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REVIEW

FODMAPs, inflammatory bowel disease and gut microbiota: updated overview on the current evidence

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Abstract

Purpose Based on the fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) hypothesis, the low-FODMAP diet has been suggested as a potential therapeutic approach for inflammatory bowel disease (IBD) with promising results on disease management. However, this diet implies a specific broad food restriction, which potentially increases the risk of nutritional deficiencies and may aggravate gut microbiota dysbiosis of IBD patients. The aim of the present study is to review the effect of individual FODMAPs on the human gut microbiota. In addition, this narrative review provides an updated overview of the use of the low-FODMAP diet in IBD, namely the implementation, advantages, limitations, and the impact on the gut microbiota.

Methods The literature search strategy was applied to PubMed and Web of Science using relevant keywords, IBD, FODMAPs, Fructose, Lactose, Polyols, FOS, GOS, low-FODMAP diet and gut microbiota.

Results Current data suggest that the low-FODMAP diet may effectively improve clinical outcomes in the management of IBD and ensure better quality of life for IBD patients. However, there is evidence highlighting some issues of concern, particularly the adequacy of the diet and the impact on the gut microbiota. The various FODMAP types differently modulate the gut microbiota.

Conclusion IBD management should be achieved with the least possible dietary restriction to avoid detrimental consequences, particularly on nutritional adequacy and gut microbiota. Thus, it is important to individualize and monitor the nutrition intervention. Further studies are required to better characterize the relationship between diet, the gut microbiota, and IBD to support the generalization of this approach for clinical practice in IBD therapy and management.

Keywords Diet therapy · Inflammatory bowel diseases · Microbiota · FODMAPs · Low-FODMAP diet

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing intestinal inflammation, mainly represented by Crohn's disease (CD) and ulcerative colitis (UC). CD is characterized by the presence of ulcerations and/or granulomatous lesions affecting the entire bowel wall, while in UC the lesions start in the rectum and frequently extend in a continuous manner through the colon, being usually limited to the mucosa surface [1, 2]. IBD is considered to be a disease of westernized countries [3]. Along with the rapid industrialization and lifestyle changes of modern societies, the incidence and prevalence of this pathology has been increasing through the years [3]. Between 1990 and 2017, the global prevalent cases of IBD increased 85.1% [4]. North America and Western and Northern Europe have the highest rates and it is estimated that 1 in 198 individuals have UC and 1 in 310 individuals have CD [4]. Populations from westernized countries tend to follow hypercaloric eating patterns including ultra-processed foods and a sedentary lifestyle [5]. This lifestyle is associated with the increased incidence of chronic diseases, specifically inflammatory diseases such as IBD, as well as diabetes, obesity and cardiovascular diseases [5].

Although the aetiology of IBD remains largely unknown, this condition is considered to be a multifactorial disease

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resulting from the contribution and interaction of several factors: genetic susceptibility, immune responses, gut microbiota and environmental factors [6, 7]. Dietary pattern is a major part of the environmental triggers for the disease, particularly those diets that include a high quantity of refined carbohydrates, red meat, saturated fat, and processed foods. Diet impacts the immune system homeostasis and may contribute to intestinal inflammation through different mechanisms, including modulation of the gut microbiota [8].

The gut microbiota of a healthy adult is dominated by a small number of phyla: Firmicutes, Bacteroidetes and Actinobacteria [9–11]. In addition, lower amounts of Proteobacteria, Verrucomicrobia, Euryarchaeota, and Fusobacteria have been identified in human faecal samples [10]. The composition of the intestinal microbiota is influenced by host and environmental factors, such as diet, that continuously modulate this microbial community [12]. Although diet is deemed one of the main factors with impact on the gut microbiota, inter-individual variation may account for the majority of the compositional variation [13–15].

Homeostatic imbalance within the gut microbiota may lead to dysbiosis, i.e., an altered microbiota composition. The question of whether human gut microbiota dysbiosis is truly causative or merely a consequence of inflammation in IBD is still unclear [16]. Some studies support the hypothesis that the overall dysbiosis observed in IBD patients might be a result of the disturbed gut environment rather than the direct cause of disease [17, 18]. Conversely, other studies support the idea that gut dysbiosis is a prerequisite for inflammation rather than being driven by it [19–21]. In fact, changes in the composition of the gut microbiota do lead to microbial metabolite alterations that may have a role in IBD pathogenesis [22, 23]. It is likely that failure to adequately regulate the microbiota composition is at the onset of many chronic diseases since a dysbiotic configuration is commonly linked to impaired epithelial barrier function and inflammation [24]. Dysbiosis of the gut microbiota may contribute to IBD pathogenesis as a result of a breakdown in the equilibrium between putative protective species and inflammatory species [25]. Protective species interact with the immune system contributing to the homeostatic mechanism while inflammatory species promote non-immunogenic inflammatory reactions, disturbing homeostasis. An abnormal immune response to the gut microbiota in genetically susceptible subjects is one of the most accepted theories behind the aetiology of IBD [26]. Most of the studies in IBD patients reported alterations in the abundance of specific bacterial taxa within the phyla Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria, with an expansion of putative inflammatory groups combined with a reduction of protective groups [27, 28].

