
Article:
Dionne, J, Ford, AC orcid.org/0000-0001-6371-4359, Yuan, Y et al. (5 more authors) (2018) A Systematic Review and Meta-Analysis Evaluating the Efficacy of a Gluten-Free Diet and a Low FODMAPs Diet in Treating Symptoms of Irritable Bowel Syndrome. American Journal of Gastroenterology, 113 (9). pp. 1290-1300. ISSN 0002-9270

https://doi.org/10.1038/s41395-018-0195-4

A systematic review and meta-analysis evaluating the efficacy of a gluten free diet and a low FODMAPs diet in treating symptoms of irritable bowel syndrome

Joanna Dionne MD MSc FRCP PhD (c) (1), Alexander C Ford MB ChB FRCP (2, 3), Yuhong Yuan (1) MD, William D Chey MD FACG (4), Brian E Lacy MD PhD FACG(5), Yuri A. Saito MD, MPH (6), Eamonn MM Quigley MD FRCP FACP MACG FRCPI (7) and Paul Moayyedi MB ChB PhD FACG (1, 8).

1. Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada
2. Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.
3. Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.
4. Division of Gastroenterology, University of Michigan Health System, Ann Arbor, Michigan, USA
5. Mayo Clinic, Jacksonville, FL USA
6. Mayo Clinic, Rochester, MN USA
7. Division of Gastroenterology and Hepatology, Department of Medicine, Houston Methodist Hospital, Houston, Texas, USA
8. Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada

Abbreviations:

ACG	American College of Gastroenterology
CI	confidence interval
GI	gastrointestinal
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhea
IBS-M	mixed stool pattern irritable bowel syndrome
MeSH	medical subject headings
NNH	number needed to harm
NNT	number needed to treat
RCT	randomized controlled trial
RR	relative risk
GFD	Gluten Free Diet
FODMAP	fermentable oligo-, di-, and mono-saccharides, and polyols

Correspondence: Professor Paul Moayyedi
Audrey Campbell Chair of Ulcerative Colitis Research
Room 3V31 Hamilton Health Sciences
McMaster University Medical Centre

1200 Main Street West
Hamilton
Ontario, Canada
L8N 3Z5

Email: moayyep@mcmaster.ca
Telephone: +1 905 521 2100 ext. 76764
Facsimile: +1 905 521 4958

Keywords: Irritable bowel syndrome
Meta-analysis
Gluten Free Diet
Low FODMAPs Diet

Word count:

Funding: This work was supported by the American College of Gastroenterology Institute and the Canadian Institute for Health Research. Paul Moayyedi is the Principal Investigator for the Inflammation, microbiome, and alimentation: gastro-intestinal and neuropsychiatric effects (IMAGINE) - a Strategy for Patient Oriented Research (SPOR) chronic disease network that evaluates the role of the microbiome and diet in IBS.

Abstract

Objective: Dietary triggers such as gluten and highly fermentable oligo-, di- and monosaccharides and polyols (FODMAP) containing foods have been associated with worsening irritable bowel syndrome (IBS) symptoms. However, the true impact of dietary restriction on IBS symptoms has remained unclear. The aim of this study was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) examining the efficacy of exclusion diets (we focused on low FODMAP and gluten free diets (GFD)) in IBS.

Methods: We conducted a search of the literature using the electronic databases MEDLINE (1946- November 2017), EMBASE (1974-November 2017), Cochrane Central Register of Controlled Trials (November 2017), Cochrane Database of Systematic Reviews (2005-November, 2017) for RCTs of exclusion diets in IBS. Two independent reviewers screened citations and a third reviewer resolved disagreement. Two independent reviewers performed eligibility assessment and data abstraction. For inclusion, RCTs that evaluated an exclusion diet versus an alternative or usual diet, and assessed improvement in either global IBS symptoms or abdominal pain were required. Data were synthesized as relative risk of symptoms remaining using a random effects model. Quality of evidence was assessed using GRADE methodology.

Results: 1726 citations were identified. After full text screening a total of nine studies were eligible for the systematic review. There were two RCTs of a GFD, involving 111 participants. Both selected patients that responded to a GFD and then randomized them to continue the diet or have the diet "spiked" with gluten. A GFD was associated with reduced global symptoms compared with a control diet (RR 0.42; 95% CI 0.11 to 1.55. I^2 = 88%), although this was not statistically significant. There were seven RCTs comparing a low FODMAP diet with various control interventions in 397 participants. A low FODMAP diet was associated with reduced

global symptoms compared with control interventions (RR 0.69; 95% CI 0.54 to 0.88. I^2 = 25%). The three RCTS that compared low FODMAP diet with rigorous control diets had the least heterogeneity between studies, but also the least magnitude of effect. The overall quality of the data was “very low” according to GRADE criteria.

