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Dietary Support in Elderly Patients with Inflammatory Bowel Disease

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Abstract: Ageing of the human population has become a big challenge for health care systems worldwide. On the other hand, the number of elderly patients with inflammatory bowel disease (IBD) is also increasing. Considering the unique clinical characteristics of this subpopulation, including many comorbidities and polypharmacy, the current therapeutic guidelines for the management of IBD should be individualized and applied with caution. This is why the role of non-pharmacological treatments is of special significance. Since both IBD and older age are independent risk factors of nutritional deficiencies, appropriate dietary support should be an important part of the therapeutic approach. In this review paper we discuss the interrelations between IBD, older age, and malnutrition. We also present the current knowledge on the utility of different diets in the management of IBD. Considering the limited data on how to support IBD therapy by nutritional intervention, we focus on the Mediterranean and Dietary Approaches to Stop Hypertension diets, which seem to be the most beneficial in this patient group. We also discuss some new findings on their hypothetical anti-inflammatory influence on the course of IBD.

Keywords: inflammatory bowel disease; malnutrition; Mediterranean diet; older age

1. Introduction

The frequency of Crohn's disease (CD) and ulcerative colitis (UC), two forms of inflammatory bowel disease (IBD), is increasing worldwide [1–3]. Simultaneously with the demographic ageing of the human population observed in recent decades, especially in developed countries, the number of elderly IBD patients is also increasing [4–8]. Considering the definition of elderly as aged 60 years and above, it is estimated that 25–35% of CD and UC patients meet this criterion. These data encompass both those who were diagnosed before reaching 60 and those who were diagnosed when over 60 (elderly onset). The latter group, representing 10–15% of all IBD patients, reflects the second peak of CD and UC morbidity [9]. UC is the more frequent IBD subtype in this age range, since one in eight UC patients is older than 60, compared to one in 20 CD cases [9]. A population-based cohort study by Charpentier et al. revealed that, among elderly people suffering from IBD, 65% are between 60 and 70 years old, 25% between 70 and 80 years old, and 10% are older than 80 [10].

There is an increasing body of evidence showing several differences in the clinical course and management of elderly IBD patients, compared with those suffering from UC or CD at a younger age. One of the most important characteristics is a tendency for less aggressive therapeutic regimens [11–13]. On the other hand, the significance of non-pharmacological and non-surgical interventions is higher. Since both IBD and older age are independent risk factors of nutritional deficiencies, appropriate dietary

support is needed, especially in the cases of patients older than 60 with UC or CD [12,14,15]. In this review, we discuss the influence of older age on the physiology of the gastrointestinal tract and the mechanisms leading to malnutrition, especially in the context of IBD in the elderly. We summarize the main differences in the clinical course and management of IBD in the elderly with special emphasis on the role of diet. We also present some recommendations for nutritional support for this unique population.

In order to analyze the current literature on dietary support among elderly IBD patients, we searched the PubMed and Web of Science databases using the key words "diet and IBD", "elderly IBD", "diet in elderly people", and "nutrition in elderly IBD patients". We identified mainly review papers, meta-analyses, and guidelines published after 2010. Moreover, we analyzed conference abstracts from the Congresses of the European Crohn's and Colitis Organisation (ECCO) in 2018 and 2019.

1.1. Elderly IBD Patient—Differences in Clinical Course and Management

There are several characteristic features of elderly IBD. The delay in the diagnosis of CD or UC is longer than that in younger patients. This is related to less specific symptoms and to a frequent co-existence of other comorbidities and polypharmacy. Differential diagnosis encompasses many entities like ischemic colitis, infectious diseases, drug adverse reactions (non-steroidal anti-inflammatory drugs, anticoagulation, anti-platelet drugs, chemotherapy, etc.), diverticulitis, radiation colitis, and microscopic colitis. Performing invasive diagnostic investigations (like colonoscopy) can also be challenging, since older age, other comorbidities and drugs used are risk factors for severe complications [5,6,16,17].

