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Altobelli E, Del Negro V, Angeletti PM, Latella G. Low-FODMAP Diet Improves Irritable Bowel Syndrome Symptoms: A Meta-Analysis. Nutrients. 2017;9(9):940.

What We Know, Think We Know, or Are Starting to Know

The acronym FODMAP stands for: Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols. FODMAPs thus refer to a group of compounds, not any single dietary entity. Oligosaccharides include fructans and galacto-oligosaccharides [GOS] that humans lack the necessary enzymes capable of degrading these short-chain carbohydrate and fibre types, and which undergo microbial fermentation in the colon [(1)]. Disaccharides refer to the milk sugar, lactose, for which there is ethnic variation in response due to higher prevalence of reduce activity of the lactase enzyme responsible for lactose breakdown [(1)]. The simple sugar fructose is the monosaccharide FODMAP that occurs both naturally and as an artificial sweetener, while the 'P' stands for polyols, a sugar alcohol also found both naturally and as artificial sweeteners [(1)].

FODMAPs may exert different, but related effects on gut function, which coalesce into symptoms of Irritable Bowel Syndrome (IBS). The fermentation of oligosaccharides may increase gas production, contributing to sensations of bloating, pain, and distention [(2)]. Monosaccharides and polyols may exert osmotic effects, i.e., pull water into the bowel, contributing to distention and associated IBS symptoms [(3)]. Thus, the intestinal microbiota and fermentation of FODMAPS has been implicated in generating IBS symptoms of bloating, pain, and distension [(4)].

As a Functional Gastrointestinal Disorder, IBS is defined as a disorder of gut-brain interaction involving microbial dysbiosis [i.e., imbalance in gut bacteria], altered mucosal immune function, visceral hypersensitivity, and central nervous system [CNS] dysregulation of gut signalling and motor function [i.e., gut motility] [(5)]. IBS is characterised by abdominal pain, distension, and alterations in bowel habits on a spectrum from diarrhoea to constipation, including a mix of both [and periods with normal stools], which occur in the absence of biochemical, structural or metabolic abnormalities [(5)].

Due to the potential mechanistic role of FODMAPs in generating IBS symptoms, the Low FODMAP Diet* has been developed as a clinical nutrition intervention for patients with IBS [(6)]. Due to the potential differential effects of FODMAP types, it may be relevant to consider different compounds, rather than FODMAPs as a single entity. The present study examined the effects of studies on different FODMAP types.

*Geek Box: Stages of the Low FODMAP Diet

The Low FODMAP Diet [LFD] is often referred to as a diet choice, the way an individual may adopt a vegan diet, for example, but it is important to bear in mind that it is a relatively short-term and specifically defined intervention. The first line intervention for an individual with IBS is not the LFD, but a preliminary adjustment to diet with regard to fatty and spicy food, alcohol and caffein, and promoting of basic general healthy eating advice. This is following exclusion of other potential gastrointestinal conditions and food allergies and intolerances. If the first-line intervention does not lead to improvements in symptoms, the LFD would be implemented as a second-line intervention. The LFD may be divided into three distinct phases. Phase 1 is 'Restriction', which requires strict adherence to the LFD for a period of 4-8 weeks, and during which the individual would be guided to maintain nutritional adequacy while replacing FODMAP foods with alternatives. It is often misunderstood that the LFD is a diet for life: this is incorrect. If no symptom improvement occurs during the Restriction phase of the LFD, the diet is discontinued. However, if the Restriction phase provides symptom relief, then the individual enters into the Phase 2 'Reintroduction' period. This period is particularly important, because FODMAPs appear to exhibit a dose-dependant effect and the onset of symptoms often relates to the global diet. For example, while an individual with IBS may be able to consume some milk in coffee, or have a single apple, if they ate a bowl of ice cream or if they had an apple with 2 slices of toast, this may trigger symptoms. Therefore, the goal of the Reintroduction phase is the systematic use of food challenges with FODMAP foods, under the guidance of a nutrition professional, to test individual tolerance to different FODMAP foods and establish a personal threshold for tolerance, for example, 1 slice of bread or 200ml milk, within which the individual does not experience increased symptoms. The aim of the Reintroduction phase is to transition to long-term individual management, where the patient is aware of their own personal tolerance levels to specific FODMAP foods. Thereafter, Phase 3 is 'Long-term Management', with the aim of helping the individual patient find a balance between symptom management and minimising dietary restrictions. This results in an individualised modified diet to the patients particular needs, the exact composition of which for FODMAP foods will differ from person to person. For more on implementation of the LFD, see references [1,6].