Conclusions: There is insufficient evidence to recommend a GFD to reduce IBS symptoms. There is very low quality evidence that a low FODMAP diet is effective in reducing symptoms in IBS patients.

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by symptoms of altered bowel habits (e.g. constipation and/or diarrhea), abdominal pain, and bloating without evidence of organic disease (1). The worldwide prevalence of IBS is 10-20% (2) and it is associated with a significant reduction in quality of life, as well as anxiety and depression (3). A positive diagnosis of IBS can be made on symptom-based criteria (4) and there are a number of different therapies including manipulating the microbiome, pharmacological and psychological approaches (5).

Pharmacological therapies can be effective, but surveys suggest that about 50% of patient with IBS use other approaches either in addition to, or instead of, conventional medical therapy (6), and over 60% report that particular foods trigger their symptoms (7, 8). Patients with IBS are therefore often interested in exploring dietary interventions for their symptoms. It is important to give patients evidence-based advice on which diets may be effective in reducing their symptoms. Initial approaches that based dietary recommendations for food sensitivities had disappointing efficacy in randomized trials (9), but recent dietary approaches have shown more promise. It has been hypothesized that a subset of patients with IBS may have an intolerance of gluten, despite not having celiac disease (10). This has led some to recommend a gluten-free diet (GFD) in IBS. Another approach has been to reduce fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in the diet. This is the most widely adopted diet in IBS and may improve IBS symptoms (11). Systematic reviews of studies evaluating a GFD and a low FODMAP diet have provided conflicting conclusions (12, 13), but all have suggested more data are needed.

Since publication of these systematic reviews, there have been additional randomized controlled trials (RCTs) evaluating exclusion diets in IBS (14, 15)

The aim of this study was to conduct an updated systematic review of RCTs assessing the impact of a GFD or low FODMAP diet in improving IBS symptoms, in order to provide clinicians with an evidence-based assessment of the efficacy of both.

Methods

Search Strategy and Study Selection

We conducted a search of the literature using the electronic databases MEDLINE (1946-November 2017), EMBASE (1974-November 2017), Cochrane Central Register of Controlled Trials (September 2017), Cochrane Database of Systematic Reviews (2005- November, 2017) via OVIDSP for RCTS of exclusion diets in IBS (See Box 1 for eligibility criteria). We included abstracts and conference proceedings from Digestive Diseases Week (2014 to 2017). There were no language restrictions. We conducted the literature search as part of the American College of Gastroenterology's updated monograph on the management of IBS (in press). Search terms included "irritable bowel syndrome", "irritable colon", "gluten free diet", "gluten free", "fructose oligosaccharide" "FODMAP or FODMAPs", "diet restriction", "fructan", "carbohydrate diet", "sweetener", etc, combined with AND terms. Additional combined terms included "clinical trials", "double blinded", "blind", or "randomized controlled trials", etc (for search strategy see appendix 1). We contacted authors for dichotomous outcomes if these were not reported, as well as for missing data. Two independent reviewers performed screening of citations and a third reviewer resolved disagreement.

Outcome Assessment

The primary outcome was global improvement in IBS symptoms. If global improvement was not reported, we used abdominal pain as the outcome of interest. If different definitions of symptom improvement were provided in the same study, we used the most stringent outcome reported that minimized placebo response rate (e.g. an improvement in IBS symptoms of >50% would be chosen ahead of an improvement in symptoms of > 25%). Secondary outcomes included general quality of life and any occurrence of adverse events.

Data Extraction

Two independent reviewers (JD and YY) performed data abstraction. Data extracted (Table 4) included data on year of publication, country of origin, type of diet used, duration of therapy, primary and secondary outcomes used, IBS definition used (e.g., Rome criteria versus clinician diagnosis), the comparator intervention, and predominant stool pattern (constipation versus diarrhea) of recruited patients. Data were abstracted as an intention-to-treat analysis, with drop outs treated as treatment failures. Disagreements were resolved by a third reviewer (PM).