Protective groups generally reduced in IBD patients include members of the phylum Firmicutes, such as the butyrate producers belonging to the genera *Faecalibacterium*, *Roseburia*, *Oscillibacter* and *Coprococcus* [19, 29]. A reduction of these genera contributes to a decrease in the production of butyrate that may predispose the intestinal mucosa to inflammation [30]. In addition, recent evidence suggests that mucosal inflammation in IBD patients may alter the capacity of the epithelium to respond to butyrate, suggesting a potential role of inflammation in decreasing butyrate uptake and metabolism [31]. Furthermore, the genus Bifidobacterium (phylum Actinobacteria) and the mucolytic bacteria *Akkermansia muciniphila* (phylum Verrucomicrobia) are also generally decreased in IBD patients compared to healthy subjects [32, 33]. The presence of *A. muciniphila* reduces histological damage of the intestinal mucosa, and tissue mRNA expression of pro-inflammatory mediators in an animal model [34]. The expansion of putative inflammatory groups including members the family Enterobacteriaceae (phylum Proteobacteria) such as *Escherichia coli*, and *Fusobacterium* spp. (phylum Fusobacteria), has been strongly associated with IBD [35]. Moreover, the species *Ruminococcus gnavus*, producer of an inflammatory polysaccharide, is enriched in IBD patients [36].

Although a gut microbiota imbalance occurs in IBD patients, dysbiosis associated with CD and UC seems to be disease specific [37, 38]. Differences in the gut microbial composition have been reported between members of the same family and twins discordant for IBD [39], suggesting that dysbiosis is primarily associated with disease state rather than environmental or genetic factors [16].

Abdominal pain, bloating and modification in stool consistency and frequency are the most frequent symptoms of IBD [40]. In addition, approximately 30% of IBD patients exhibit abdominal pain associated with changes in intestinal motility [40]. IBD is associated with severe intestinal damage and requires lifelong treatment especially if onset of the disorder is early in life [1]. Moreover, the progressive increase in IBD prevalence, particularly in western countries, may increase the risk of surgery and morbidity, with higher healthcare costs [1]. Thus, appropriate, lifelong management of IBD is of utmost importance.

The current evidence on dietary strategies as primary therapy in IBD is growing and there are promising results and ongoing research. Nutrient composition of daily diets including protein, fat, carbohydrate and dietary fibre have different effects on IBD management [41]. Therefore, nutrition interventions may play an important role in the improvement of IBD symptoms and in disease remission [42]. In the past few years, several dietary interventions have been studied for potential therapeutic effects on IBD [43]. Among those interventions are the specific carbohydrate diet [44], exclusive enteral nutrition [45], gluten-free diet [46], and the anti-inflammatory diet [47]. However, these diets are either

very restrictive and not tolerated, or there is lack of evidence as to their efficacy on IBD.

Recently, the benefits of the Mediterranean diet in the treatment and management of IBD have also been studied and the results, although scarce, seem to be promising [48]. This diet is characterized by an abundance of beneficial nutrients such as phytonutrients, monounsaturated and n-3 polyunsaturated fatty acids, fibre, and a low intake of saturated fatty acids [49]. These features have been associated with anti-inflammatory effects, particularly in CD patients [50]. Moreover, when compared with other approaches, individuals following this diet are less susceptible to nutrient deficiencies [51]. However, further research is needed on the anti-inflammatory potential of the Mediterranean diet. A promising nutritional approach directly targeting the gut microbiota was proposed by Gibson et al. [52]. This approach consists of a diet low in Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAP). The use of the low-FODMAP diet in IBD has been reviewed previously [53, 54]. This narrative review, besides discussing the implementation of the low-FODMAP diet in IBD, provides an updated overview of the effect of individual FODMAPs on the human gut microbiota. The literature search strategy was applied to PubMed and Web of Science in the last 20 years using relevant keywords, IBD, FODMAPs, Fructose, Lactose, Polyols, FOS, GOS, low-FODMAP diet and gut microbiota. No systematic assessment was performed.

