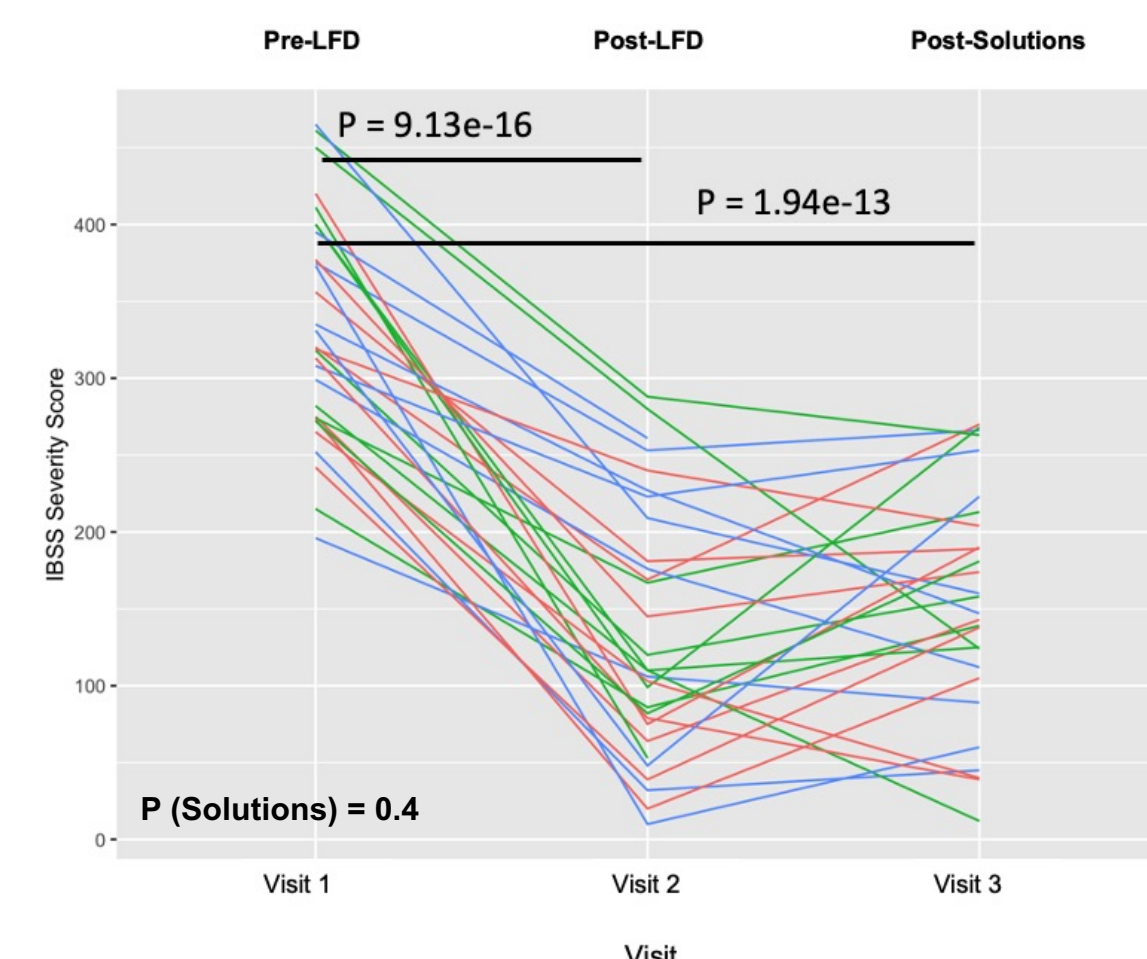


Figure 1. Changes in IBS Symptom Severity Score at the three study visits in patients reintroduced to Glucose, Fructose, and Glucose + Fructose (Excess Fructose).

Solution Type

- Glucose
- Fructose
- Glucose/Fructose

Low FODMAP Diet Phase

- Responders' IBS-SSS (P = 9.16⁻¹⁶) and Overall Symptom Severity VAS scores decreased significantly between the pre-LFD to post-LFD visits.

