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Review article: implementation of a diet low in FODMAPs for patients with irritable bowel syndrome—directions for future research

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Summary

Background: Despite the efficacy of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) for patients with irritable bowel syndrome, many questions remain unanswered with respect to its clinical implementation.

Aim: To review literature to identify, synthesise, and provide direction for future research in the implementation and evaluation of the low FODMAP diet.

Methods: Bibliographical searches were performed in Ovid Medline, CINAHL, Scopus and PubMed from database commencement until September 2018, with search terms focused on the population (irritable bowel syndrome) and intervention of interest (FODMAP).

Results: Predictors of response to a low FODMAP diet remain under investigation, with preliminary data supporting faecal microbiota or faecal volatile organic compound profiling. Training of clinicians, and standards for the education of patients about the phases of a low FODMAP diet, as well as the role of Apps, require formal evaluation. There are limited data on the longer term efficacy and safety of the low FODMAP diet with respect to sustained symptom control, effect on quality of life and healthcare utilisation, nutritional adequacy, precipitation of disordered eating behaviours, effects on faecal microbiota and metabolomic markers, and subsequent translation to clinical effects.

Conclusions: Many gaps in implementation of the low FODMAP diet in clinical practice, as well as long-term safety and efficacy, remain for further investigation.

The Handling Editor for this article was Professor Jonathan Rhodes and this uncommissioned review was accepted for publication after full peer-review.

1 | INTRODUCTION

There are now extensive data outlining the symptomatic benefit of restricting fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in approximately 50%–80% of patients with irritable bowel syndrome (IBS).[1–9] The low FODMAP diet has been recommended as a first-line dietary therapy for IBS.[2,10–12]

Despite the efficacy of the low FODMAP diet, many questions remain unanswered with respect to its clinical implementation. First, given that between 20% and 50% of patients do not respond to a low FODMAP diet,[13] better validated and practical approaches to identify predictors of response are required. The efficacy of different methodical and personalised approaches to restriction and reintroduction of FODMAPs remains to be assessed,[14] as does the question of how education of patients and supportive resources are administered across different healthcare settings internationally. Training for clinicians including specialised dietitians has not been well evaluated, which has implications for responses in clinical trial settings as well as in routine clinical practice.

Irritable bowel syndrome is a complex lifelong condition that typically fluctuates in severity and subtype. Though there is a strong evidence base for the efficacy of the low FODMAP diet in the treatment of IBS in the short-term,[13,15] few studies have investigated the medium to long-term efficacy and safety of this approach. This review examines the literature to identify, synthesise, and provide direction for future research in the implementation and evaluation of the low FODMAP diet in patients with IBS. Current understanding of the mechanisms of how the low FODMAP diet impacts on symptoms in IBS has been detailed elsewhere.[16] There are limited data to date for the low FODMAP diet for the treatment of functional gastrointestinal disorders other than IBS, including functional dyspepsia.[17,18] These indications will not be specifically addressed in this review.[19]

2 | METHODS

A literature review was conducted by systematically synthesising published studies identified through bibliographical searches performed in electronic databases; Ovid Medline, CINAHL, Scopus, and PubMed from database commencement until 1 September 2018. The search criteria included combinations of the following search terms and keywords: FODMAP*, "low FODMAP", "fermentable oligosaccharide*", fructo*, "irritable bowel syndrome*", IBS. No language or date restrictions were applied. No restrictions were placed on study design, with reviews and commentaries included. Articles were reviewed for clinical studies focusing on predictors of response, implementation of diet, long-term effects of the low FODMAP diet in patients with IBS. Reference lists of the included articles were also reviewed. A narrative synthesis was undertaken to describe and compare the included literature.

3 | PREDICTORS OF RESPONSE TO THE LOW FODMAP DIET

Irritable bowel syndrome is a complex and heterogeneous disorder, with multiple genetic, environmental, and psychosocial factors leading to the risk of development and perpetuation of this syndrome. Alterations in intestinal microbiota, intestinal permeability, immune regulation, intestinal motor function, visceral sensitivity, autonomic function, as well as variability in food sensitivities, and associations with psychological co-morbidities have been reported in subgroups of patients with IBS.[20,21] It is, therefore, unsurprising that any one mode of treatment is unlikely to benefit all patients, and that more than a quarter of patients with IBS do not respond to a low FODMAP diet.[13]

3.1 | Impact of IBS subtype on response

Given the lifestyle imposition involved in the institution of a low FODMAP diet for patients, it is imperative to identify factors that predict response to this therapy. The predominant subtype of IBS may be one such factor, but results to date have been inconsistent. There are three main subtypes of IBS: constipation predominant (IBS-C), diarrhoea predominant (IBS-D), and those with mixed bowel habits (IBS-M). Those who do not fit into these categories are considered to have IBS unclassified (IBS-U).[23] Most studies have focused on IBS-D patients,[1,3,5,6,24,25] which, in some cases, is due to small numbers of IBS-C volunteers.[24] Less effective symptom improvement for IBS-C subtype were found in some but not all studies.[2,3,26,27] In a study of patients with functional gastrointestinal disorders who had a positive breath test to fructose or lactose, including those with conditions other than IBS such as functional dyspepsia, chronic diarrhoea predicted positive response (odds ratio 2.62 [95% confidence interval 1.31-5.27], $P = 0.007$) but nausea was negatively associated with response to a low FODMAP diet (odds ratio 0.33 [0.16-0.67], $P = 0.002$).[18]

3.2 | Utility of breath testing as a predictor

Breath hydrogen testing was previously used in clinical practice to identify whether malabsorption of a specific sugar such as fructose, mannitol, or sorbitol could direct a low FODMAP diet. In one retrospective study, response rates for those patients with a positive fructose breath test were as much as a 54% higher than those with a negative test outcome.[28] A positive breath test has served as somewhat of a "diagnosis" for many patients, which, for many aided to build trust and adherence to the dietary advice. Since then, using breath testing to drive the need for FODMAP restriction has been proven unreliable due to poor reproducibility of the tests.[29,30] As a result, there is pressure on the dietetic clinician to build rapport and educate these patients about the role of individual FODMAP carbohydrates, their mechanism and food sources, and requirement for initial FODMAP restriction to improve their symptoms.