FODMAPs

FODMAPs are short-chain carbohydrates with a small molecular size and a high osmotic effect that are poorly absorbed in the gastrointestinal tract. Consequently, a significant portion of the ingested FODMAPs reach the distal ileum and colon intact and are available to be used by the gut microbiota. These characteristics potentiate increasing fermentation by the gut microbiota with associated symptoms that include gas production, abdominal pain, bloating, cramping, distension and diarrhoea [40]. Excessive delivery of FODMAPs to the distal small intestine promotes bacterial overgrowth that may lead to increased intestinal permeability as a result of reduced expression of mucosal tight junctions [55, 56]. According to the FODMAP hypothesis, excessive intake of monosaccharides, disaccharides, oligosaccharides and polyols is associated with, although not proven to cause, higher susceptibility to the development of IBD and exacerbation of symptoms within IBD patients [52, 57]. The impact of the ingestion of individual FODMAPs on the human gut microbiota composition is summarized in Table 1.

Monosaccharides

Monosaccharides are the simplest form of carbohydrates that are able to traverse the intestinal epithelium by facilitated diffusion or active transport [58]. Fructose is a 6-carbon monosaccharide, mainly absorbed through carrier-mediated facilitative diffusion by glucose transporter 2 (GLUT2) and GLUT5 [59]. GLUT2 transports not only fructose but also glucose and galactose, whereas GLUT5 has exclusive affinity for fructose [59]. The ingestion of high fructose levels may compromise fructose absorptive capacity leading to malabsorption. In addition, low expression of GLUT5 in infants potentially explain fructose malabsorption in young children [59]. Common contributors to fructose intake include fresh fruits, fruit-derived products, and products containing high-fructose sweeteners such as corn syrup.

The impact of a high-fructose diet on the human gut microbiota is still largely unknown. A recent study investigated the influence of two consecutive short-term fructose-rich diets (100 g/day) on the gut microbiota composition of female subjects: first a high-fructose diet rich in fruits and vegetables (fruit diet) followed by a high fructose syrup diet, both implemented after a low-fructose phase [60]. At the genus level, specific deviations were observed including an increase in *Faecalibacterium* and *Anaerostipes* and a reduction in *Parabacteroides* and *Barnesiella* after the fruit-rich diet. Conversely, the high-fructose syrup diet induced a decrease of *Ruminococcus*, *Faecalibacterium* and *Erysipelatoclostridium* whereas the abundance of *Barnesiella* increased. Although the amount of fructose ingested in both diets was similar, the fruit diet contained a higher fibre content than the high fructose syrup diet. Therefore, the alterations in gut microbiota composition observed may reflect the different intake of fibre rather than changes in response to the high-fructose consumption [60]. The genera *Anaerostipes*, *Coprococcus*, *Ruminococcus* and *Erysipelatoclostridium* are butyrate-producing bacteria of the phylum Firmicutes. Butyrate is a short chain fatty acid (SCFA) that is absorbed by the intestinal mucosa where it is the main energy source for colonocytes and is involved in the regulation of immunity and inflammation [61]. In addition, butyrate has anti-inflammatory effects, it modulates cytokine production, induces expansion of regulatory T cells, and positively modulates intestinal homeostasis [61]. On the other hand, *Barnesiella* is implicated in the induction of the proinflammatory IFNγ response [62]. Therefore, while a high fructose fruit diet promotes the growth of beneficial butyrate-producing bacteria, a high-fructose syrup diet reduces their abundance, promotes proinflammatory cytokine production and consequently compromises gut homeostasis [60].

Table 1 Effect of individual FODMAPs on human gut microbiota composition

FODMAP	Study description	Gut microbiota effect[a]	References
Fructose	Intervention study, $n=12$, 1-week low-fructose diet (10 g/day), 1-week Fruits and vegetables diet (100 g/day)	↑*Faecalibacterium,* ↑*Anaerostipes,* ↓ *Barnesiella,* ↓ *Parabacteroides*	[60]
	Intervention study, $n=12$, 1-week low-fructose diet (10 g/day), 1-week High-fructose syrup diet (100 g/day)	↓ *Ruminococcus,* ↓ *Faecalibacterium,* ↓ *Erysipelatoclostridium,* ↑ *Barnesiella*	[60]
Lactose	Cross-sectional study; $n=1068$, Assessment of dairy products intake through a 7-day Food frequency questionnaire	↑ *Bifidobacterium*	[64]
	Cross-sectional study; n = 959 Assessment of dairy products intake through a Brief-type diet history questionnaire	↑ *Bifidobacterium*	[65]
FOS	Randomized clinical trial; $n=36$, 14-day supplementation: 16 g/day FOS	↑ *Bifidobacterium*	[71]
	Randomized controlled trial; $n=80$, 75-day supplementation: 2.5, 5 and 10 g/day FOS or placebo (maltodextrin)	↑ *Bifidobacterium*, ↑ *Lactobacillus,* ↑ *Faecalibacterium*	[72]
	Randomized controlled trial; $n=25$, 6-week supplementation: 16 g/day inulin-type fructan or placebo (maltodextrin)	↑ *Bifidobacterium*	[73]
GOS	Randomized controlled trial; $n=151$, 3-week supplementation: 5 g/day GOS	↑ *Bifidobacterium,* ↑ *Lactobacillus*	[70]
	Randomized clinical trial; $n=36$, 14-day supplementation: 16 g/day GOS	↑ *Bifidobacterium*	[71]
Xylitol	In vitro human fecal culture from five healthy donors	↑ *Anaerostipes*	[82]
Lactitol	Randomized clinical trial, $n=75$, 7-day intake of a chocolate bar containing 10 g sweetener in the ratios 10:0, 5:5 or 0:10 sucrose:lactitol	↑ *Bifidobacterium*	[88]
Isomalt	Double-blind controlled trial, $n=19$, 2×4-week controlled basal diet enriched with either 30 g isomalt or 30 g sucrose daily	↑ *Bifidobacterium*	[86]