The Study

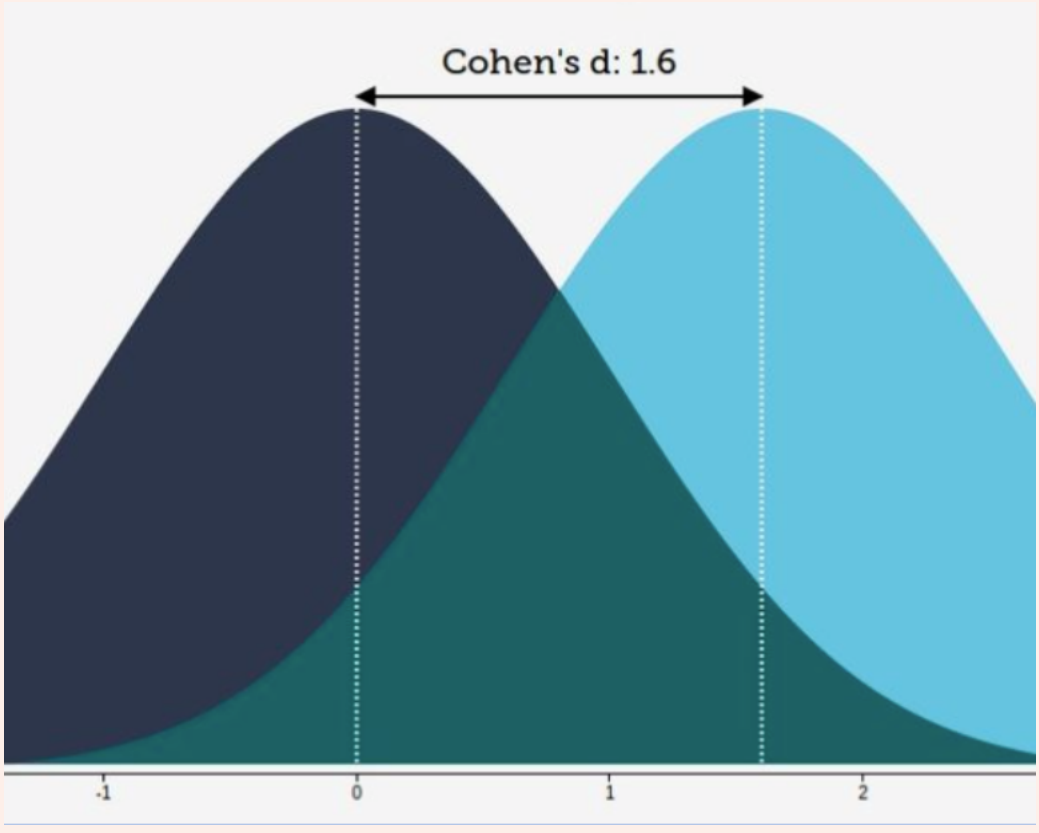
A meta-analysis was conducted of studies published in the English language within the past 10 years, on the effects of FODMAP diets in IBS. To be eligible, studies had to include the following:

- RCTs comparing a LFD vs. General IBS Diet [i.e., first-line recommendations]
- RCTs comparing a LFD vs. High FODMAP Diet [HFD]
- Prospective cohort studies of patients receiving a LFD with both baseline and post-treatment data available

Effect sizes were calculated using Cohen' s d*, which is common in behavioural sciences to compare the difference in mean effects in a treatment and control group, and also using Odds Ratios. The primary outcomes were abdominal pain and bloating. In the RCTs comparing the LFD vs. General IBS Diet, stool consistency and frequency were also examined as outcomes.