Assessment of risk of bias and GRADE Methodology

The risk of bias assessment was performed by two independent reviewers using the Cochrane Risk of Bias Tool with ReviewManager (RevMan) (Version 5.3, Cochrane Collaboration). Each study was evaluated based upon reporting of randomization, allocation, blinding, and outcome assessment and reporting. Grading of the evidence was performed according to GRADE methodology using GRADEPro GDT (16).

Data synthesis and statistical analysis

Data analysis was performed using RevMan 5 (Version 5.3, Cochrane Collaboration). We calculated relative risk (RR) with 95% confidence intervals of symptoms not improving in IBS compared with control. Data were pooled with a random effects model. Heterogeneity was evaluated with the I^2 statistic, with >25% considered to be significant heterogeneity. We used forest plots with RRs for primary and secondary outcomes. Funnel plots were generated to assess for publication bias, if more than 10 studies were identified. Reasons for heterogeneity were explored using subgroup analyses. These include evaluation by low risk of bias trials versus unclear/high risk of bias, type of active dietary intervention, type of control intervention, definition of IBS, subtype of IBS according to predominant bowel habit, and setting.

Results

The literature search identified 1725 citations, and 72 studies underwent full manuscript review. After full text screening, 63 articles were excluded, leaving a total of nine studies eligible for the systematic review (Figure 1).

Gluten Free Diet and IBS

There were two RCTs (17, 18) of a GFD, involving 111 participants. Both selected patients that had already responded to a GFD, and then randomized them to continue the diet, or to have the diet "spiked" with gluten. The description of the trial characteristics is given in Table 1. One trial (17**)** was low risk of bias, and the other (18) was of unclear risk of bias. A greater

proportion of participants had an exacerbation of their IBS symptoms among those allocated to have their diet spiked with gluten, compared with those remaining on a GFD. Both trials reported a statistically significant result, but when the two trials were pooled the results were not statistically significant (RR = 0.42; 95% CI 0.11 to1.55, I^2 = 88%) due to the marked heterogeneity between individual trial results (Figure 2). Neither study reported on adverse events or general quality of life.

Low FODMAP Diet and IBS

There were seven RCTs (14, 115, 19-23) comparing a low FODMAP diet with various control or control comparator interventions in 397 participants. A summary of the trial characteristics is given in Table 1. There were no low risk of bias trials, and this was mainly due to lack of blinding. More recent studies have made excellent efforts to maintain blinding (14) but we classified studies as not blinded as the contents of a low FODMAP diet are readily available on the internet and on cell phone applications. A low FODMAP diet was associated with a reduction in global symptoms compared with controls (RR 0.69; 95% CI 0.54 to 0.88, I^2 = 25%) (Figure 3). One trial (14) reported general quality of life, with no difference between the two groups (mean difference = 1.30; 95% CI = -6.82 to 9.42). Two trials reported on adverse events (14, 15) but did not present data that could be extracted. Both trials reported that diets were well tolerated with no serious adverse events.

We explored reasons for heterogeneity between studies using subgroup analyses and the largest contributor to this was the choice of comparator diet with 52% of the variation in effect size between subgroups not due to chance (Figure 3).

Low FODMAP versus an Alternative Diet

Three studies (14, 15, 19) examined a low FODMAP versus an alternative diet encompassing 271 patients. There was a trend for a low FODMAP diet to reduce global IBS symptoms compared with alternative diets (RR = 0.82; 95%CI = 0.66 to 1.02) but this was not statistically significant.

Low FODMAP versus High FODMAP Diet

Only one study by McIntosh et al. (20) compared a low FODMAP with a high FODMAP diet in 40 patients. This study also found that a low FODMAP diet led to a reduction in global IBS symptoms compared with a high FODMAP diet (RR = 0.44; 95% CI = 0.23 to 0.83).

Low FODMAP versus Usual Diet

Two studies evaluated a low FODMAP diet versus a usual diet (21, 22) and included a total of 71 patients. There were fewer patients with persistent IBS symptoms in the low FODMAP diet arm, compared with a usual diet (RR = 0.46; 95% CI = 0.25 to 0.84).

LOW FODMAP exclusion followed by LOW FODMAP challenge versus placebo

Hustoft et al. (23) implemented a low FODMAP diet and 15 patients that responded to the diet were subsequently randomized to receive a supplement, either a placebo or one containing a FODMAP. Patients receiving placebo maintained the reduction in their IBS symptoms compared with placebo, but this small study was not statistically significant (RR = 0.44; 95% CI = 0.11 to 1.71).