3.3 | Pattern of symptom course as a predictor of response

The underlying pattern of symptom course in patients with IBS may also be useful. The unvalidated Copenhagen IBS disease course adapted from four visual disease activity courses observed in patients with inflammatory bowel disease (IBD),[33] has shown that patients with mild indolent disease responded best to a low FODMAP diet.[34]

3.4 | Impact of microbiota on response

An emerging area of research has focused on the prediction of response to a low FODMAP diet based on faecal bacterial profiling. A "GA-map Dysbiosis Test" has recently been used to create a "Dysbiosis Index" score which provides a numeric score of how the bacterial composition of an individual compares to a healthy reference group.[35] Using this test non-responders to a low FODMAP diet were found to have higher bacterial abundance and higher "Dysbiosis Index" scores compared to responders, with certain bacteria being higher in abundance including *Bacteroides stercoris*, *Pseudomonas*, *Acinetobacter*, and the genus *Desulfitispor*.[36] Applicability of this test in predicting responders or non-responders in the clinical setting, as well as its reproducibility, remain to be evaluated. In a study of children with IBS, responders to a two-day low FODMAP diet had greater baseline abundance of bacteria with saccharolytic metabolic capacity, including *Bacteroides*, Ruminococcaceae, *Dorea*, and *Faecalibacterium prausnitzii*.[26,37] In contrast, another study found no difference in alpha, beta diversity or operational taxonomic units in responders versus non-responders, but the statistical strength of the baseline dataset were compromised by loss of samples by thawing due to an electrical failure in this study.[24]

3.5 | Metabolomics as a predictor of response

A potential low cost, non-invasive strategy to predict response to a low FODMAP diet has been identified. In a study comparing 37 responders to a low FODMAP diet to nine non-responders, faecal volatile organic compound (VOC) profiling at baseline accurately predicted response in 97%.[9] These faecal VOCs may reflect bacterial metabolism of undigested food substrates. In patients with IBS, these products may reflect a susceptibility to dietary stimuli, and hence be associated with a response to a low FODMAP diet.[9] However, how well this test performs in a prospective cohort is yet to be tested.

Faecal metabolite profiling in another study revealed L-urobilin associated with responders, and cholate with non-responders, to a "low fermentable substrate diet", but the FODMAP composition of this diet not defined.[26]

Research into who will respond best to a low FODMAP diet remains preliminary, testing of these hypotheses in larger prospective trials is required. To be able to be implemented in daily practice and be acceptable to patients and clinicians, any predictive tests to stratify patients on the basis of response will need to consider factors such as cost, accessibility of testing, variability and reproducibility of results, and have sufficient discriminatory value in identifying the most appropriate management strategy. The risk associated with studies of the microbiota as published, for instance, is that many patients who might potentially respond will be excluded.

4 | ADMINISTRATION OF THE LOW FODMAP DIET

4.1 | Phases of the low FODMAP diet

Administering a low FODMAP diet involves three phases: initially a strict low FODMAP diet for 2-6 weeks, followed by a reintroduction phase, then FODMAP personalisation.[14,38,39] (Figure 1). Limited published literature exists on the FODMAP reintroduction phase, in particular whether tolerance to FODMAPs changes over time and what the ideal quantity is to reintroduce, but inherent heterogeneity of patient responses means evidence to guide re-challenging of FODMAPs poses significant complexity to collect.[14]

Current practice suggests that in the FODMAP personalisation phase of the diet, patients interpret their food challenge results with a dietitian, repeat challenges of poorly tolerated foods, and reintroduce restricted foods based on symptom response to these challenges.[14,38] For example, foods which did not induce symptoms are reintroduced back into the diet freely, foods which induced mild symptoms may be reintroduced in smaller doses or less frequently. Foods identified to trigger severe symptoms responses should continue to be avoided for optimal symptom control, however patients are encouraged to attempt re-challenges to poorly tolerated foods as symptoms can change over time. In the long-term, patients develop an individualised and varied low FODMAP diet, albeit one that may modify over time.[14]

Replacement of the introductory phase of a strict low FODMAP diet by a more selective "step-up" approach may be required in certain situations, such as when nutritional concerns are present, there is excessive FODMAP intake but mild symptoms, known lactose intolerance, or limited access to cooking facilities or cooking skills.[40] However, this approach has not been formally evaluated and should only be used in these situations, as there is a risk it may not result in adequate symptom relief, leading to a loss of faith in the FODMAP approach.[41]

4.2 | Provision of low FODMAP education

Dietary adherence is considered to be positively associated with the provision of assessment and education from a specialised dietitian, as recommended by national guidelines.[40,42] This model has been effectively implemented internationally. However, in some countries, particularly where services are largely publicly funded, dietetic capacity is limited.[43] Increasingly, other health professionals may provide FODMAP education, with limited evidence as to the clinical or cost-