The clinical course of elderly IBD seems to be less aggressive [6,8]. In CD, there is a higher frequency of colonic location [16,18]. On the other hand, complications like strictures or perianal involvement and extraintestinal manifestations are less common. As a result, the clinical presentation of elderly CD can be similar to UC, with rectal bleeding as a main symptom. Abdominal pain, weight loss, and diarrhea are less typical [16,18–20]. In the case of elderly UC, the predominant location is E2 or E3 according to the Montreal classification, whereas isolated proctitis is rare [20,21]. The disease is more stable over time and there is a low frequency of proximal disease colonic extension [19,20]. The need for a colectomy is also relatively low. A French population-based registry (EPIMAD) showed that only 16% of elderly onset UC patients underwent a colectomy in a ten-year follow-up period [6,8,22–24].

Despite a milder clinical course in long-term observation, the first IBD episode can be paradoxically more severe than in younger patients [18]. Older age also seems to be related to a more frequent hospitalization rate in IBD [18,20]. A study by Ananthakrishnan et al. revealed that hospitalized IBD patients older than 65 are at a higher risk of significant malnutrition, anaemia, and hypovolemia [25]. The frequency of thromboembolic complications is increased due to hypercoagulability, dehydration, prolonged bed rest, and immobilization. This is why the hospitalization of elderly IBD patients seems to be connected with higher fatality [18,26–29].

Although there are no randomized, controlled trials assessing the therapeutic strategies for IBD in the elderly, medical and surgical management is often different from patients of a younger age [30–34]. The usage of many medications is limited due to their higher toxicity (e.g., corticosteroids), the risk of interactions (e.g., thiopurines with allopurinol, mesalamine with anticoagulants), contraindications (e.g., renal insufficiency in the case of mesalamine, severe congestive heart failure in the case of anti-tumor necrosis factor alpha antibodies), and higher rates of adverse events (e.g., serious infections, diabetes, arterial hypertension, mental disorders in the case of corticosteroids or neoplastic complications in the case of thiopurines) [7,35–53]. The safety of newly registered immunosuppressive molecules and biological agents (tofacitinib, anti-integrins–vedolizumab, or anti-IL-12/23 antibodies–ustekinumab) in elderly IBD patients has not been studied at all [54].

General indications for surgery in IBD patients aged >60 are similar, when compared with the younger subgroup, however, a decision to use surgical intervention should be taken with caution since there is a higher risk of post-operative complications and mortality [5,11]. Nevertheless, in many cases surgery is inevitable, which is why, in order to improve therapeutic outcomes, optimal treatment

should be applied preoperatively, with minimization of corticosteroid use and extensive nutritional support [5,11,55–57].

The rules for disease monitoring in elderly IBD patients should be also adjusted for age and concomitant morbidities. Since repeated endoscopic assessment is often impossible, the importance of non-invasive markers of inflammatory activity, like fecal calprotectin or C-reactive protein, is high [58,59]. In terms of cross-sectional imaging methods, repeated computed tomography or magnetic resonance (MR) imaging can be difficult and, in many cases, contraindicated [60]. This is due to the fact that a significant proportion of older patients suffer from renal insufficiency or are at a high risk of this complication, which makes the administration of an intravenous contrast agent impossible. Another limitation for MR imaging is the high frequency of metallic implants (e.g., after a total hip or knee replacement or after the implantation of a cardiac rhythm control device) in elderly people. This is why more common use of an abdominal ultrasound should be advised for the objective assessment of morphological abnormalities in the gastrointestinal tract [60].

1.2. Ageing, IBD, and Malnutrition—What Are the Connections?

As discussed above, there are many limitations for the routine application of classical therapeutic approaches in the case of IBD in elderly patients. Thus, non-pharmacological and non-surgical interventions are of great importance. The role of dietary support is especially high, since ageing by itself increases the risk of malnutrition. Epidemiological analyses show that 5%–20% of European citizens aged 60 and older suffer from malnutrition, while for hospitalized patients or those in long-term care, these numbers are even higher [61]. Thus, obligatory assessment of the nutritional status of all older patients is recommended by both the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Parenteral and Enteral Nutrition (ESPEN). A Mini Nutritional Assessment (MNA) is believed to be the most appropriate tool for this purpose [62–64].