*Geek Box: Cohen's *d*

The Cohen's d is a measure of effect size, most commonly used in behavioural science, for example psychology. It compares two means: one from a treatment group and one from a control group or comparison group. The difference between the Cohen's d and a p-values is that the p-value simply tells you whether there is an effect that is statistically significant, while the Cohen's d tells you the size of the effect, i.e., how much did the magnitude of effect in the treatment group differ to the magnitude of effect in the control group. Similar to the p-value being set at <0.05 for significant being arbitrary, interpreting the Cohen's d results have been subject to similar classifications, with an 0.2, 0.5, and 0.8 considered small, medium, and large, respectively. What these numbers represent is units of standard deviation. The Cohen's d is based on the mean level in an overall distribution of data . Therefore the Cohen's d value represents the standard deviation of the treatment group from the mean. Look at the figure below: you can see the dark and light blue respective distributions overlap [shaded in green]. You can see the mean of the control group is the dotted horizontal white line in the dark blue distribution. And you can see the treatment group mean effect is the corresponding dotted horizontal white line in the light blue distribution: this is 1.6 standard deviations from the mean of the control group. The green shading is also important: it represents that there are still many individuals who do not fall within either distribution. The effect size interpretation for Cohen's d is just a general guideline and - similar to the way in which a statistically insignificant finding does not mean 'there is no effect' - the relevance of a 'small' or 'large' effect size will depend on the exposure and specific context being studies. A Cohen's d of 0.4, for example, may be small-medium, but represents a clinically meaningful difference.



Results: A total of 3 RCTs were included for the analysis comparing the LFD vs. General IBS Diet, and a further 3 RCTs were included in the analysis comparing the LFD vs. HFD. The trials ranged from 11-days to 4-weeks in duration. 6 prospective studies were included in the analysis, ranging from 3-weeks to 15-months follow-up.

LFD vs. General IBS Diet

- **Abdominal Pain*:*** The LFD resulted in a 56% [OR 0.44, 95% CI 0.24-0.77] lower odds of abdominal pain compared to the General IBS Diet.
- **Bloating*:*** The LFD resulted in a 68% [OR 0.32, 95% CI 0.15-0.66] lower odds of bloating compared to the General IBS Diet.
- **Stool Consistency*:*** The LFD resulted in a Cohen's *d* effect size of 0.24, which was statistically insignificant.
- **Stool Frequency*:*** The LFD resulted in a Cohen's *d* effect size of 0.54, which was statistically significant and indicates that 64% of participants in the treatment group would have improved scores relative controls.

LFD vs. HFD

- **Abdominal Pain*:*** The LFD resulted in a 83% [OR 0.17, 95% CI 0.08-0.34] lower odds of abdominal pain compared to the HFD.
- **Bloating*:*** The LFD resulted in a 87% [OR 0.13, 95% CI 0.04-0.40] lower odds of bloating compared to the HFD.

Cohort Studies

- **Abdominal Pain*:*** The LFD resulted in a Cohen's *d* effect size of 0.56, which was statistically significant and indicates that 65% of participants in the treatment group would have improved scores relative controls.
- **Bloating*:*** The LFD resulted in a Cohen's *d* effect size of 0.64, which was statistically significant and indicates that 67.5% of participants in the treatment group would have improved scores relative controls.

The Critical Breakdown

Pros: The research question was focused, and relevant databases searched. Over half the participant in all included studies were female, which is relevant given the sex differences in prevalence of IBS. The study selection, eligibility assessment, and inclusion were conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The included interventions compared different FODMAP level diets, providing a comparison of effects sizes relative to the comparison/control diet.

Cons: The statistical methodology is sparse on detail, and it is unclear whether the Cohen's *d* statistic was only used for cohort studies [although it is implied and appears to be the case]. Sensitivity analysis is mentioned, but no further details given in relation to moderating factors considered. A very small number of primary studies were included, with only 3 RCTs in each of the meta-analysis comparing to General IBS diet or HFD. 3 of the included studies were under 4-weeks duration, which may influence the results given the recommendation for the restriction phase is a minimum of 4-weeks. There was no discussion of the symptom rating tools used in the primary studies.