[a]Main genus affected

Disaccharides

Disaccharides are composed of two monosaccharide units linked by glycosidic bonds. Lactose is a disaccharide composed of glucose and galactose residues. While dairy products are the main dietary sources of lactose, it is also added to commercial foods such cakes and breads. Lactose is hydrolyzed at the intestinal brush border by the enzyme lactase. However, humans present lactose malabsorption due to a lower level of or inability to produce lactase, or inadequate enzyme activity [63]. This impairment causes an increase of undigested lactose in the colon, where it is fermented by the gut microbiota with production of SCFAs and gases [63], leading to abdominal discomfort, bloating, burping, flatulence, and nausea. These symptoms may result from increased abundance of *Bifidobacterium* spp. in the gut rather than being a direct effect of lactose intake [64, 65].

Oligosaccharides

Oligosaccharides are a class of carbohydrates containing up to 10 monosaccharide units such as fructooligosaccharides (FOS) and galactooligosaccharides (GOS). Humans are unable to digest these oligosaccharides since they lack the enzymes to break them down [66]. FOS are fructans, i.e. fructose polymers, composed of a small number of fructose units linked by (2 → 1)-β-glycosidic bonds with a single D-glucosyl unit at the non-reducing end [67]. Dietary fructans are mostly FOS and food sources include garlic, rye, barley, pistachio, peach, watermelon, artichoke, leek, wheat and onion [52, 66]. Commercial fructans are increasingly added to processed foods due to their sensory and textural properties and potential health benefits such as prebiotic effect and low-energy content. GOS are composed of galactose monomers with a terminal glucose unit at the reducing end linked by β-glycosidic bonds. The dietary forms of GOS are raffinose and stachyose that are not hydrolysed in the gastrointestinal tract due to the lack of the enzyme β -galactosidase [68]. Common food sources include lentils, beans, cabbage, chickpeas, Brussels sprouts, chicory, onion, some grains, nuts and seeds.

FOS and GOS are dietary fibres that resist the hydrolytic actions of intestinal enzymes. These oligosaccharides are considered prebiotics, i.e., a "non-digestible food ingredient

that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thereby improving the host's health" [69]. FOS and GOS confer growth-promoting effects on beneficial microbes such as *Bifidobacterium* spp. and *Lactobacillus* spp. [68, 70–73]. The members of these genera mainly produce the SCFA acetate and propionate, and also lactate, which downregulate the proinflammatory response of intestinal epithelial cells and inhibit the growth of potentially pathogenic organisms [74], contributing to the maintenance of colonic homeostasis. However, recent studies have reported that these prebiotic carbohydrates may also be metabolized by the extraintestinal avian-pathogenic strain *Escherichia coli* BEN2908 [75], and by the human commensal *E. coli* CCFM 8331 [76], contributing to their intestinal colonization which may constitute an increased risk to human health.

Polyols

Polyols are a specific group of sugar alcohols that are formed via the catalytic hydrogenation of carbohydrates, and include substances such as sorbitol, mannitol, maltitol, lactitol and xylitol. Only approximately one-third of polyols that are consumed in the human diet are absorbed in the small intestine via passive diffusion. The rate of absorption varies depending on multiple factors such as the molecular size of the polyol, the amount ingested, the pore size in the distal small intestine and the presence of gastrointestinal disorders [77]. Polyol malabsorption varies according to the substrate, is generally dose-dependent, and increases when polyols are ingested in combination with other carbohydrates. An exception is erythritol, which is relatively well absorbed compared with the other polyols. Unabsorbed polyols that reach the colon are available to be fermented by the gut microbiota with production of gas (hydrogen, carbon dioxide, and methane) and other end products of fermentation [78]. Therefore, polyols may induce dose-dependent gastrointestinal symptoms of abdominal pain, flatulence, bloating and osmotic diarrhoea [79]. Polyols such as sorbitol and mannitol occur naturally in fruits and vegetables such as apple, pear, apricot, cherry, nectarine, peach, plum, watermelon, mushroom, cauliflower, and also honey [78, 80, 81]. Polyols also include artificial sweeteners (e.g., xylitol, lactitol and isomalt) frequently used by the food industry as sugar substitutes to produce sugar-free and low-calorie content products as well as to fulfil technological functions, such as emulsifiers, stabilizers and texturizers [79].