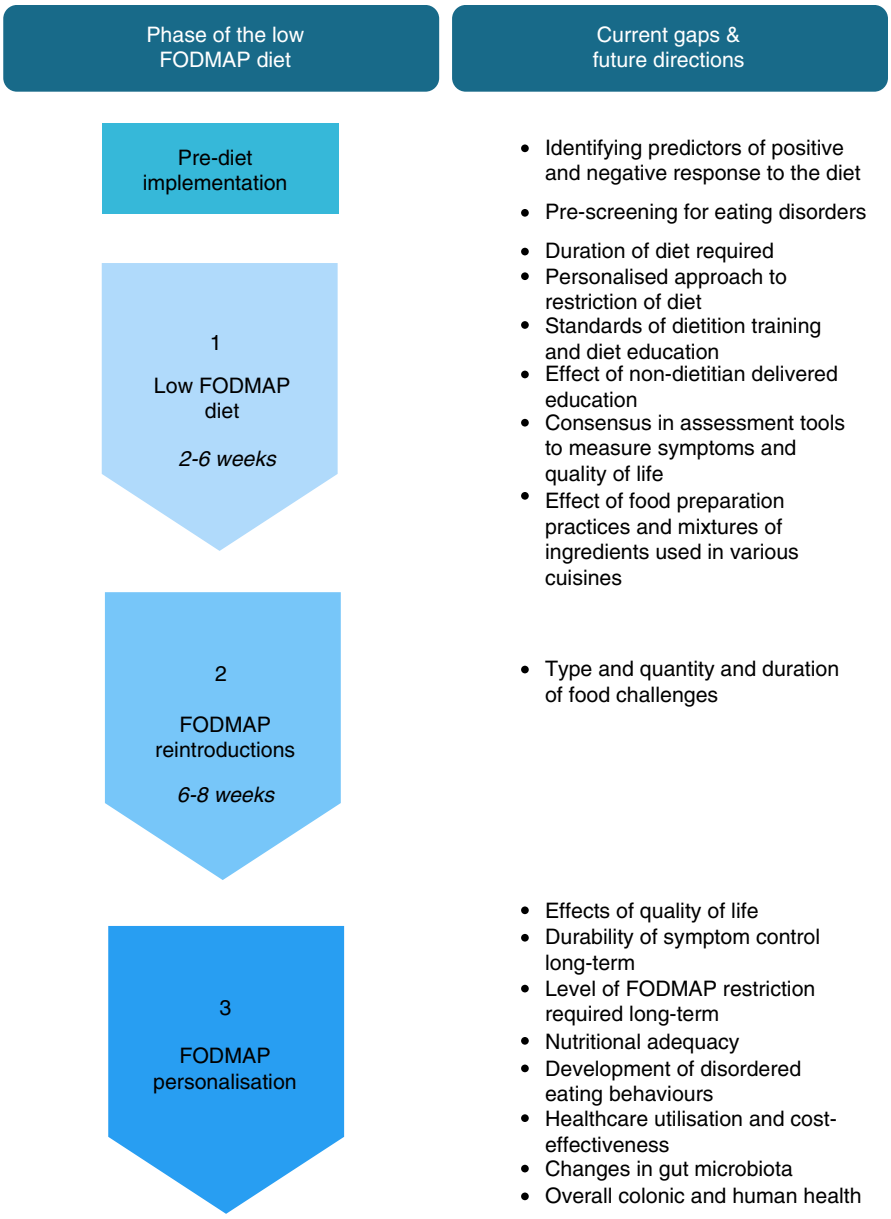

FIGURE 1 Gaps in current knowledge of the low FODMAP diet and future directions

effectiveness of such approaches.[43] Symptom severity of dietitian-led group FODMAP education has been shown to be comparable to traditional one-to-one education, delivered at a considerably reduced cost per patient. However, this study comprised screening of patients by a dietitian for 15 min by telephone to determine baseline nutrition and dietary intake.[44] Education materials may be sought via the internet, but the quality may be incomplete or incorrect, with patients and health professionals potentially lacking discrimination as to reputable sources.[43] Indeed, the inconsistencies of food lists and dietary information availability on the internet have been highlighted.[45,46]

4.2.1 | Use of web-based or App-based teaching of the low FODMAP diet

Digital applications through smartphones provide another opportunity for the delivery and evaluation of low FODMAP education. Nutrition and health-related apps have been recommended for patients by 83% of US dietitians,[47] with 84% of dietitians in a three-country study of Australia, NZ, and the UK recommending apps.[48] This study reported that the Monash University Low FODMAP diet app was the second highest nutrition-related app that was recommended by dietitians, or self-initiated by patients. The Mobile Nutrition Care Process Grid,[48] provides dietitians with a framework for incorporating apps into practice. Whether a web-based or App-based teaching of the low FODMAP diet for the patient is able to replace formal dietitian-directed consultations remains untested, and cannot be recommended currently.

4.2.2 | Specialist dietitian training programs

There are many purported specialist training programs for dietitians specifically devoted to the administration of the low FODMAP diet.

As for printed information, these present problems in identifying quality training and accuracy in information transmitted. Evaluation of the effectiveness of these in translating to quality patient care is difficult. Since delivering the diet is only one part of the management of patients with IBS, education in the diet that is divorced from education in the nature of IBS and other options available, ideal education is likely to need to be broader than just simple instruction on the phases of the diet. Thus, the originators of the diet at Monash University have developed a comprehensive online course of dietitians,[49] and the team at King's College London who have made multiple important contributions to the evidence base have been conducting a successful comprehensive face-to-face course.[50]

4.3 | Cross-cultural dietary advice and FODMAP quantification

Irritable bowel syndrome is recognised at a prevalence of 10%–15% throughout the world, with studies performed in countries from all inhabited continents.[51] The quantification of FODMAP content of foods has progressed rapidly over the past decade to incorporate diverse products consumed in many countries.[52,53] Nonetheless, the effect of food preparation practices, as well as the impact of mixtures of ingredients used in various cultures, are limited. Given the basis of many cuisines include onion, garlic, shallots, legumes, pulses, and wheat-based products, the low FODMAP diet holds potential to be effective across many cultures if food knowledge and access to appropriate substitutions are available in that region.[54,55] The perceived cost of appropriate foods, poor labelling of FODMAP content and low availability of low FODMAP foods in local stores were reported as barriers to adherence in one small Malaysian study, with limitation in knowledge of FODMAP content of foods a factor in a south Asian study.[54,56]

5 | LONG-TERM EFFICACY OF LOW FODMAP DIET

Irritable bowel syndrome is a lifelong condition associated with fluctuating disease course and severity, as well as variability in symptom pattern and associated comorbidities.[57,58] Consequently, any therapeutic approach to the management of IBS must be adaptable to such changing symptoms, and ideally empower patients to wean and reinitiate treatment based on underlying severity. Furthermore, any such changes in management, or prolonged treatment, should be weighed against potential risks of long-term continued treatment. The low FODMAP diet aims to achieve a personalised plan following reintroduction of foods, such that strict ongoing elimination of a wide variety of foods is minimised.[14]

Initial short-term studies based upon the elimination phase only of FODMAPs reported response rates of 68%–70%.[1,2] More recent studies, focussed on evaluating longer term efficacy and safety of the low FODMAP diet, have been limited to 6-18 months duration in prospective[4,8,24,28,60] and retrospective cohorts (Table 1).[34] A higher reported efficacy was demonstrated in randomised control trials (79% and 82%)[4,8] than in the retrospective and prospective observational studies of the personalised phase of the low FODMAP diet (29% and 57%).[34,60] Significant variability in study design with respect to definition of dietary protocols, whether breath hydrogen testing was used to refine restrictions, structure of FODMAP reintroductions (including the health professional delivering this education), assessment tools, and reporting methods have limited inter-study comparisons and generalisability of results.[4,8,24,28,34,60] In four of these studies, the personalisation phase was self-administered with only one follow-up appointment provided in the short term.[4,24,34,60] The intensity of dietetic follow-up during this phase has not been well defined, but will likely depend on the requirements each patient with respect to symptom control and understanding.[14,38]

Limitations in the performance of dietary interventional studies have been discussed previously.[39] Standardisation of clinical trials has been recommended,[39] but rigid long-term dietary alteration especially in reintroduction and personalisation phases may be logistically difficult in the clinical trial setting and of limited value to clinical practice.