Key Characteristic

The inclusion of two distinct comparisons: LFD vs. General IBS Diet and LFD vs. HFD, and the inclusion of cohort studies to consider effects over the longer-term. The first comparison is useful because many interventions to date have compared the LFD against a habitual diet, or a standard Western diet, or against non-IBS controls. While useful in themselves, they provide little additional insights to the effect of diets with varying FODMAP levels in participants with IBS, and of the LFD compared to routine dietary advice as the 'first line' intervention. Thus, the present meta-analysis allowed for the separate consideration of the overall effects of the LFD vs. different relevant comparison diets. The inclusion of cohort studies provided a means of assessing the longer-term effects of the intervention. The consistency of the effect with regard to abdominal bloating and pain is consistent with the effects observed in the intervention studies, and the Cohen' s d scores for effect size suggesting a meaningful difference in the post-treatment effect of the LFD may be sustained over time.

Interesting Finding

The effect size for bloating was greater for the studies comparing LFD vs. HFD than studies comparing LFD vs. General IBS diet. This could reflect the fact that the participants in the trials were IBS patients, i.e., a diet high in FODMAPs would be expected to have worse effects on abdominal pain and bloating compared to an LFD. This is a relevant comparison for investigating the magnitude of benefit to decreasing FODMAPs in individuals with IBS. The fact that the strength of the effect relates to abdominal pain and bloating between a LFD vs. HFD is also instructive for what we currently understand about mechanisms in IBS.

As short-chain carbohydrates with low molecular weight, FODMAPS draw water into the colon, in addition to undergoing fermentation in the large bowel [(1)]. The increase in proximal distal bowel fluid and fermentation precipitate IBS symptoms, including diarrhoea, gas, pain and distension [(1)]. Mechanistically, FODMAPS exert an osmotic effect in all individuals, however, subjects with IBS appear more susceptible to colonic distention from gas generated from fermentation, and from osmotic effects of fructose in causing increased small bowel distension, compared to healthy controls [(7)]. The increase in gas production on a high FODMAP diet has been shown to occur in both healthy subjects and subjects with IBS, however, only in IBS subjects was prolonged hydrogen production observed, corresponding to increased abdominal pain and/or bloating [(2)]. Thus, the comparison between a low and high FODMAP diet in participants with IBS may exaggerate the effects of the LFD, but is a relevant comparison given the experiential nature of IBS.

Relevance

To some extent, this study confirms what is evident in the literature: that the LFD may be effective at reducing IBS symptoms. But it isn' t necessarily the full story. Not all studies comparing the LFD to routine first-line IBS dietary management have found differences between diets on symptom severity [8]. Further, IBS relates to the patients' subjective interpretation and reporting of symptoms, being an experiential change from normal physiological function [5]. This is central to the difference between an individual with IBS and a healthy individual, as psychosocial factors influence gastrointestinal dysfunction in IBS [5]. Patients with IBS frequently present with accompanying psychological disorders, in particular anxiety and depression, which may be modulated by the microbiome and bi-directional gut-brain axis communication [9].

Patient' s with IBS display altered microbial composition compared to healthy controls, with reduced levels of species specialising in the degradation of fibres and short-chain carbohydrates, in particular the *Bifidobacteria* which preferentially ferment oligosaccharides [10]. Reduced levels of *Bifidobacteria* may contribute to visceral hypersensitivity and abdominal pain symptoms in IBS [10]. However, a cause-and-effect relationship between *Bifidobacteria* concentrations and IBS symptoms is difficult to establish, as a low-FODMAP diet [LFD] leads to reductions in these bacteria in the colon, which is why the LFD should be confined to the short-term: it can reduce levels of these highly beneficial bacteria [11].

The fact that individuals with IBS exhibit similar levels of osmosis in the bowel, and similar gas production, compared to healthy controls, suggests IBS symptoms are triggered by an exaggerated bowel response to hydrogen-induced distension, rather than by FODMAPS directly [2]. One possible mechanistic explanation for this is that, compared to healthy controls, patients with IBS have greater numbers of mast cells in intestinal mucosa, and increased mast cell activation in response to food has been shown to correspond to visceral hypersensitivity in subjects with IBS [12,13]. While the exact underlying mechanism remains to be fully elucidated, what is clear is that gas production increases in both healthy and IBS subjects, and subjects reporting increases in symptoms have not been shown to produce more gas than asymptomatic subjects [14]. This demonstrates a hypersensitivity in response to colonic distention in subjects with IBS [2,14]. This evidence provides mechanistic plausibility to the reduction of abdominal pain and bloating observed in the present meta-analysis.