The etiology of malnutrition in older people is multifactorial. There are multiple medical conditions associated with a high risk of weight loss and nutritional deficiencies, like cancer, pulmonary disorders (chronic obstructive pulmonary disease), diabetes, cerebrovascular and neurological diseases, and gastrointestinal disorders. Many of those conditions are characterized by an increased catabolism, loss of appetite, and dysphagia. Multimorbidity and polypharmacy—typical phenomena among elderly people—are also connected with higher hospitalization rates, and increased probability of significant drug interactions [65]. These factors can independently promote malnutrition [65–67]. Another important problem is poor oral health and dental status leading to chewing difficulties and mouth dryness, which can cause lower food intake [68,69]. Depression, anxiety, dementia, and many other neuropsychological factors can result in unintentional weight loss and nutritional deficiencies [70–72]. There are also many social determinants of malnutrition risk, like poverty, loneliness and isolation, an inability to shop or cook, secondary to cognitive disorders and/or physical disability [73,74]. Interestingly, although ageing per se is not always associated with malnutrition, there are several physiological phenomena increasing the risk of weight loss. Decreasing appetite among elderly and otherwise healthy people can be explained by a reduction in stomach capacity and impairment of gastric relaxation, accompanied by lower gastric emptying. One of the etiological hypotheses for these processes in older people is fluctuation in the production and secretion of several enterohormones. There are data suggesting that higher levels of cholecystokinin and lower concentration of ghrelin can contribute to early satiation after food consumption. Moreover, degenerative processes in the gastrointestinal tract can result in the reduction in the number of taste buds, which can be accompanied by a deterioration in the sense of smell. These phenomena can additionally demotivate the patients to consume regularly [75–77].

Since the mechanisms underlying malnutrition in elderly people are complex, three types of weight loss proposed by Roubenoff can coexist: wasting, cachexia, and sarcopenia [78,79]. Wasting is associated with inadequate dietary intake and results in involuntary weight loss [80]. Cachexia is caused by induced catabolic processes, with pro-inflammatory cytokines like interleukin-1 (IL-1), tumor necrosis factor–alpha (TNF-alpha), IL-6, and others having a predominant role. The main

consequence of cachexia is a decrease in fat-free mass and body cell mass [81]. Sarcopenia is defined as a loss of muscle mass [78,79,82]. The etiology of this phenomenon is poorly understood, however, a dominant role is hypothetically played by a lack of physical activity, induction of the pro-inflammatory response, and dysregulation of anabolic hormones, like testosterone or growth hormone [83,84].

IBD is independently associated with an increased risk of malnutrition. Epidemiological data shows that 65%–75% of CD patients and 18%–62% of UC patients have nutritional deficiencies [85]. The discrepancies in these numbers are a consequence of the different definitions of malnutrition. Body mass index (BMI) is among the most frequently used criteria, but it has been widely criticized recently, since it does not take into account several qualitative and quantitative parameters like the relation between fat and muscle mass, the concentration of micro- and macronutrients, recent changes in body mass or disease activity [86]. There are many data showing that low body mass is only one of the dimensions reflecting malnutrition in IBD. Among other parameters, which have been frequently reported, are deficiencies in iron, calcium, selenium, vitamin D and/or vitamin K [85].

The etiology of malnutrition in IBD is complex. It encompasses disease-related and treatment-related factors [85]. In the first group, a decrease in food intake seems to be the most important. This phenomenon can be related to IBD symptoms, like nausea, vomiting, abdominal pain, diarrhea, fever or fatigue. Also, it has been shown that hospitalization is associated with a higher risk of inappropriate food intake due to a frequent need to fast in preparation for different investigations or due to an inadequate hospital diet [85,87]. Moreover, disease activity by itself, with the production of multiple pro-inflammatory cytokines, induces catabolic processes, and promotes increased energy expenditure, contributing to malnutrition. The absorptive functions of the gastrointestinal tract are also impaired due to bowel wall damage with a loss of epithelial integrity, bacterial overgrowth, and increased intestinal motility. The same factors contribute to enhanced nutrient loss [85,88]. Considering the treatment-related causes of malnutrition, there are data on the negative impact of steroids on body composition. Moreover, nitroimidazoles or immunosuppressive drugs (thiopurines, methotrexate) can also alter the appetite, leading to reduced food intake [85]. On the other hand, multiple surgical resections limit the absorptive gastrointestinal surface, in spite of the high compensatory potential of the remaining parts of the intestines [85].