The effects of polyols on the human gut microbiota have been studied for the artificial sweeteners xylitol, isomalt, and lactitol. To our knowledge there are no data available about the effect of naturally occurring sorbitol and mannitol on gut microbiota.

Xylitol supplementation (0.5%) of faecal cultures in vitro increased the abundance of the species within the *Anaerostipes* genus, and bacteria within the *Bacteroides fragilis* group [82]. *B. fragilis* has been associated with the increase of Interleukin 10 (IL-10)–producing regulatory T cells, which limit the proinflammatory mechanisms and consequently contribute to reduction of intestinal inflammation [83]. In addition, *Anaerostipes* has been identified as a potential biomarker for Irritable Bowel Syndrome (IBS) and IBD since the abundance of the genus is reduced in patients with these gastrointestinal disorders, more pronouncedly in IBD [84]. In addition, xylitol stimulated the formation of butyrate, in higher amounts than supplementation with the same amount of FOS and GOS [82, 85].

The effect of a diet enriched with isomalt on the gut microbiota of healthy individuals has been assessed through a double-blind placebo-controlled study and compared to a diet enriched with the same amount of sucrose [86]. The isomalt diet resulted in a statistically significant increase of Bifidobacteria when compared to the sucrose diet, whereas the abundance of *Lactobacillus*, *Bacteroides*, *Enterococcus,* and *E. coli* did not differ between the two diets. According to the study, isomalt is a potential prebiotic that may contribute to a healthy gut environment by stimulating the growth of beneficial bacteria [86].

Lactitol is a sweet-tasting sugar alcohol derived from lactose [87]. The effect of a low dose lactitol on the faecal microbiota has also been studied in a randomized, longitudinal, double-blind study with 75 healthy volunteers who consumed 25 g tablets of milk chocolate containing 10 g sucrose and lactitol in ratios of 10:0, 5:5, or 0:10 daily for 7 days [88]. While the faecal microbiota of the individuals consuming 0 and 5 g of lactitol remained relatively stable, the consumption of 10 g of lactitol resulted in a significant increase in the abundance of *Bifidobacterium* spp., increased production of propionate and butyrate and a significant decline in faecal pH that may contribute to the reduction of pathogenic bacteria such as members of the family Enterobacteriaceae [88]. Although Bifidobacteria are not butyrate producers, the production of acetate may stimulate the growth of beneficial butyrogenic species. Therefore, low doses of lactitol may function as a prebiotic and be beneficial in inducing a healthy gut microbiota.

Generally, polyol malabsorption is dose-dependent in healthy individuals. The simultaneous ingestion of different polyols tends to aggravate the malabsorption [78]. However, studies on polyol malabsorption and their effect on gut microbiota composition in patients with gastrointestinal disorders are limited, particularly in IBD. Polyols may induce dose-dependent symptoms of flatulence, abdominal discomfort, intestinal dysmotility and laxative effects when consumed by both healthy volunteers and patients with IBS [78]. Further research is needed to better understand

the effects of specific polyols on gastrointestinal function and microbiota composition in both healthy individuals and those with gastrointestinal disorders such as IBD.

Low-FODMAP-Diet in IBD

Based on the FODMAP hypothesis, the low-FODMAP diet has been suggested as a potential therapeutic approach for IBD patients, mainly due to the promising results on disease management, especially on controlling functional intestinal symptoms [89, 90].

The self-reported perception of the influence of specific foods on IBD symptoms was evaluated by Cohen et al. [91] in a cohort study of 6,768 IBD patients. The study assessed dietary consumption patterns and identified foods that patients more often associated with the improvement or worsening of their IBD symptoms. The reported dietary patterns differed by disease type and disease activity [91]. IBD patients restrict their dietary patterns due to the presence of active symptoms or the fear of exacerbation [90]. Given patients' self-reported perception of the influence of specific foods on IBD and considering the effects of FODMAPs on disease worsening, the role of diet as a triggering factor for intestinal functional symptoms becomes clear [66, 92, 93]. The low-FODMAP diet has been applied in patients with IBD mainly due to the success of its implementation in patients with IBS, with great efficacy in reducing intestinal functional symptoms [94].