5.1 | Symptom control

Accounting for variability in measures of response, sustained symptom control has been observed in the majority of patients following FODMAP reintroduction and personalisation in recent long-term studies.

One 24-week single-blind RCT compared 29 patients undertaking a low FODMAP diet (comprising a 12-week elimination phase followed by reintroduction, with a total of four nutritional counselling sessions) with 30 patients undergoing yoga intervention.[8] Researchers reported a significant reduction in IBS-Severity Scoring System (IBS-SSS) in the low FODMAP group from baseline (260 ± 80) to 12 weeks (164 ± 95), sustained to 24 weeks (144 ± 110). A large proportion (79%) of participants had adequate symptom relief of their IBS symptoms at 3 months, reported as the extent to which they experienced adequate relief and/or general global improvement in daily food diaries.[8] Similar results were noted in another 6-month non-blinded parallel randomised controlled trial comparing 23 patients initiating a low FODMAP diet at baseline vs 27 patients commencing a low FODMAP diet at 3 months.[24] A reduction in IBS-SSS in the former group from baseline 272 ± 60 to 129 ± 83 at 3 months on a strict low FODMAP diet, and slight increase following reintroduction of FODMAPs to 160 ± 102 at 6 months was found. A third prospective randomised controlled trial that compared a low FODMAP diet with gut-directed hypnotherapy, using a 100-point gastrointestinal visual analogue scale as the primary endpoint, noted a change from baseline overall gastrointestinal symptom score of 61 (54-68) by −30 (−43 to −16) points following a 6-week elimination period, with maintenance of effect at 6 months following reintroduction of FODMAPs. Eighty-two per cent of individuals had improvement in overall gastrointestinal symptoms at 6 months while

following an adapted low FODMAP diet defined as a ≥ 20 mm decrease on the visual analogue scale.[4]

In a prospectively recruited cohort of 103 patients commenced on a low FODMAP diet who were administered a postal questionnaire between 6 and 18 months later, satisfactory relief of symptoms was reported at short-term on a strict low FODMAP diet in 61%, and maintained at 6-18 months on an "adapted" FODMAP diet in 57% of patients.[60] Based upon self-administered patient questionnaires administered retrospectively to 131 patients with IBS with median follow-up of 15 (range 2-80) months, a further study found that 29% of patients with IBS reported "full effectiveness", with a larger proportion experiencing partial symptom relief.[34] A third study of 90 prospectively recruited patients who returned follow-up questionnaires at a mean of 15.7 (±9) months, 72% of patients reported satisfaction with overall symptoms.[28] In this study, patients had a 1 hour appointment initially, then a 30 min appointment at 6 weeks, with provision of written information concerning the "limited reintroduction of a restricted group of carbohydrates" without formal consultations.[28]

Long-term symptom control has been most effective and statistically significant with respect to abdominal pain,[4,24,34,60] bloating,[4,8,24,60] and flatulence,[4,60] decreasing by at least a third at long-term follow-up in one study (Table 2).[60] A significant reduction in

TABLE 1 Studies investigating the effect of low FODMAP diet on long-term efficacy and the different tools used to assess symptom control and quality of life

Low FODMAP Study	Study design	Study duration	Intervention(s)	Method of FODMAP reintroduction	Percentage reporting overall sustained symptom relief at longer term follow-up	Tools used to assess symptom control and QOL
Schumann (2017)[8]	Single blind RCT	3-6 mo	LFD (n = 29, at 6 mo n = 22) vs Yoga (n = 30)	Educator: not stated • Review at 12 wk • Education on FODMAP reintroduction phase • Different FODMAP food tested each week over 2-3 d until all groups tested • Written information produced by the German Association for Nutrition provided • Two review appointments and one additional group appointment—timing not stated	79 ("adequate relief" recorded in diaries by 14/22 patients)	• IBS-SSS • IBS-QOL • SF-36 • Adequate symptom relief and/or general global improvement (daily diaries)
O'Keeffe et al (2017)[60]	Prospective observational	6-18 mo	LFD (n = 103)	Educator: Dietitian • Review at 6 wk • Educated on FODMAP reintroduction if symptom control achieved • FODMAP food challenges for 3 consecutive days using increasing food portion sizes • Development of personalised FODMAP diet by patients • 82% continued to follow a personalised FODMAP diet at 6-18 mo	57 (global symptom response)	• Global symptom response question • Gastrointestinal Symptom Rating Scale • Adapted food related QOL tool using SWFL +NQOL • Bristol stool chart
Harvie et al (2017)[24]	Non-blinded RCT	6 mo	LFD (n = 23) reintroduction at 3 mo vs Delayed LFD group (n = 27)	Educator: Dietitian • One follow-up appointment at 3 mo • Systematic reintroduction of FODMAPs if symptom improvement • Resource provided based on those from Monash University • Further follow-up provided on demand • Development of personalised FODMAP diet by patients, reviewed at 6 mo	"vast majority"	• IBS-SSS • IBS-QOL

(Continues)

TABLE 1 (Continued)