Taking into consideration the complex etiology and high frequency of malnutrition among elderly people and IBD patients analyzed separately, the significance of this phenomenon among CD and UC patients aged 60 and older becomes especially challenging. In order to prevent and/or adequately treat this unique subpopulation, proper dietary support is needed.

1.3. The Role of Diet in IBD and the Elderly

There are no strict dietitian recommendations for patients with IBD, since there are insufficient data for promoting any special diet. The general rule is that patients should cover their energy demand by eating well-balanced meals containing complex carbohydrates, proteins and fats, mainly of plant origin, rich in vegetables and fruits, with the elimination of highly processed foods [89]. Special attention should be paid to appropriate iron and vitamin D consumption. In each case, however, a highly individualized recommendation should be defined in order to adjust the nutritional needs to a concrete, clinical scenario, especially in older people.

According to current knowledge, in the case of physiological ageing special recommendations should be given for protein, vitamin D, and water consumption. In order to maintain muscle mass, the PROT-AGE study group defined the daily protein requirement, which is 1.0–1.2 g protein/kg body weight [90]. Moreover, all individuals should supplement vitamin D3 in a dose of 800–2000 IU per day [91]. Adults should drink 30–35 mL/kg body weight (at least 1500 mL/day or 1–1.5 mL/1 kcal) of water (preferably medium-carbonized and still water). Since there is an increased risk of dehydration among older people, the recommendations for daily water consumption in this subpopulation (similar to the pediatric population) are more precisely defined as 100 mL of water for the first 10 kg, then 50 mL for second 10 kg, and 15–20 mL for each additional kilogram of body weight [92,93]. In addition,

older adults are in the groups at risk of vitamin B12 deficiency. The usual dietary sources of vitamin B12 are animal products, including fish, meat, poultry, eggs, milk, and milk products. Vitamin B12 is generally not present in plant foods, but a lot of these products are fortified. The vitamin B12 recommended dietary allowance for older adults is 2.4 µg/day [94,95].

In the case of high IBD activity, especially in patients with severe diarrhea and abdominal pain due to stricturing CD, it is advisable to avoid a high intake of fiber and lactose, in order to prevent bacterial overgrowth and reduce the number of bowel movements [96]. The daily protein requirement is 1.2–1.5 g protein/kg body weight [96]. Resting energy expenditure during a flare is 25–30 kcal/kg standard body weight [96–98]. Moreover, according to the ESPEN recommendations, oral nutrition supplements (ONS) should be considered in addition to a normal diet for the treatment of nutritional deficiencies in the case of IBD exacerbation [96]. ONS contain high amounts of all (complete) or selected (incomplete) macro- and microelements in relatively small volume products. ONS can be also divided into two categories: standard ONS which contain different nutritional compounds in proportions characteristic for a normal oral diet and specific ONS which is composed adequately for some particular patient populations (e.g., Parkinson's disease, Alzheimer's disease, etc.). ONS can be used together with meals; they contain no lactose, gluten, purines or cholesterol and should be considered in each case of increased malnutrition risk or diagnosed malnutrition [96,99].