Risk of Bias and GRADE

The overall quality of the data was "very low" according to GRADE criteria (Table 2 and Table 3) as most studies were unclear or high risk of bias, there was heterogeneity between study designs, and there was imprecision in the estimate of effect.

Discussion

The management of IBS should be evidence-based and any therapy should ideally be supported by high quality RCTs. For many years, this had been lacking for dietary interventions in IBS, with only three eligible RCTs identified in our last systematic review on this topic (13). There has been an increase in the quantity and quality of RCTs evaluating dietary therapies for IBS in recent years and this systematic review identified 11 RCTs, involving 508 participants, evaluating either a low FODMAP diet or a GFD. We found there was insufficient evidence to recommend a GFD, but there was very low quality evidence to support recommending a low FODMAP diet in IBS. A further RCT (24) suggested any benefit of GFD may relate to the reduction in FODMAPs consequent on this dietary change.

Proponents of a low FODMAP diet for IBS may be disappointed that the quality of the evidence is not rated higher. We used GRADE methodology (25) to evaluate the quality of the evidence, which is the most widely accepted approach, and one that is used by over 100 organizations throughout the world. The reason for the very low quality rating is the different comparator groups used in individual trials, and the relatively modest numbers of patients with an improvement in global IBS symptoms. Specifically, there were only a total of 189 participants in the low FODMAP diet trials who experienced an improvement in their symptoms, whereas

GRADE would ideally require 300 events for data to be classified as robust (26). These factors could be improved with further trials using similar comparators and providing more data, although this is a challenge given there is no pharmaceutical industry support and most federal funding agencies do not rate IBS as a priority area for research funding. Indeed, researchers in this area should be congratulated on the number of participants they have recruited to RCTs to date, despite these challenges. The area that will be more difficult to address is the issue around lack of blinding. Many IBS patients are aware of the concept of a low FODMAP diet, and information on this diet is freely available. An IBS patient can, therefore, easily deduce which diet they have been allocated to if they participate in an RCT. Asking the participant which group they think they have been randomized to (so the proportion with incorrect "guesses" can be calculated) may not identify this problem as participants that have identified which group they were allocated to may not admit to this. The only robust approach would be a double-blinded challenge study, where everyone is placed on a low FODMAP diet and then randomized to continue on that diet or have their diet spiked with a high FODMAP product. Even this is challenging to interpret, as any change in diet, even if it is unrelated to IBS, can cause gastrointestinal symptoms as the GI tract is exposed to new foods. In addition, even brief dietary interventions can change the gut microbiome, making rechallenge studies difficult to interpret. Ideally, challenge studies should, therefore, be long term in order to account for any short-term non-specific effects of foods that the GI tract has not experienced recently. Defining "long term" is a challenge in this context, but we would suggest at least 8-12 weeks of follow up and all studies in this review were of a shorter duration.

Providers recommending the low FODMAP diet should bear in mind that exclusion of FODMAPs is only the first phase of the diet program. Exclusion for 2-6 weeks should be viewed

as a diagnostic test to identify IBS patients who are sensitive to FODMAPs. Those who fail to improve should not continue the diet. Those that improve should be instructed on reintroducing foods which contain FODMAPs to determine their sensitivities. This information should then be used to liberalize and personalize the low FODMAP diet with the intention of improving adherence and minimizing effects on the gut microbiome.

There is much less data for a gluten-free diet or elimination diets based upon IgG antibody testing. As has already been pointed out, there is little to no data which addresses the long term efficacy, adherence, or harms of diet therapies for IBS. Recommendations regarding other diets (e.g. dairy-free, lactose-free, vegetarian, etc.) cannot be made due to lack of objective information. Regardless of the gaps in the data, it is clear that diet therapies are here to stay. The complexity of diet therapies for IBS, potential for inducing nutritional deficiencies, and time and resources required to provide proper counseling provides tangible incentives to utilize a properly trained dietician. If a trained dietician is not available or a patient cannot afford to see a dietician, it is important for providers to have assembled high quality teaching materials which can allow an IBS patient to implement diet therapy in a medically responsible manner.