Low FODMAP Study	Study design	Study duration	Intervention(s)	Method of FODMAP reintroduction	Percentage reporting overall sustained symptom relief at longer term follow-up	Tools used to assess symptom control and QOL
Peters et al (2016)[4]	Non-blinded RCT	6 mo	LFD (n = 24) vs Hypnotherapy (n = 25) vs LFD+ hypnotherapy (n = 25)	Educator: Dietitian • Review at 6 wk • Systematic reintroduction of FODMAPs for those with symptom improvement • If symptoms were experienced, participants waited until symptom free then tried half the initial serving size • If symptoms were not experienced participants either gradually increased the number of foods containing that FODMAP until usual consumption amount was reached or maintained the test amount of FODMAP in their diet and continued onto the next FODMAP subgroup • Development of personalised FODMAP diet by patients, reviewed at 6 mo • Only two patients continued with strict FODMAP restriction at 6 mo	82 (IBS-SSS)	• IBS-SSS (≥20 mm improvement) • IBS-QOL
Maagard et al (2016)[34]	Retrospective observational	Median 15 mo (2-80 mo)	LFD in IBS (N = 131) and IBD (N = 49)	Educator: Dietitian • Review at 6-8 wk • "reintroduction of small amount of foods high in FODMAPs in order to determine individual tolerance level and ensure variety in diet" • 47% who remained on a LFD • 84% personalised FODMAP diet with varying levels of FODMAPs • 16% continued on a strict LFD	29 ("full effectiveness" on IBS-SSS)	• IBS-SSS • IBS-QOL • Copenhagen IBS disease courses • Bristol stool chart
de Roest et al (2013)[28]	Prospective observational	Mean 15.7 mo (6.7-24.7 mo)	LFD (N = 90)	Educator: Dietitian • Review at 6 wk • Provided with information by a dietitian concerning "the limited reintroduction of restricted group of carbohydrates" • 76% adherence to diets reported	72 reported satisfaction with overall symptoms	• IBS Satisfaction Survey using validated Likert scale taken from IBS Global Improvement Scale
Staudacher et al (2011)[96]	Retrospective observational	9 mo	LFD (N = 43) vs NICE diet (n = 39)	• No reintroductions recommended	76 using a global symptom response question	• IBS Satisfaction Survey using validated Likert scale taken from IBS Global Improvement Scale • Global symptom response question

FODMAP: fermentable oligosaccharides, disaccharides, monosaccharides and polyols; IBS-QOL: Irritable Bowel Syndrome Quality of Life questionnaire; IBS-SSS, Irritable Bowel Syndrome Severity Scoring System; LFD: low FODMAP diet; NICE: the National Institute for Health and Care Excellence, VAS: visual analogue scale; NQOL: Nutrition Quality of Life survey; QOL: quality of life; RCT: randomised controlled trial; SF-36:36-Item Short-Form health survey; SWFL: Satisfaction With Food-related Life.

reports of abnormal stool frequency and consistency was also maintained at 6-month follow-up.[4,8,24,34,60] However, there is heterogeneity in symptom reporting across studies. It has been recommended that global symptom severity questions should be combined with tools that measure and specify changes in specific symptoms.[38,61]

5.2 | Diet acceptability

Studies evaluating adherence to the low FODMAP diet over the long-term have reported variable adherence rates of between one-third to over 80%.[4,28,34,60]

A disruption to eating out with family and friends and an increased cost of the diet were reported as factors impacting on dietary acceptability of a long-term low FODMAP diet following FODMAP personalisation.[34,60] Interestingly, the taste of a low FODMAP diet was "liked" by just over half of respondents in one study, with almost a quarter of participants reporting that the diet was too expensive.[28]

Detailed quantification of FODMAP intake among patients longer term remains an area of future study. Thresholds of FODMAP intake and extent of liberalisation for maintenance of symptom control and patient acceptability in relation to pre-low FODMAP diet initiation have not been well-characterised.

5.3 | Effect on quality of life

IBS is associated with significant impaired quality of life comparable to that with other chronic diseases.[62] Symptom severity has been significantly associated with perceived general health and quality of life.[63] There is an association between illness perception and IBS outcomes, with an indirect effect of the clinician-patient relationship and quality of life through illness coherence and acceptance.[64] Quality of life is an important outcome measure for patients with IBS, where impacts of the disease influence patients at a personal and social level.[65] Although previous studies have described a correlation with symptom control and quality of life,[66,67] specific evaluation of quality of life in patients following a low FODMAP diet has been limited.

5.3.1 | Quality of life tools used to evaluate low FODMAP research

Various quality of life assessment tools have been incorporated into studies evaluating the low FODMAP diet, including the disease specific Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire,[68] 10-item Short Form of the Nepean Dyspepsia Index (SF-NDI),[69] non-validated tools focusing on food-related quality of life such as the Nutrition Quality of Life (NQOL) survey[70] and those validated in the general population such as the Satisfaction with Food-related life (SWFL) questionnaire.[71] Generic quality of life measures such as the 36-Item Short-Form Health Survey (SF-36)[72] have also been reported. The IBS-SSS includes a single question for evaluating symptom management and the Gastrointestinal Symptom Rating-Scale for IBS has been validated against several other quality of life questionnaires, and found symptoms of bloating, pain, and diarrhoea correlated highly with quality of life domains.[66]

5.3.2 | Quality of life in long-term studies

Quality of life has been shown to improve from baseline and be maintained on a personalised FODMAP diet at 6 months using a variety of tools and reporting methods. Four studies assessed quality of life using the IBS-QOL tool with a mean improvement from baseline of 21 (12-30),[4] 11[24], and 6.18[8] in points at 6 months follow-up. One study did not assess baseline quality of life but found most participants had a good quality of life (arbitrarily defined by the authors as ≤102 points) with a median score of 75 (range 37-145).[34] A change of 10 points has previously been described as clinically significant.[68] Quality of life improved over time in two of these studies,[4,8] potentially as patients maintained symptom control as they relaxed the dietary restrictions.

Using the SWFL, no change in food-related quality of life between those on a habitual diet and those on an adapted FODMAP diet was reported at 6-18 months follow-up.[60] In a cohort of 22 patients, the SF-36 was used in addition to the IBS-QOL and showed statistically significant improvement in bodily pain, vitality, social role functioning, and mental health seen at 6 months on an adapted FODMAP diet.[8]

The impact of a low FODMAP diet on short and long-term quality of life remains uncertain. Though symptom improvement clearly improves quality of life, restriction in food intake and choices, real or perceived, appear to counter-balance this effect in at least some of the studies. This area requires further interrogation.

5.4 | Healthcare utilisation and cost-effectiveness

Patients with IBS have greater rates of absenteeism from work and healthcare utilisation than healthy controls.[73,74] The effect of a low FODMAP diet on these measures, as well as the cost-effectiveness of this therapy, have not formally been evaluated in detail. Based upon recall by patients at 6-18 months, no significant differences in healthcare utilisation as measured by frequency of visits to their general practitioner or gastroenterologist, rates of absenteeism, or the overall rates of medication use, were seen between patients with IBS following a personalised FODMAP diet compared with those on a habitual diet.[60] These data are susceptible to recall error, and prospective studies evaluating this outcome particularly in comparison to emerging pharmacotherapies remains an area for further study.