Application to Practice

While the LFD is not a panacea, and does not necessarily lead to symptom resolution in all persons with IBS, the evidence for the effects of the LFD shows that in responsive individuals, the diet may lead to significant - and meaningful - improvements in IBS symptoms. The diet is often misconceived as a day-to-day diet, and it is important to reiterate the the LFD is a specific clinical nutrition intervention, and should be undertaken under supervision from a qualified nutrition professional.

References

1. Barrett, J. How to institute the low-FODMAP diet. *J Gastro Hepatol*. 2017;32:8-10.

2. Ong, D., Mitchell, S., Barrett, J., Shepherd, S., Irving, P., Biesiekierski, J., Smith, S., Gibson, P. and Muir, J. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. J Gastro Hepatol. 2010;25(8):1366-1373.

3. Barrett JS, Gearry RB, Muir JG, Irving PM, Rose R, Rosella O, Haines ML, Shepherd SJ, Gibson PR. Dietary poorly absorbed, short-chain carbohydrates increase delivery of water and fermentable substrates to the proximal colon. Aliment Pharmacol Ther. 2010 Apr;31(8):874-82.]

4. Jiang X, Locke GR 3rd, Choung RS, Zinsmeister AR, Schleck CD, Talley NJ. Prevalence and risk factors for abdominal bloating and visible distention: a population-based study. Gut. 2008 Jun;57(6):756-63.

5. Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. Gastroenterology. 2016 May;150(6):1257-61.

6. McKenzie YA, Bowyer RK, Leach H, Gulia P, Horobin J, O' Sullivan NA, Pettitt C, Reeves LB, Seamark L, Williams M, Thompson J, Lomer MC; (IBS Dietetic Guideline Review Group on behalf of Gastroenterology Specialist Group of the British Dietetic Association). British Dietetic Association systematic review and evidence-based practice guidelines for the dietary management of irritable bowel syndrome in adults (2016 update). J Hum Nutr Diet. 2016 Oct;29(5):549-75.

7. 7. Murray K, Wilkinson-Smith V, Hoad C, Costigan C, Cox E, Lam C, Marciani L, Gowland P, Spiller RC. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. Am J Gastroenterol. 2014 Jan;109(1):110-9.

8. Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson K. A Randomized Controlled Trial Comparing the Low FODMAP Diet vs. Modified NICE Guidelines in US Adults with IBS-D. Am J Gastroenterol. 2016 Dec;111(12):1824-1832.

9. Lee KN, Lee OY. Intestinal microbiota in pathophysiology and management of irritable bowel syndrome. World J Gastroenterol. 2014 Jul 21;20(27):8886-97.

10. 10. Rajilić-Stojanović M, Jonkers DM, Salonen A, Hanevik K, Raes J, Jalanka J, de Vos WM, Manichanh C, Golic N, Enck P, Philippou E, Iraqi FA, Clarke G, Spiller RC, Penders J. Intestinal microbiota and diet in IBS: causes, consequences, or epiphenomena? Am J Gastroenterol. 2015 Feb;110(2):278-87.

11. Staudacher HM, Lomer MC, Anderson JL, Barrett JS, Muir JG, Irving PM, Whelan K. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. J Nutr. 2012 Aug;142(8):1510-8.

12. Lee KN, Lee OY. The Role of Mast Cells in Irritable Bowel Syndrome. Gastroenterol Res Pract. 2016;2016:2031480.

13. Uranga JA, Martínez V, Abalo R. Mast Cell Regulation and Irritable Bowel Syndrome: Effects of Food Components with Potential Nutraceutical Use. Molecules. 2020 Sep 20;25(18):4314.

14. Major G, Pritchard S, Murray K, Alappadan JP, Hoad CL, Marciani L, Gowland P, Spiller R. Colon Hypersensitivity to Distension, Rather Than Excessive Gas Production, Produces Carbohydrate-Related Symptoms in Individuals With Irritable Bowel Syndrome. Gastroenterology. 2017 Jan;152(1):124-133.e2.