Overall, the sample size within each trial was small and some studies utilized a cross-over design. These two factors raise concern regarding the external validity of the results, given the high prevalence of IBS within the general population, but relatively small sample sizes recruited in the current studies. Further studies could elucidate factors that limit study enrolment. In addition, future studies should utilize a parallel RCT design rather than a cross-over RCT methodology for a common disorder. The main reason for this is that we do not know the mechanism by which exclusion diets may reduce symptoms in IBS. It could relate to the direct effect of the food, such as osmotic load to the intestine, a subtle immune response to a certain

food group, or an influence on the gut microbiome that leads to GI symptoms (27). As we do not know the mechanism, it is difficult to recommend a definitive wash-out period, and, therefore cross-over trials should be avoided. RCTs could further improve our knowledge of how exclusion diets may impact on IBS by collecting mechanistic, as well as symptom, data. Indeed, some of the trials did collect microbiome and metabolomics data (14, 20). Studies rarely reported on general quality of life or adverse events and it would be important for future trials to address this deficit. Exclusion diets may have nutritional implications for patients or adversely impact on the microbiome, so it would also be important to evaluate long term safety concerns with a low FODMAP diet.

This study has several strengths. We used robust systematic review methodology and rigorously evaluated the quality of the evidence. The number of eligible studies has also increased significantly since this topic was last evaluated. There are, however, a number of limitations to this systematic review. As stated above, more events are needed before results can be considered robust, and there was variation in the comparator diet between trials. Freely available information on the low FODMAP diet is an issue for adequate blinding, and if new diets are developed in the future it would be advisable to keep them as confidential as possible until sufficient RCT data are collected. Finally, there was insufficient information to evaluate whether GFD or low FODMAP diet was more effective in certain subgroups of IBS patients, such as those with predominant diarrhea or bloating.

The findings of this review demonstrate that, at present, there is insufficient evidence to recommend a GFD to reduce global IBS symptoms. There is very low quality evidence that a

low FODMAP diet is effective in reducing global symptoms in IBS patients. More data are needed, but of the available dietary interventions, a low FODMAP diet currently has the greatest evidence for efficacy in IBS.

References

1. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel Disorders. Gastroenterology 2016; 150: 1393-407.
2. Lovell R.M., Ford, A.C. Global Prevalence of and Risk Factors for Irritable Bowel Syndrome: A Meta-analysis. Clin Gastroenterol Hepatol 2012; 10: 712-21
3. Pintos-Sanchez, M.I., Ford, A.C., Avila,C.A.,Verdu, E.F., Collins, S.M., Morgan, D.G., Moayyedi, P., Bercik, P. Anxiety and Depression Increase in a Stepwise Manner in Parallel With Multiple FGIDs and Symptom Severity and Frequency. American Journal of Gastroenterology 2015; 110: 1038-48.
4. Palsson, O.S. , Whitehead, W.E. , van Tilburg, M.A. , Chang, L. , Chey, W. , Crowell, M.D. , Keefer, L. , Lembo, A.J. , Parkman, H.P. Rao, S.S. , Sperber, A. , Spiegel, B., Vanner, S., Walker, L.S. , Whorwell, P. ,Yang Y. Rome IV diagnostic questionnaires and tables for investigators and clinicians. Gastroenterology Feb 2016pii: S0016-5085(16)00180-3. doi: 10.1053/j.gastro.2016.02.014.
5. Ford, A.C., Moayyedi, P., Lacy, B.E., Lembo, A.J., Saito, Y.A., Schiller, L.R., Soffer ,E.E., Spiegel, B.M.R., Quigley, E.M.M. American College of Gastroenterology Monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. American Journal of Gastroenterology 2014; 109: S1-S26

6. Lahner, E., Bellentani, S., de Bastiani, R. et al. A survey of pharmacological and nonpharmacological treatment of functional gastrointestinal disorders. United European Gastroenterol J 2013; 1: 385-93
7. Simrén, M., Månsson, A., Langkilde, A.M. et al. Food-related gastrointestinal symptoms in the irritable bowel syndrome. Digestion 2001; 63: 108–11.
8. Bohn, L., Storsrud, S., Tornblom, H. et al. Self-Reported Food-Related Gastrointestinal Symptoms in IBS Are Common and Associated With More Severe Symptoms and Reduced Quality of Life. Am J Gastroenterol 2013; 108: 634-41
9. Atkinson, W., Sheldon, T.A., Shaath, N. et al. Food elimination based on IgG antibodies in irritable bowel syndrome: A randomised controlled trial. Gut 2004; 53: 1459-64
10. Verdu,E., Armstrong, D., Murray, J.A. Between celiac disease and irritable bowel syndrome: The "no man's land" of gluten sensitivity. American Journal of Gastroenterology June 2009, 104 (6), 1587-1594.
11. Krogsgaard, L.R. , Lyngesen, M. ,& Bytzer, P.. Systematic review: quality of trials on the symptomatic effects of the low FODMAP diet for irritable bowel syndrome. Alimentary Pharmacology and Therapeutics 2017; 45: 1506-1513
12. Rao, S.S., Yu, S., Fedewa, A. Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. Aliment Pharmacol Ther 2015; 41: 1256-70
13. Moayyedi, P., Quigley, E.M., Lacy, B.E., Lembo, A.J., Saito, Y.A., Schiller, L.R., Soffer, E.E., Spiegel, B.M., Ford, A.C. The Effect of Dietary Intervention on Irritable Bowel Syndrome: A Systematic Review. Clinical Translational Gastroenterology 2015; Aug 20;6:e107. doi: 10.1038/ctg.2015.21