Recent years, however, have brought plenty of data about the crucial role of impaired microbiota in the pathogenesis of intestinal inflammation. Moreover, there is a growing body of evidence that also ageing is associated with changes in intestinal microbiota composition. In 2007 the ELDERMET consortium was established to investigate this topic [100]. They found (by using the pyrosequencing of 16S rRNA method) that there was an increase in *Bacteroidetes* and a concomitant decrease in *Firmicutes* species among older people, however there was a significant inter-individual variability in the composition of elderly gut microbiota [101]. One of the reasons was the health status of the investigated subjects. The statistical analysis indicated a clear separation between community-dwelling subjects and long-stay home residents [101]. Another observation was that health status and the diversity of the intestinal microbiota in the ELDERMET study correlated with the patients' nutritional habits. It was shown that the diversity index of the fecal microbiota was significantly associated with a low-fat and high-fiber diet [101]. It is, however, still not known whether changes in gut microbiota are a result of dietary intervention or are more related to unhealthy ageing by itself.

Nevertheless, the possibility of shaping the intestinal microbiota by nutritional interventions would be very attractive. The hypothetical promotion of a "healthy" in-vironment (microbiota) by environmental factors (diet) seems to be an interesting concept for therapeutic intervention also in IBD. This is why dietary intervention is currently considered not only in the context of sufficient nutritional support, but also as a potential modulator of intestinal inflammation [102,103]. Our understanding of the link between nutrition, intestinal microbiota, and inflammatory response is still poor, however, due to the development of new technologies such as metabolic profiling and next-generation DNA sequencing, we know that microbiota composition changes after exposure to different modifying factors [104]. For example, there are data showing that a high-fat and low-fiber diet, as well as an animal-based diet, increase the abundance of *Bacteroidetes* and *Prevotella*, which are believed to participate in the development of chronic inflammation in the gastrointestinal tract [105]. On the other hand, dietary fiber can promote short-chain fatty acids synthesis by colonic microbiota, which can lead to the suppression of pro-inflammatory cytokines from dendritic cells and macrophages [104,106,107]. Another hypothetical association between the diet and inflammation is the epigenetic regulation of gene expression by different nutritional components. There is some evidence that the typical Western diet, deficient in micronutrients, like selenium and folate, can influence DNA methylation, which promotes pro-inflammatory phenomena and seems to increase colorectal cancer susceptibility [104]. What is more, in an experimental model of IBD it was shown that selenium supplementation prevented tissue damage through interfering with the expression of the key genes responsible for inflammation [104,108]. Nevertheless, although these concepts of the associations between diet, microbiota, and inflammatory

response are very promising, we are still not able to translate this knowledge into clinical practice. We hope that it will be possible in the future to modulate our microbiota by changing the in-vironmental milieu via nutritional intervention, but we still need more data.

Among different diets already studied in the context of IBD, main attention is being paid to the low-fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) and anti-inflammatory diet (IBD-AID), although supporting scientific evidence is relatively poor [104]. Recently, the advantages of the Mediterranean or the Dietary Approach to Stop Hypertension (DASH) diets in the context of chronic inflammation have also been discussed [105,106].

The main rule of the low-FODMAP diet is to exclude highly fermentable and poorly absorbed carbohydrates and polyols. In this diet, consumption of different food types is strongly discouraged, such as many fruits (e.g., apple, blackberry, grapefruit, mango, nectarine, peach, plum, watermelon), vegetables (e.g., artichoke, asparagus, avocado, onion, cabbage, garlic, leek, pea), dairy (e.g., cow, goat, sheep, condensed and evaporated milk), beverages (e.g., green tea, soft drinks, white tea, coconut water) and many nuts, seeds and legumes. Moreover, breaded meat or meat made with high fructose corn syrup should be avoided. This is not a long-term diet and the dietary limitations should last for only 6–8 weeks. Then patients should gradually restart foods high in FODMAPs in order to establish an individual tolerance to specific oligosaccharides, disaccharides, monosaccharides, and polyols. The utility of the low-FODMAP diet has been shown mainly for patients with irritable bowel syndrome (IBS), since there is a hypothesis that high fermentation in the gastrointestinal lumen can lead to increased intestinal permeability and provoke intestinal hypersensitivity in a genetically susceptible host [107,108]. Data on the usefulness of this diet in IBD are limited and mainly come from retrospective cohorts. It is advised that a low-FODMAP diet can be used in selected IBD patients with IBS-like symptoms in addition to conventional therapy, but only under strict dietitian supervision [104–115].