6 | LONG-TERM SAFETY CONCERNS OF THE LOW FODMAP DIET

6.1 | Nutritional adequacy

Given that the low FODMAP diet involves the restriction of a variety of foods including wheat, dairy products, pulses, fruit, and vegetables, concerns regarding the adequacy of this diet with respect to

TABLE 2 Percentage improvement in individual symptoms which were statistically significant at long-term follow-up on a personalised FODMAP diet

Study	Abdominal pain	Bloating	Flatulence	Stool frequency/consistency	Diarrhoea
O'Keefe et al[60]	[c]	[c]	[c]	14 Bristol Stool Chart	
Schumann et al[8]	—	47 IBS-SSS	—	—	—
Harvie et al[24]	48 IBS-SSS	56 IBS-SSS	—	94 IBS-SSS	—
Peters et al[4]	57 IBS-SSS	49 IBS-SSS	52 IBS-SSS	48 IBS-SSS	—
Maagard et al[34]	—	—	—	41 Bristol Stool Chart	21 Bristol Stool Chart

GSRS, Gastrointestinal Symptom Rating Scale; IBS-SSS, Irritable Bowel Syndrome Severity Scoring System.
[a]Raw or % scores not provided, results depicted in graphical form Results from GSRS.

energy and nutrition have been raised. However, data from studies so far have been inconsistent.

6.1.1 | Energy

Though comparative trials reported a decline in energy intake by 300-400 kcal per day from baseline following the initiation of a low FODMAP diet,[3,25,76] a reduction was also noted in the comparator arms of these studies—diets based on recommendations from National Institute for Health and Care Excellence (NICE)—and, therefore, attributable at least partially to a trial effect. Energy intake was not significantly different between the low FODMAP diet and typical Australian diet or a sham diet in other studies, with this first involving provision of all food, and the second study involving provision of detailed food lists to all participants.[2,5] In a longer term study, energy intake declined by about 500 kcal per day from month 0 to 3 following initiation of a low FODMAP diet according to a food frequency questionnaire, but returned to baseline levels by 6 months following reintroduction of FODMAPs.24. Taken together, it is likely that a small reduction in energy levels occurs in the elimination phase of a low FODMAP diet, but the clinical significance of this, as well as the impact of FODMAP reintroductions and establishment of FODMAP personalisation on overall daily energy intake and effect on bodyweight, remain uncertain.

6.1.2 | Fibre

Fibre intake may be reduced in a low FODMAP diet if recommendations are not made to supplement with low FODMAP fibres and adequate reintroduction of FODMAPs is not achieved long-term. In particular, there may be a reduction in long-chain carbohydrates such as non-starch polysaccharides, due to a reduction in wheat products, and in short chain carbohydrates such as fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS). Foods such as wheat, onion, and garlic are high in FOS, while legumes, some nuts and some vegetables are food sources high in GOS.[77] Positive effects of long-chain carbohydrates include faecal bulking, faster colonic transit time,[78] as well as production of beneficial short chain fatty acids (SCFA) through the process of fermentation.[79]

The effect of a low FODMAP diet on dietary fibre intake is inconsistent within the literature. Three short-term studies assessing a strict low FODMAP diet noted similar fibre levels compared to baseline,[5,25,76] while one short-term study reported a significant reduction in fibre intake.[3] Long-term, fibre intake has been shown to return to baseline levels with FODMAP reintroductions.[24] Similar fibre levels were observed in a follow-up study of patients on a personalised FODMAP diet compared to patients who had returned to their habitual diet.[60] Supplementation using low FODMAP fibre has been variably reported across the studies, and may account for some of the differences in fibre intake observed between low FODMAP and comparator arms.

6.1.3 | Protein, fat, and micronutrients

Protein and fat intake do not generally alter with a low FODMAP diet, with a reduction in these in some clinical trials likely secondary to a trial effect.[3,5,25,76]

Concerns regarding potential micronutrient deficiencies following a low FODMAP diet have been raised due to potential inadequate substitution with low FODMAP foods and inadequate personalisation of a low FODMAP diet long-term, but have not been well researched to date. Restriction of dairy carries the risk of calcium deficiency and was noted during the elimination phase in one study,[80] but two studies which evaluated calcium intake during the reintroduction phase by food frequency questionnaires detected no reduction.[24,60]

6.2 | Disordered eating behaviours

Up to 40% of patients with IBS have co-morbid psychological disorders including depression and anxiety.[81,82] Furthermore, there is a significant overlap between gastrointestinal symptoms experienced by patients with formal eating disorders and patients with IBS, and treatment of each condition becomes more complex and difficult.[85]

An obsessive and restrictive focus on food as a source of nutrition, health and well-being, or impaired functioning in work or social life, termed *orthorexia nervosa*, has also been increasingly recognised, with cultural phenomena such as the internet and social media influencing this condition.[86,87] Disordered eating has been defined as "any deviation from cultural norms, including food restriction, skipping meals and over-eating [which] may lead to but not necessarily indicate an eating disorder is present".[89] Altered and abnormal eating behaviours are more common amongst adults and adolescents with IBS than those without IBS.[89,90]

The implementation of dietary restrictions such as a low FODMAP diet with its entailed attention to food, therefore, has the potential to create or reinforce maladaptive eating behaviours in a vulnerable group of patients. This risk is amplified with other risk factors often present in those with IBS such as GI symptoms, food awareness, and the burden of chronic disease.[89] These altered eating practices have the potential for positive reinforcement through weight loss,[91] which may be seen during the implementation of a low FODMAP diet with reduced caloric intake.[1,60] In addition, a fear of being contaminated by unknown food sources, as seen in orthorexia,[92] may feed into the development of disordered eating patterns where individuals become too afraid to consume a variety of foods and subsequently begin to restrict their intake.[93,94] Overly strict adherence to a diet low in fermentable carbohydrates was described by many participants in three early studies.[28,95,96] Follow-up between 2 and 40 months found 38%–64% of patients reported following a restricted diet at all times except on some occasions or strictly all of the time, but how reintroduction was taught to these patients was variably reported. Nearly half of the patients did not regularly relax the diet when eating away from home.

