The FODMAP diet: more than just a symptomatic therapy?

Peter R Gibson , Emma P Halmos

The introduction and adoption of the FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols) diet has been a major change in the management of patients with irritable bowel syndrome (IBS) towards integrated care.[1] The diet has been seen as an effective symptomatic therapy, but one that carries risks associated with exacerbating disordered eating, challenging nutritional adequacy and putatively inducing dysbiotic gut microbiota. The concept that FODMAPs are involved in pathogenic mechanisms that underlie visceral hypersensitivity[2] might explain ongoing symptom control in patients after reintroducing dietary FODMAPs up to a level taken before FODMAP restriction.[3] The report by Vervier *et al* in *Gut* goes one step further.[4] Their study has suggested that initial FODMAP restriction might actually correct dysbiosis in a proportion of patients with IBS with consequent durable symptomatic benefit without the need for major FODMAP restriction. Furthermore, they may have provided another mechanism by which we can explain the wide variation of responses to FODMAP restriction from complete symptom resolution to worsening in a very small minority.

Reasons behind such heterogeneity of outcomes need to be defined so that the diet can be directed to the candidates more likely to respond or, more importantly, away from those highly likely not to respond. Dietary non-adherence, poor food selection, sometimes directed by misinformation on websites,[5] or overall lack of FODMAPs in the habitual diet[6] are easily understood explanations for poor response. Additional factors that might limit symptomatic response include the lack of visceral pain hypersensitivity[7] in some patients; functional characteristics of the gut microbiota, such as underrepresentation of saccharolytic bacteria with less vigorous gas production in response to exposure to FODMAPs[8]; or inadvertently increased consumption of unrecognised FODMAPs when following the FODMAP diet, such as sucrose and starch, in patients who might have hypomorphic forms of sucrase-isomaltase[9] with worsening of symptoms.[10]

Vervier *et al* have provided clues about the last two of these factors. They applied sophisticated phylogenetic analyses of the faecal microbiota before dietary intervention to 56 patients with IBS and enabled two equal and distinct profiles to be identified, which were designated 'healthy' (IBS^H; similar to that of paired household controls) and 'pathogenic-like' (IBS^P; characteristics included lower bacterial diversity, depleted Bacteroidetes and enriched Firmicutes). The two groups also had distinct metabolic gene signatures, especially in amino acid biosynthetic pathways and carbohydrate metabolism. In the IBS^P group, there was enrichment of genes involved in the metabolism of two FODMAPs, lactose and fructose, and of trehalose, a disaccharide hydrolysed by brush border trehalase into two glucose molecules.

Patients and their household controls were then coached on the low FODMAP diet, and the results from 36 pairs were reported. Three key observations were made. First, 75% of patients responded symptomatically (50-point reduction in IBS symptom severity score (IBS-SSS)), but the overall change in IBS-SSS was greater (median 80 points) in the IBS^P group. Second, the microbiota (diversity, taxonomic and metabolic gene profiles) were not altered in those with an initially 'healthy' profile despite apparent adherence to the diet, but most of the indices 'normalised' in the IBS^P group. Third, those who continued on the study maintained both symptomatic benefits and the healthy microbiota profiles despite a return to pre-diet FODMAP intake.

Three tentative conclusions can be drawn from these observations. First, as shown elsewhere, the structure of faecal microbiota might predict the degree of response to restriction of FODMAPs. Second, restricting FODMAPs can correct IBS-associated dysbiosis in the community structure and also in the metabolic pathways, and this correction appears to be maintained even when FODMAPs are reintroduced into the diet with concomitant symptom control. Perhaps the correction of pathogenic dysbiosis might be causally related to the reduced sensitivity to FODMAPs during the personalised phase.

The other intriguing finding was that trehalose metabolic pathways were 'activated' in those with dysbiosis. Current belief is that trehalose is effectively digested by brush border trehalase, except in indigenous Greenlanders.[11] So, what is the origin of the trehalose that is feeding the bacterial trehalose-metabolising metabolic pathways? There may be heterogeneity in the small intestinal trehalase activity, reminiscent of the identification by genetic analysis of hypomorphic forms of another brush border hydrolase, sucrase-isomaltase,[12] whose reduced activity might explain why some patients do not respond to FODMAP restriction.[9] It may be that trehalose is yet another unrecognised FODMAP, at least in a proportion of those with IBS. This is suggested by one study showing variable absorption of 30–60 g ingested trehalose based on diarrhoea and blood glucose/insulin levels compared with lactulose in female Japanese subjects.[13] Trehalose is not well described in food composition, but is crudely estimated to provide <2.0 g daily in a Japanese diet,[14] most found in mushrooms and in baker's yeast breads, foods incidentally limited during FODMAP restriction. However, trehalose is also synthesised by human pathogenic fungi and is associated with pathogenicity.[15] Study of the gut mycobiome is in its infancy, but the relative abundance of faecal Candida spp may be increased in patients ith IBS compared with that of healthy subjects.[16] Unfortunately, Vervier *et al* did not examine the mycobiome. Thus, the colonic microbial population may be exposed to trehalose—both dietary and fungal in origin—in more people than conventional teaching tells us, and its subsequent bacterial fermentation may play a role in symptom genesis.