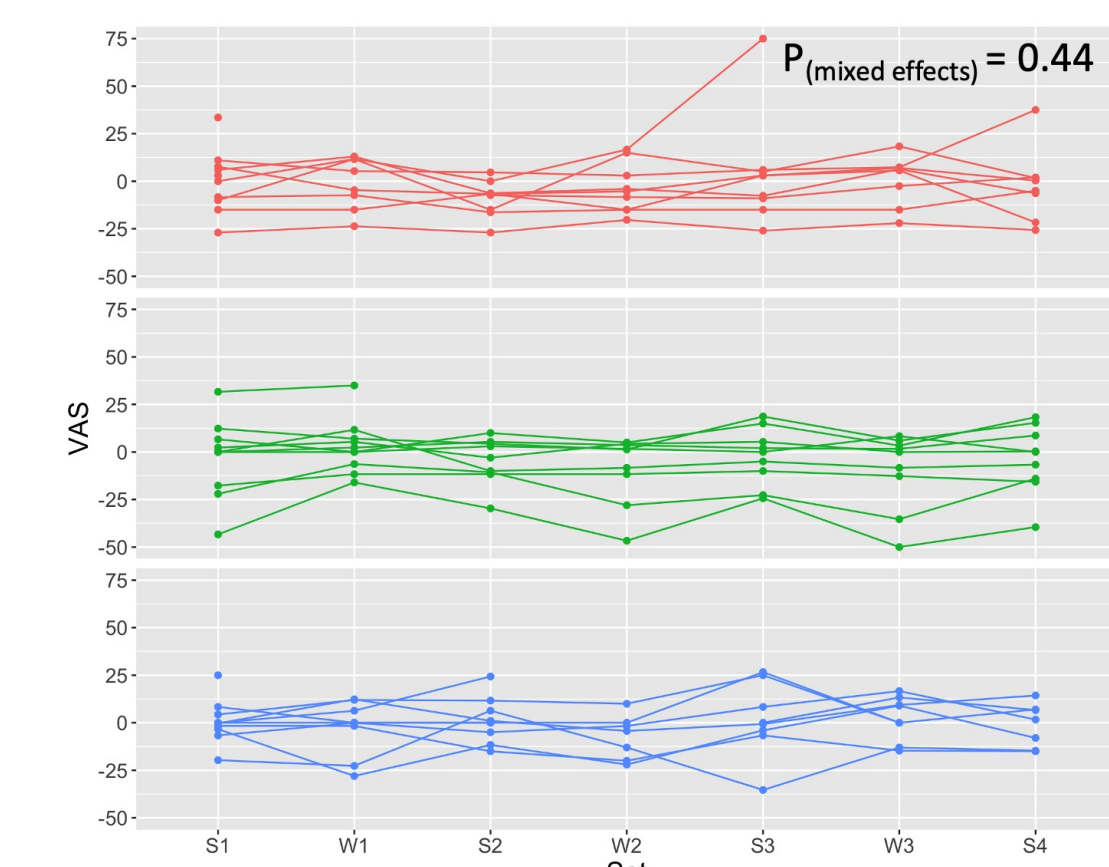


Figure 2. Change in daily VAS scores during the solution and washout phases. Change was measured by subtracting the average of each 3-day solution set or wash period from baseline VAS measured after completing the Low FODMAP diet. VAS: 0 – 100 MM

Solution Type

- Glucose
- Fructose
- Glucose/Fructose

Reintroduction Phase

- No significant difference in IBS-SSS, VAS (Figure 2), or Overall GI symptom severity, pain, or (Table 2) bloating between the three different solution groups.

- Average tolerance was similar between groups, P = 0.56
- mean (sd)
- Fructose 13.75 (3.95) g
- Glucose 13.25 (4.09) g
- Glucose/Fructose 11.75 (4.71) g

Conclusions

- There were no IBS symptom differences in the fructose or fructose in excess of glucose compared to glucose alone in participants with non-constipated IBS who responded to a low FODMAP diet.
- Fructose may be tolerated at higher quantities than those typically assessed in the reintroduction phase in IBS patients who respond to a LFD.
- Future studies should investigate symptomatic responses to higher quantities of fructose in both the fructose alone and fructose excess groups.
- Optimal symptom assessment endpoints and duration of FODMAP reintroduction needs to be studied.

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