The implementation of a low-FODMAP diet can follow two different approaches: top-down or bottom-up [94]. The top-down approach consists of restricting all or almost all foods rich in FODMAPs, for a period of 4–8 weeks. The bottom-up approach, on the other hand, entails the reduction of specific FODMAPs or foods that are very rich in FODMAPs for a certain period of time, and subsequently restricting other foods if deemed necessary [94]. However, most of the available guidelines mention that the elimination of FODMAPs should be based on a global restriction [95]. There are few studies reporting results on the implementation of the low-FODMAP diet in IBD patients.

Gearry et al. [89] implemented the low-FODMAP diet in a pilot study with 72 IBD patients. Most of the symptoms improved significantly after following this approach.

Prince et al. [90], in a case note review of electronic medical records of 88 IBD patients who had been on a low-FODMAP diet, reported that at follow-up there was an increase in the proportion of patients with satisfactory relief of functional bowel symptoms along with normal stool frequency and consistency when compared to patients at baseline.

Through a randomized controlled clinical trial, Pedersen et al. [96] studied 89 patients with remission IBD or with mild to moderate disease activity with coexistence of IBS-like symptoms. In this clinical trial, two distinct groups were studied: the low-FODMAP diet (intervention group) and normal diet (control group) for 6 weeks. At the end of the intervention period, there was a reduction in the severity of symptoms in the low-FODMAP diet group, indicating that patients following this diet are more likely to experience reduction of IBS-like symptoms than patients on a regular diet [96].

Furthermore, Bodini et al. [97] reported a significant decrease of disease activity in CD patients during a six-week low-FODMAP diet implemented in 55 IBD patients in remission or with mild disease activity. Moreover, the median value of faecal calprotectin, a sensitive marker for inflammation in the gastrointestinal tract, decreased significantly in the follow-up of patients on the low-FODMAP diet when compared with the values obtained by those following a standard diet [97].

Maagaard et al. [98] conducted a retrospective cross-sectional study with patients with IBS ($n = 131$) and IBD ($n = 49$) treated with a low-FODMAP diet, to assess long-term adherence and the effect on the course of the disease. Most of the patients reported total or partial efficacy of the low-FODMAP diet with great improvement to bloating and abdominal pain [98]. After intervention with the low-FODMAP diet, the number of patients with chronic continuous disease progression decreased while the number of patients with mild and indolent disease progression increased. Patients with mild and indolent disease progression improved quality of life and presented a normal stool pattern [98]. In addition, 24% of patients with IBD became asymptomatic after following the low-FODMAP diet [98]. Higher patient compliance was associated with a longer duration of dietary treatment in this study. However, only half of the patients followed the recommendations of the low-FODMAP diet continuously, while the others adopted the diet according to the severity of the symptoms [98]. The change of IBD patients' eating patterns according to the activity of the disease is in line with the results mentioned above.

The success of the low-FODMAP diet is associated with patients' perception of the ongoing effectiveness that the diet has in the management of symptoms [99]. Nevertheless, the effectiveness of the diet depends on the continuous adherence of patients and commitment to the diet is critical to achieving a better outcome [89, 98].

It is worth mentioning that the consumption of foods rich in FODMAPs is associated with aggravated gastrointestinal symptoms in patients with IBD [66, 92]. However, these FODMAPs also have a number of physiological effects that can play a beneficial role on immune function modulation, improvement of calcium absorption and stool bulk, reduction of serum cholesterol and triglycerides levels, and prebiotic effect [92, 100]. This apparent contradiction highlights

the importance of a personalized nutritional intervention and the need for constant monitoring. Moreover, despite the unequivocal benefits of a low-FODMAP diet in relieving the symptoms of patients with IBD, it is important to consider the possible adverse effects. There is evidence highlighting a number of issues of concern, particularly the adequacy of the diet and the impact on the gut microbiota [40, 101, 102] during the exclusion phase. However, it is worth noting that the exclusion phase should be applied for a short period of time. The main goal should always be to achieve the greatest symptom control with the least dietary restriction.