14. Staudacher, H.M. , Lomer, M.C.E. , Farquharson, F.M. , Louis, P. , Fava, F. , Franciosi, E., Sholz, M. , Tuohy, K.M. , Lindsay, J.O. , Irving, P.M. ,Whelan, K.. A diet low in FODMAPs reduces symptoms in patients with irritable bowel syndrome and a probiotic restores bifidobacterium species: A randomized controlled trial. Gastroenterology October 2017; 153: 936-947.
15. Eswaran, S.L., Chey, W.D. , Han-Markey, T. , Ball, S. , Jackson, K. A randomized controlled trial comparing the low FODMAP diet vs. modified NICE guidelines in US with IBS-D. American Journal of Gastroenterology 2016; 111: 1824-1832.
16. GRADEpro. [Computer program on www.gradepro.org]. Version [v20160405]. McMaster University, 2016.
17. Biesiekierski, J.R. , Newnham, E.D., Irving, P.M , Barrett, J.S. , Haines, M. , Doecke, J.D. ,.Shepherd, S.J, Muir, J.G., Gibson, P.R.. Gluten causes of gastrointestinal symptoms in subjects without Celiac Disease: A double-blind randomized placebo controlled trial. American Journal of Gastroenterology March 2011;106:508-514.
18. Shahhbazkhani, B., Sadeghi, A., Malekzadeh, R. , Khatavi, F. , Etemadi, M. , Kalantri, E., Rostami-Nejad, M. , Rostami, K.. Non-celiac gluten sensitivity has narrowed the spectrum of irritable bowel syndrome: A double-blind randomized placebo controlled trial. Nutrients 2015; 7: 4542-4554.
19. Bohn, L. , Storsrud, S. , Liljebo, T. , Collin, L. , Lindfors, P. , Tornblom, H. , Simren, M. Diet low in FODMAPs reduces symptoms of Irritable Bowel Syndrome as well as traditional dietary advice: A randomized controlled trial. Gastroenterology 2015; 149: 1399-1407.

20. McIntosh, K. , Reed, D.E.,.Schneider, T., Dang, F., Keshteli, A.H. , De Palma, G. , Madsen, K. , Bercik, P., Vanner, S. FODMAPs alter symptoms and the metabolome of patients with IBS: A randomized controlled trial. Gut 2017; 66: 1241-51.
21. Halmos, E.P, Power, V.A. , Shepherd, S.J. , Gibson, P.R. , Muir, J.G.. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology 2014; 146: 67-75.
22. Staudacher, H.M., Lomer, M.C.E, Anderson, J.L., Barret, J.S. , Muir, J.G. , Irving, P.M., Whelan, K. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. The Journal of Nutrition June 2012; 142: 1510-1518.
23. Hustoft, T.N. , Hausken, T., Ystad, S.O. , Valeur, J. , Brokstad, K., Hatlebakk, J.G. ,Lied, G.A. Effects of varying dietary content of fermentable short-chain carbohydrates on symptoms, fecal microenvironment and cytokine profiles in patients with irritable bowel syndrome. Neurogastroenterology Motilit Sept 2016;29.
24. Biesiekierski, J.R. , Peters, S.L. ,Newnham, E.D. , Rosella, O. , Muir, J.G.,Gibson, P.R No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed short-chain carbohydrates. Gastroenterology 2013;145:320-328.
25. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924-6.
26. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines 6. Rating the quality of evidence – imprecision. J Clin Epidemiol 2011; 64: 1283-93.

27. David LA, Maurice CF, Carmody RN et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014; 505: 559-63.