IBD-AID is a multistep and highly individualized dietary intervention, limiting some specific carbohydrates (e.g., refined sugar, gluten-based grains, certain starches). Olendzki et al., who developed IBD-AID, hypothesized that this can decrease the growth of several pro-inflammatory bacteria in the gastrointestinal tract, preventing dysbiosis [116]. In the next step, the patient should ingest prebiotics and probiotics (e.g., leek, onion, fermented food) to promote restoration of the microbiota. Moreover, the consumption of total and saturated fat, and hydrogenated oils should be avoided, together with the individual identification of dietary intolerances and nutritional deficiencies. The rules of IBD-AID were first published in 2017 and until now there were no randomized, controlled trials conducted in order to confirm the initial, promising reports on the use of this diet as an adjunct therapy for the treatment of IBD [104,116].

Lack of sufficient data for the usefulness of the low-FODMAP diet and IBD-AID in IBD result in a high skepticism of clinicians to promote this kind of dietary intervention. In the case of elderly IBD patients, another important limitation for the use of these diets is their complexity. Moreover, there is a high risk of several nutritional deficiencies due to the restriction and avoidance of different foods, especially when the dietary intervention is conducted without professional support. This can have serious negative consequences, considering the general increased risk of malnutrition and the presence of serious comorbidities in older people. This is why it seems to be more reasonable to promote safer diets, with more robust data in the context of elderly patients.

Considering the nutritional requirements and characteristics of elderly patients with IBD discussed above, as well as the most common disorders among older people (arterial hypertension and other cardiovascular diseases, type 2 diabetes, hypercholesterolemia), the DASH or Mediterranean diet could be recommended for this unique population. The main restrictions in the DASH diet concern carbohydrates and fats, in particular by limiting simple carbohydrates (glucose, fructose, saccharose) and reducing the intake of saturated fats. This means a significant reduction in the consumption of sweets, sugar confectionery, sweeteners, fruit preservatives (less than five portions per week), as well as red meat and highly processed food. Vegetables and fruits should be eaten 4–5 times/day, and whole grain products 6–8 times/day. The DASH diet also includes medium-fat dairy products

(2–3 portions/day), however, this needs to be accompanied with regular consumption of vegetable oils (preferably raw, inter alia, to enable the absorption of fat-soluble vitamins). The recommended frequency for eating fatty saltwater fish (herring, salmon, mackerel, halibut, sardine, codfish, flounder) is 2–4 times/week. Different seeds, nuts, legumes are also an important part of the DASH diet, since they contain (similar to vegetable oils—linseed, soybean or rapeseed oil— and fatty saltwater fish) high amounts of omega-3 polyunsaturated fatty acids (PUFA). Another main rule of this type of diet is a significant reduction in salt (sodium) consumption [117].

Although there are no data on the utility of the DASH diet in IBD, its beneficial effect on general health status and cardiovascular risk is well known [118–121]. Moreover, Nilsson et al. showed that adherence to a DASH-style diet was significantly associated with a lower clustered metabolic risk among older women, and it promoted a systemic anti-inflammatory environment, independently of physical activity [122]. The authors concluded that the DASH diet should be considered as a key target for nutritional intervention among elderly people to prevent age-related metabolic abnormalities.

The general recommendations of the Mediterranean diet are very similar to DASH. It emphasizes eating primarily plant-based foods (fruits, vegetables, whole grains, legumes, nuts, seeds, olive oil), which should be consumed several times per day, together with dairy products (mainly different types of cheese, yogurts). Low or moderate alcohol drinking (preferably red wine with a meal) is also advised. Fish, eggs, and poultry can be consumed several times per week. In contrast, consumption of sweets and red meat should be significantly reduced (a few times per month). The details of the Mediterranean diet can vary depending on the region of the Mediterranean Basin; however, the general rule is to eat foods coming from this geographic area [123,124].