6.2.1 | Screening for disordered eating

Screening for such behaviours and formal eating disorders should be performed in patients with IBS prior to and during dietary management. Current tools used in IBS research such as the IBS-QOL appear inadequate to pick up potential risk of disordered eating, asking in regard to body image questions such as "I feel fat because of my bowel problems.", "my bowel problems limit what I wear", "I feel unclean because of my bowel problems".[68] Screening of adolescents with IBS has been suggested[91] using the Eating Disorders Examination Questionnaire which is a self-reported measure containing 36 questions measuring concerns, symptoms, and behaviours characteristic of eating disorders developed identify dieters most at risk of developing an eating disorder.[97] However, in clinical practice, the "SCOFF" eating disorder screen questionnaire may be a more realistic option for identifying cases of anorexia nervosa, bulimia nervosa, and other specified feeding or eating disorder. It consists of five short questions, with key words (do you make yourself Sick when uncomfortably full, worry about lost Control, weight loss of more than One stone in 3 months, believing yourself to be Fat when others say you are thin, belief that Food dominates your life) making up the acronym "SCOFF", with a score of 2 or more indicating an eating disorder is likely and further assessment is required.[98] Whether these tools may identify patients with or predict the development of eating disorders and orthorexia during treatment with a low FODMAP diet is uncertain, and the development of new IBS-specific screening tools may be required. Routine screening as part of standard clinical practice has not been reported in the literature to date.

Most studies report exclusion of participants with a history of eating disorders, but the impact of the dietary restrictions on precipitation of eating disorders at long-term follow-up has not been evaluated.[8]

6.3 | Impact on gut microbiota

The gut microbiota is considered an "endogenous" organ contributing to the modulation of host physiology[99] and may be a significant factor in the aetiology of IBS.[100] A low FODMAP diet reduces the intake of many foods with a prebiotic effect at least short-term during the strict phase of the diet and potentially longer term if adequate reintroductions are not made.[77] Nonetheless, study of the effect of the low FODMAP diet on intestinal microbiota has been difficult, and vulnerable to oversimplification of what is, essentially, a complex ecological interaction between dietary intake and bacterial composition.

6.3.1 | Prebiotic effect of FODMAPs

Short-chain carbohydrates reduced in the low FODMAP diet, such as FOS and GOS[1,3] (as well as the medium-chain carbohydrate inulin), selectively stimulate the growth of putatively beneficial bacteria, and, therefore, may be classified as prebiotics.[101] However, differences in FOS and GOS intake have been observed across studies, which may account for differences in results regarding gut microbiome profiles. Benefits attributed to these prebiotics include stimulating the gastrointestinal immune system,[101] improving laxation,[102,103] increased calcium absorption,[104] and reduced risk of gastrointestinal infection.[105] Higher dietary fibre intake, especially that derived from cereals and fruit, is associated with reduced risk of colon cancer in humans,[106,107] and animal data suggest this may be at least partly related to SCFA production.[108,109] Concerns have, therefore, been raised about the potential for a low FODMAP diet to negatively impact the gut microbiota. Though total SCFA intake and saccharolytic fermentation index was noted to decline following a 4-week low FODMAP diet in patients with IBS, multiple divergent changes in specific SCFAs, and a rise in proteolytic fermentation, were seen, as well as an absence of a relationship between these and symptom response.[110] Long-chain fibre intake was not specifically reported in this study.

6.3.2 | Changes to the microbiota and metabolomic markers

Multiple studies to date have attempted to address changes in microbiota, mostly during the strict low FODMAP phase,[1,5–7,26,111]

TABLE 3 Studies of the effect of a low FODMAP diet (LFD) on faecal microbiota and metabolome

Reference	Study design and duration	Number of participants	Microbiota findings	Method	Metabolomic findings
Staudacher et al (2012)[1]	RCT, 4 wk	19 LFD vs 22 habitual diet	Reduction in absolute and relative abundance in *bifidobacteria* in LFD, no change in total bacteria or other specific bacteria including *Faecalibacterium prausnitzii*	FISH 1 stool sample, placed on ice, then homogenised within 1 hour. Stored at −20 until analysis	No change in faecal SCFA or pH
Chumpitazi et al (2014)[26]	Uncontrolled trial (low fermentable substrate diet), 2 d	33—cross over LFD vs typical American childhood diet	No overall change in alpha diversity or OTU richness. Trend towards increased clostridiales and decreased *Bacteroides* following LFSD	16s rRNA of V3-V5 region. 1 stool sample, immediately frozen, then stored at −80	10 faecal metabolites differed following LFSD
Halmos et al (2015)[111]	Cross-over RCT, 21 d	33—cross over LFD vs typical Australian diet	Reduced total bacterial abundance by 47%. Reduced absolute bacterial abundance of Clostridium cluster IV, *F. prausnitzii*, Clostridium cluster XIVa, *Roseburia*, *lactobacilli*, *bifidobacter*, *Akkermansia muciniphila*, but increase in *Ruminococcus torques* with LFD compared with typical Australian diet Reduced relative abundance of Clostridium cluster XIVa, *A. muciniphila*	qPCR 5 d stool collection, stored −4°	Increased pH, no change in SCFA total or specific
Valeur et al (2016)[110]	RCT, 4 wk	61 baseline on average Norwegian diet vs LFD	No significant change from baseline in patients classified as "dysbiotic" post-intervention	16S rRNA of V3-V9 region. Multiple samples immediately frozen at −20 then −80	
McIntosh et al (2017)[6]	RCT, 3 wk	18 LFD vs 19 HFD	No difference in overall alpha or beta diversity. Higher actinobacteria richness and diversity with LFD, higher firmicutes richness. Reduced abundance of *Bifidobacteria*	16s rRNA sequencing. V3 region. 1 stool sample stored at −80	Urinary histamine reduced significantly with LFD
Staudacher et al (2017)[5]	RCT, 4 wk	LFD vs sham diet with or without probiotic	No difference in overall alpha or beta diversity with LFD compared with sham diet. Lower absolute and relative abundance of *Bifidobacteria* following LFD compared with sham diet	qPCR and 16s rRNA sequencing One sample collected within 1 h, stored on ice, homogenised. Stored at −80	
Harvie et al (2017)[24]	RCT (unblinded), 3 and 6 mo	LFD vs usual diet at 3 mo, then reintroduction in LFD arm, and introduction of LFD in second arm	No change in diversity, no differences in OTUs found	16S rRNA sequencing of V4 region. Multiple samples, frozen at −20 within 4 h	
Hustofet al (2017)[7]	RCT double blind crossover, 9 wk	20 habitual diet vs LFD +3 wk FOS then 3 wk placebo	Decrease in abundance of Actinobacteria, *Bifidobacteria*, and *Facealibacterium prausnitzii*. *Bifidobacteria* and *F. prausnitzii* increased in abundance post-supplementation with FOS	16S rRNA of V3-V9 region. Multiples samples stored in fridge for 3 days then frozen at −80	Decreased SCFA and n-butyric acid
Huaman et al (2018)[113]	RCT, 4 wk	21 LFD vs 19 Mediterranean diet	Decreased abundance of *Bifidobacteria*, increased *Bilophila wadsworthia*	16s rRNA of V4 region. Multiple samples homogenised then frozen at −20, later stored at −80°	