Effects of a low-FODMAP diet on IBD patients

Dietary adequacy

The major problem is the restrictive nature of the low-FODMAP diet that limits the intake of several nutrients. In the exclusion phase, foods such as fruit, vegetables, legumes, grains and grain-based products, important sources of fibre, folate, and vitamin C, are eliminated. Calcium intake may also be deficient due to the restriction of lactose-containing dairy products. In addition, this diet potentially worsens nutritional deficiencies in a population already at high risk of malnutrition [1, 40, 92, 101]. IBD patients are particularly susceptible to zinc and vitamin D deficiencies [1, 103]. There is a high probability of vitamin D deficiency in IBD patients since vitamin D receptor polymorphisms have already been identified as a genetic factor in these patients [103]. Furthermore, due to the essential role of vitamin D in the normal functioning of the immune system, particularly in the gastrointestinal tract [1], low levels of vitamin D may be associated with dysbiosis and increased IBD-related hospitalization [104, 105]. Moreover, zinc deficiency has been linked with excessive loss of gastrointestinal secretions during chronic diarrhoea and drainage of fistulas [103]. Given that zinc is an essential enzyme cofactor for wound healing, cell immunity and growth, low levels of this micronutrient are also associated with increased hospitalization, surgery and other complications [106]. In the exclusion phase of the low-FODMAP diet, the elimination of lactose-containing dairy products and the subsequent deficient calcium intake may impair vitamin D intestinal absorption which can possibly aggravate vitamin D deficiency in these patients [107]. In addition, the elimination of dietary zinc sources, such as legumes, grains and grain-based products, may also aggravate zinc deficiency [108].

Maagaard et al. reported that 29% of patients experienced weight loss during the low-FODMAP diet, although the real impact of this reduction on the impairment of the patients' nutritional status remains unknown [98]. In addition, a randomized controlled trial carried out by Cox et al. [109] revealed that patients with IBD during the low-FODMAP diet have a significantly lower intake of energy, protein, fat, sugars, calcium, phosphorus and iodine when compared to those on a sham diet. Furthermore, the low-FODMAP diet appears to frequently affect the fibre content ingested [110], which is why constipation is reported to be the symptom that least improves with the low-FODMAP diet [89, 110]. This seems to be explained by the restriction of the substrates responsible for supplying fluids to the intestine [89].

Through interactions with the intestinal microbiota, fibre helps in maintaining the function of the intestinal barrier, preserving the inner mucosal layer and acting as the first line of defence against mucosal pathogens [111]. Thus, a reduction in fibre intake leads to a decrease in the production of SCFA, which are known to have the capacity to improve intestinal inflammation, as well as affect the composition of the intestinal microbiota [112]. Such changes are associated with the thinning of the inner mucus layer and, consequently, with the increased proximity of bacteria to the intestinal epithelium [112].

The low-FODMAP diet and gut microbiota

Data on the effect of the low-FODMAP diet on the gut microbiota and inflammatory markers or disease activity are scarce. Halmos et al. investigated the effects of two controlled diets, typical vs low-FODMAP diet, on faecal microbiota and other biomarkers of colonic health in patients with quiescent CD [113]. The low-FODMAP diet reduced the abundance of specific intestinal bacterial groups, particularly *A. muciniphila* and bacteria belonging to the *Clostridium cluster* XIVa that includes the acetate and lactate-converting butyrate producers *Roseburia intestinalis* and *Eubacterium rectale*, which are important for the health of the mucosa-associated microbiota [113]. Conversely, the low-FODMAP diet increased the relative abundance of the mucolytic *Ruminococcus torques* [113], which may lead to excessive degradation of mucus and bacterial invasion [114]. Although both diets had no effect on calprotectin levels, gastrointestinal symptoms were significantly less severe in patients on the low-FODMAP diet.

Cox et al. investigated the effect of a four-week low-FODMAP diet on the faecal microbiota composition of quiescent IBD patients [109]. The diet involved the restriction of dietary fructans, GOS, lactose, fructose in excess of glucose, and polyols, including sorbitol and mannitol. A significant decrease in the abundance of Bifidobacteria, in particular *Bifidobacterium longum* and *Bifidobacterium adolescentis*, and *F. prausnitzii* was reported following the low-FODMAP diet, most likely due to changes in the available fermentable substrates in the colon [109]. The decrease in the concentration of these bacteria is of particular concern given their immunoregulatory effects. *F. prausnitzii* exhibit protective effects via inflammatory cytokine regulation or,

alternatively, stimulation of IL-10 production [115]. However, no detrimental effects of a low-FODMAP diet on the inflammatory marker faecal calprotectin were observed in the study, possibly because other bacteria, such as *R. intestinalis* and *Lactobacillus* spp., also exert immune-modulatory effects and were not altered by the diet [109]. Moreover, much of the evidence of the immune-regulatory effects of *F. prausnitzii* relate to strain A2-165 that did not differ between the sham diet and the low-FODMAP diet groups [109].

Discussion

Nutritional intervention has gained prominence in the treatment of IBD since food is among the main triggers of functional intestinal symptoms in these patients [1, 93].

After the presentation of the FODMAP hypothesis [52], several studies have been conducted in order to demonstrate the effectiveness of a low-FODMAP diet in the management of functional intestinal symptoms [92, 101]. Furthermore, the use of a low-FODMAP diet in the management of IBD can modulate the course of the disease and increase remission periods [98]. Thus, higher adherence to the diet is associated with better outcomes and better quality of life [96–99]. However, despite the positive impact of low-FODMAP diet on symptom relief, it is essential to consider the adverse effects and concerning issues associated with the implementation of this diet [40, 94, 103].