In contrast to the DASH diet, there are some data on the usefulness of Mediterranean diet in IBD. Marlow et al. demonstrated that even a short-term (six weeks) nutritional intervention is beneficial for patients with CD, decreasing the concentration of several pro-inflammatory markers with a trend to normalize the composition of intestinal microbiota. Transcriptomics analyses confirmed small changes in many genes, providing a cumulative anti-inflammatory effect of the diet [125]. In another study, Godny and colleagues showed that the Mediterranean diet is associated with decreased fecal calprotectin in patients after pouch surgery in UC, which is accompanied by an improvement in gut microbiota composition [126]. Moreover, Molendijk et al. demonstrated a beneficial effect of long-term nutritional intervention in IBD. In this study, six months of the Mediterranean diet improved the quality of life and reduced CRP levels. The level of improvement was associated with adherence to the rules of this type of diet [127].

The question remains, which hypothetical mechanisms could be related to the anti-inflammatory properties of the Mediterranean diet in IBD. As discussed above, this diet is characterized by a low intake of omega-6 PUFA, high intake of omega-3 PUFA, and dietary fiber, which seems to be important in the context of IBD. In line with that, the most recent epidemiological data indicate that a higher ratio of omega-6/omega-3 PUFA in the diet can be associated with an increased UC incidence [128]. Moreover, Hou et al. noted that a high intake of omega-6 PUFA, saturated fats, and meat is correlated with an increased risk of developing UC and CD [129]. It was also shown in a murine dextran sulfate sodium (DSS)-induced colitis model that omega-6/omega-3 PUFA ratio in the diet can influence the inflammatory processes in the gastrointestinal tract [130]. The authors observed that an α-linolenic acid (ALA)-enriched diet with a decreased uptake of linoleic acid (LA) resulted in less severe colitis in mice, with a markedly alleviated intestinal inflammation [130]. This was supported by Pearl et al. who showed the association between severity of intestinal inflammation and increased content of omega-6 PUFA in inflamed mucosa in UC patients [131]. Furthermore, Uchiyama et al. investigated the influence of a diet therapy involving the use of an "omega-3 PUFA food exchange table". The authors showed that omega-3 PUFA significantly increased the erythrocyte membrane omega-3/omega-6 PUFA ratio in IBD patients, what was associated with clinical remission of the disease [132]. Recently, another experimental study on the protective role of omega-3 PUFA has been published. Charpentier et al. showed that supplementation of omega-3 PUFA significantly decreased

colon inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression, as well as IL-6 and leukotriene B4 production in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis [133].

Dietary fiber is also believed to have a protective effect on the development of inflammation in the gastrointestinal tract. Moreover, the short-chain fatty acids, regarded as one of the major microbial metabolites of dietary fiber, have the potential to improve intestinal mucosal immunity and maintain homeostasis [134]. There are several experimental and clinical data supporting these hypotheses. Liu et al. showed in a murine DSS-induced colitis model that supplementation of β-glucans at a dose of 500 mg/kg per day reduced the severity of clinical activity of the disease. β-glucans-enriched diet resulted in a smaller weight loss, improvement in the number of bowel movements, and amelioration of the inflammatory response assessed microscopically. It has been also shown that β-glucans supplementation inhibited the expression of pro-inflammatory proteins, such as TNF-α, IL-1, IL-6 or NOS [135]. On the other hand, based on the data from the Nurses' Health Study, it was suggested in a prospective study that a long-term intake of dietary fiber was associated with lower risk of CD, but not UC [136]. A meta-analysis, performed by Liu and colleagues, indicated that the intake of dietary fiber was related to a decreased risk of developing IBD [137]. In a recent study by Andersen et al. an inverse association between the consumption of cereal fiber and CD in non-smokers was confirmed [138].

The only theoretical limitation of the DASH or Mediterranean diet in IBD is the high amount of whole grain cereal products, nuts, and seeds of leguminous plants which can stimulate intestinal peristalsis and increase the frequency of bowel movements. This is why it is advised to reduce the consumption of these particular foods during an IBD flare, whereas in patients in remission the individually tolerated amount of these products should be established.