There is a risk that all these concepts are overplaying the strength of the study—after all, FODMAP intake was poorly assessed (the method of assessing intake was crude and not validated), fibre intake (which can also influence the microbiota[17]) was not reported and patient drop-out reduced the power of the study considerably. Nevertheless, the beauty of Vervier's work is not in its definitive nature, but in that it enables the creation of feasible innovative hypotheses that can be examined by focused studies. Perhaps the FODMAP diet is not just a symptomatic therapy.

Department of Gastroenterology, Monash University and Alfred Health, Melbourne, Victoria, Australia

Correspondence to Professor Peter R Gibson, Department of Gastroenterology, Monash University and Alfred Health, Melbourne, VIC 3004, Australia; Peter.gibson@monash.edu

Contributors EPH and PRG wrote, revised and approved the final version of the article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests EPH has no perceived conflicts of interest. PRG has authored two educational/recipe books on the FODMAP diet. Monash University financially benefits from the sales of a digital application, booklets and online courses on the FODMAP diet.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Gibson PR, Halmos EP. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2021-326284

Received 9 October 2021
Accepted 17 October 2021

Linked

► http://dx.doi.org/10.1136/gutjnl-2021-325177

Gut 2021;**0**:1–2.
doi:10.1136/gutjnl-2021-326284

ORCID iDs
Peter R Gibson http://orcid.org/0000-0001-9108-1712
Emma P Halmos http://orcid.org/0000-0002-6063-5118

REFERENCES

1 Chey WD, Keefer L, Whelan K, *et al*. Behavioral and diet therapies in integrated care for patients with irritable bowel syndrome. *Gastroenterology* 2021;160:47–62.
2 Gibson PR, Halmos EP, Muir JG. Review article: FODMAPS, prebiotics and gut health-the FODMAP hypothesis revisited. *Aliment Pharmacol Ther* 2020;52:233–46.
3 Staudacher HM, Rossi M, Kaminski T, *et al*. Long-term personalized low FODMAP diet improves symptoms and maintains luminal bifidobacteria abundance in irritable bowel syndrome. *Neurogastroenterol Motil* 2021:e14241.
4 Vervier K, Moss S, Kumar N. Two microbiota subtypes identified in irritable bowel syndrome with distinct responses to the low FODMAP diet. *Gut* 2021.
5 McMeans AR, King KL, Chumpitazi BP. Low FODMAP dietary food lists are often discordant. *Am J Gastroenterol* 2017;112:655–6.
6 Gibson PR, Varney JE, Muir JG. Diet therapy for irritable bowel syndrome: is a diet low in FODMAPS really similar in efficacy to traditional dietary advice? *Gastroenterology* 2016;150:1046–7.
7 Farmer AD, Aziz Q. Mechanisms of visceral pain in health and functional gastrointestinal disorders. *Scand J Pain* 2014;5:51–60.
8 Chumpitazi BP, Cope JL, Hollister EB, *et al*. Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome. *Aliment Pharmacol Ther* 2015;42:418–27.
9 Zheng T, Eswaran S, Photenhauer AL, *et al*. Reduced efficacy of low FODMAPs diet in patients with IBS-D carrying sucrase-isomaltase (*SI*) hypomorphic variants. *Gut* 2020;69:397–8.
10 Foley A, Halmos EP, Husein DM, *et al*. Adult sucrase-isomaltase deficiency masquerading as IBS. *Gut* 2021. doi:10.1136/gutjnl-2021-326153. [Epub ahead of print: 06 Oct 2021].
11 Gudmand-Høyer E, Fenger HJ, Skovbjerg H, *et al*. Trehalase deficiency in Greenland. *Scand J Gastroenterol* 1988;23:775–8.
12 Henström M, Diekmann L, Bonfiglio F, *et al*. Functional variants in the sucrase-isomaltase gene associate with increased risk of irritable bowel syndrome. *Gut* 2018;67:263–70.
13 Oku T, Nakamura S. Estimation of intestinal trehalase activity from a laxative threshold of trehalose and lactulose on healthy female subjects. *Eur J Clin Nutr* 2000;54:783–8.
14 Fujiwara A, Murakami K, Sasaki S. Relative validity of starch and sugar intake in Japanese adults as estimated with comprehensive and brief self-administered diet history questionnaires. *J Epidemiol* 2020;30:315–25.
15 Thammahong A, Puttikamonkul S, Perfect JR, *et al*. Central role of the trehalose biosynthesis pathway in the pathogenesis of human fungal infections: opportunities and challenges for therapeutic development. *Microbiol Mol Biol Rev* 2017;81. doi:10.1128/MMBR.00053-16. [Epub ahead of print: 15 03 2017].
16 Sciavilla P, Strati F, Di Paola M, *et al*. Gut microbiota profiles and characterization of cultivable fungal isolates in IBS patients. *Appl Microbiol Biotechnol* 2021;105:3277–88.
17 So D, Gibson PR, Muir JG, *et al*. Dietary fibres and IBS: translating functional characteristics to clinical value in the era of personalised medicine. *Gut* 2021. doi:10.1136/gutjnl-2021-324891. [Epub ahead of print: 20 Aug 2021].