The intake of individual types of FODMAPs has an impact on gut microbiota composition in non-IDB subjects [65, 71, 72, 88]. In addition, the food source of the individual FODMAPs, e.g., fructose from fruits and vegetables vs fructose from high-fructose syrup, differently modulate the gut microbiota of the same individual [60]. The different types of FODMAPs tend to promote the growth of gut beneficial bacteria. Therefore, a global restriction of food sources containing FODMAPs may have a pronounced detrimental effect on the gut microbiota and epithelial homeostasis. In fact, the low-FODMAP diet implies a drastic food restriction for a certain period, which naturally may lead to nutritional deficiencies and increased risk of malnutrition [103, 109]. Fibre content is one of the food components that is affected by the diet, which may consequently aggravate constipation in IBD patients [89, 110]. Moreover, fibre restriction affects the normal functioning of the intestinal barrier, gut microbiota composition and the production of SCFA [111, 112]. Since IBD patients present a dysbiotic gut microbiota profile, the impact of a low-FODMAP diet on the gut microbiota calls for special attention, since it leads to a reduction of specific bacteria such as *A. muciniphila* and the genera *Bifidobacterium* and *Faecalibacterium* [109]. These beneficial bacteria have immunoregulatory effects and contribute to the immunological modulation through the increase of intestinal specific immunoglobulins and immuno-regulatory interleukins, as well as a reduction in pro-inflammatory interleukins [68]. Although restriction of FODMAPs in the diet is generally based on a global restriction, a personalized diet based on the restriction of individual types of FODMAPs, and based on their food sources, should be considered to attenuate the adverse effects including the microbiota dysbiosis in IBD patients.

Dietary restriction during implementation of the low-FODMAP diet may affect the presence in the colon of other dietary components that co-exist in many foods, e.g., slow fermentable or non-fermentable carbohydrates such as non-starch polysaccharides. The reduction of these carbohydrates will likely exhaust substrates for carbohydrate fermentation in the proximal colon, promoting protein fermentation in the distal colon [116]. Whereas carbohydrate fermentation leads to perceived health-promoting metabolites, anaerobic degradation of proteins yields toxic metabolites, e.g., sulphur-containing compounds such as ammonia, as well as phenolic and indolic compounds [117]. Dietary planning during the low-FODMAP exclusion phase should consider the delivery of slow fermentable carbohydrates to the colon, and the amount of protein and the type of amino acids consumed so as to modulate bacterial activity away from protein fermentation, therefore minimizing its harmful effects.

Besides the health implications of the restrictive nature of a low-FODMAP diet in the exclusion phase, there is also a risk of developing eating disorders [118]. Individuals with gastrointestinal disorders, e.g., IBD, following restrictive diets may be at increased risk for dysfunctional eating behaviours. Moreover, gastrointestinal symptoms in IBD patients can cause food aversions that may lead to food anxiety and, consequently, affect psychological well-being [118].

Most of the studies reporting benefits and adverse effects of the low-FODMAP diet present some limitations such as the small sample size which in turn can impair the relevance of the results, the design, and the period of diet application. Moreover, there are only a few studies showing data on the impact of the low-FODMAP diet on inflammatory markers or disease activity [96, 97, 109]. There is also lack of information about the adequacy of the low-FODMAP diet and its safety for IBD patients in long-term use.

Nutritional interventions play an important role on the management of IBD symptoms and in extending remission of the disease. The incidence of IBD is increasing, as is the number of patients on the low-FODMAP diet. However, despite all the documented benefits of the low-FODMAP diet, information on the consequences of long-term application is still scarce. Thus, ongoing clinical and nutritional monitoring is necessary to ensure that the low-FODMAP diet is adequately implemented and to prevent adverse effects.

In conclusion, the low-FODMAP diet may effectively improve clinical outcomes in the management of IBD and ensure better quality of life for IBD patients.

Implication and future perspectives

According to the current evidence, a personalized intervention and frequent monitoring of IBD patients on the low-FODMAP diet is of utmost importance in clinical practice. Moreover, during the exclusion phase of the low-FODMAP diet, adequate amounts of slow fermentable carbohydrates, protein, and the type of amino acids should also be taken into consideration to minimize the potentially harmful effects of protein fermentation. With regard to the implementation of the diet, disease management should be achieved with the least possible dietary restriction to avoid further detrimental consequences, particularly on nutritional adequacy and gut microbiota. Further studies are required to better characterize the relationship between diet, gut microbiota, and IBD to support the generalization of this approach for clinical practice in IBD therapy and management.

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