RCT, randomised controlled trial; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; LFD, low FODMAP diet; FISH, fluorescence in situ hybridisation; SCFA, short-chain fatty acid; OUT, operational taxonomic units; LFSD, low fermentable substrate diet; rRNA, ribosomal ribonucleic acid; qPCR, quantitative polymerase chain reaction; HFD, high FODMAP diet; FOS, fructo-oligosaccharides.

with one study evaluating the impact after the reintroduction of FODMAPs at 3 and 6 months.[24] The findings overall have been varied, likely a result of various techniques and different comparator diets across studies as outlined in Table 3. Collection of stool varied with respect to a single sample to multi-day collection. Immediately frozen samples are preferential in providing the highest yield of bacterial DNA,[114] and timing of freezing and homogenisation was variable across the studies.[1,5–7,24] Techniques used to sequence the microbiota have evolved over the past decade, with earlier studies based on FISH[1] and more recent studies based upon 16s rRNA and qPCR techniques.[5–7,24,26,110,111]

No significant change in overall alpha diversity following a strict low FODMAP diet was reported in three studies,[5,6,26] with similar findings observed at 6 months following a personalised FODMAP diet where fibre and GOS returned to habitual levels.[24] The comparator arms in these studies were highly variable, and included a high fibre diet, sham diet, typical American childhood diet, or usual diet.

A change in abundance of *Bifidobacteria* has been of most interest and studied in the literature to date. A reduction in absolute abundance of *Bifidobacteria* was observed in two studies, both using qPCR analysis with one comparing a strict low FODMAP diet to a typical Australian diet,[111] the other comparing to a sham diet.[5] This study also found a reduced relative abundance of *Bifidobacteria* using 16S rRNA sequencing. A lower absolute and relative abundance of *Bifidobacteria* reported in one earlier study assessed using FISH comparing a strict low FODMAP diet to a sham diet.[1] Decreased abundance of *Bifidobacteria* observed in three studies two using 16rRNA, all comparing a strict low FODMAP diet to different diets—a high fibre diet, a Mediterranean diet, or habitual diet.[6,7,113]

Bifidobacteria are probiotic bacteria stimulated in response to FOS, GOS, and inulin[115,116] and are saccharolytic with putative anti-inflammatory properties.[117] *Bifidobacteria* abundance is reduced in patients with IBS compared with healthy controls, and this reduction has been associated with increased pain.[118,119] This does not imply causation, and the longer term implications of reduction in *Bifidobacteria* is hence uncertain, as is the effect of FODMAP reintroduction on the persistence of such an effect. Somewhat reassuringly, supplementation of *Bifidobacteria* via a probiotic was shown to restore *Bifidobacterium* species.[5]

Other changes noted following a low FODMAP diet have been an absolute reduction in the butyrate-producing Clostridium cluster IV (including *F prausnitzii*), Clostridium cluster XIVa, and *Roseburia* spp, the probiotic *lactobacilli*, and the mucus-degrading *Akkermansia muciniphila*, and increase in *Ruminococcus torques*.[111] The significance of these changes in the abundance of specific groups of bacteria on metabolomic markers, and more broadly, colonic health, remain to be clarified, with the answers unlikely to be accounted for by simple associations. It is uncertain whether a low FODMAP diet should reduce faecal SCFAs, given FODMAPs are fermented in the proximal colon and faecal SCFAs are reflective of distal colonic production. No change in SCFAs was observed in several of the studies.[1,111]

Expanding upon metabolomic effects of the low FODMAP diet, a significant eightfold reduction in urinary histamine was noted, which may reflect a reduction in mast cell activation or visceral nociception.[6] Additionally, patients with IBS were found to have higher faecal lipopolysaccharide concentrations, which were subsequently reduced following a low FODMAP diet.[122] Faecal lipopolysaccharide was demonstrated to induce intestinal inflammation, barrier dysfunction, and visceral hypersensitivity in rodents.[122] These alterations, if reproduced, may signify potential anti-inflammatory beneficial effects of a low FODMAP diet.

It is unlikely that strict initial short-term restriction of a low FODMAP diet will be associated with long-term clinical effects, but the effect of FODMAP reintroduction on the microbiota and metabolomic markers has not been well studied to date. A small study found no significant changes in alpha and beta diversity or OTUs following a low FODMAP diet during a 3-month low FODMAP diet or subsequent 3-month FODMAP reintroduction phase, but the statistical strength of the data were compromised by accidental thawing of multiple samples.[24] Further studies evaluating the effect of dietary reintroductions and long-term effects of modified FODMAP intake, together with clinical effects, are warranted. Methodological consistency in comparator diets, as well as collection, storage, processing and analysis of stool, or indeed mucosal microbiota samples, are also required to enable comparison across studies.

7 | CONCLUSIONS

Significant advances in the management of IBS using a low FODMAP diet have been made in the past decade, and there is little doubt about its efficacy in control of symptoms in most patients with IBS. Nonetheless, many gaps in implementation of the diet in clinical practice and evaluation of its long-term effects remain, and require further investigation. Future studies designed to elicit factors predicting response to a low FODMAP diet, training standards and patient education models, and effects of the low FODMAP diet on quality of life, nutritional adequacy, development of disordered eating habits, changes in the gut microbiota, and overall colonic and human health in the short and long-term are required.

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