The main rules of DASH and the Mediterranean diet are presented in Tables 1 and 2.

Table 1. The rules of Dietary Approaches to Stop Hypertension (DASH) diet [117].

The DASH Diet (Dietary Approaches to Stop Hypertension)			
Dietary Product	**The Frequency of Consumption**	**Indicated**	**Contraindicated**
Cereal products	6–8/day	whole grain	refined
Vegetables	4–5/day	all	-
Fruits	4–5/day	all	-
Protein	6 or less/day	fatty saltwater fish, lean meat, seeds of leguminous plants	fatty, red meat
Nuts and seeds	4–5/week	all	-
Fats	2–3/day	vegetable oils rich in unsaturated fatty acids	animal fat, coconut oil, palm oil
Dairy products	2–3/day	low-fat or fat-free	full-fat
Drinks	several times a day	unspecified	drinks containing simple carbohydrates
Other			
Sweets, confectionery products	5 or less/week	-	-
Sodium	Max. 2300 mg/day	-	-

Table 2. The rules of the Mediterranean diet [124].

The Mediterranean Diet			
Dietary Product	**The Frequency of Consumption**	**Indicated**	**Contraindicated**
Cereal products	several times a day	whole grains	refined
Vegetables	several times a day	all	-
Fruits	several times a day	all	-
Fish and seafood	several times a week (at least 2 times a week)	fatty saltwater fish (tuna, salmon, sardines, herring) and mussels, oysters and shrimps	-
Poultry and eggs	several times a week	all	-
Red meat	a few times a month	-	-
Nuts and seeds of leguminous plants	several times a day	all	-
Fats	several times a day	olive oil	animal fats such as lard, butter, fatty beef, fatty pork, poultry with skin
Dairy products	several times a day	all	-
Drinks	several times a day	still water	sugary drinks
Sweets, confectionery products	few times a week	-	-
Red wine	every day; women max. 1, men max. 2 glasses/day	-	-

2. Conclusions

The ageing of the human population has become a big challenge for health care systems worldwide. The increasing proportion of elderly people is a result of significant improvements in medical care, successful prophylaxis of infectious diseases, and declining birth rates in developed countries. On the other hand, the number of elderly IBD patients is also increasing and we have to face the problem of managing this unique population. Since there are several important differences in the clinical characteristics of older IBD patients, appropriate nutritional intervention and counseling should become a crucial element of the therapy. Although there are no data on the definite therapeutic influence of any diet on the course of IBD, it seems to be reasonable, considering data presented in this paper, to actively promote a healthy diet among elderly patients with IBD with special emphasis on the DASH or Mediterranean-style diet. Patients with IBD aged >60 are also at increased risk of cardiovascular diseases, type 2 diabetes, and arterial hypertension. This is why these two similar types of nutrition can cover not only the dietary requirements characteristic of a chronic inflammatory condition, but also due to its anti-inflammatory properties, they can improve the metabolic abnormalities typical in older age. Of course, it seems rational to advocate these types of diets only in parallel with classical treatment of IBD and even regardless of subsequent gastrointestinal disorders or any other disease. Nevertheless, since application of the current, aggressive therapeutic approaches in a significant proportion of elderly IBD patients is limited, the use of the Mediterranean and DASH diets is reasonable, especially in this unique population.

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Gastrointestinal and liver manifestations in patients with COVID-19

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Abstract: As the outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread over the world, the World Health Organization has declared the outbreak of COVID-19 an international public health emergency. Besides typical respiratory symptoms and signs of COVID-19, digestive symptoms and liver injury have been frequently reported during the course of the disease. In this review, we summarized the recent studies reporting of gastrointestinal and liver manifestations during the course of COVID-19. Digestive symptoms, including anorexia, nausea, vomiting, and diarrhea, are not uncommon in patients with COVID-19, and in some cases digestive symptoms may occur in the absence of any respiratory symptoms. Furthermore, SARS-CoV-2 could be detected in the stool of infected patients, implicating the possibility of fecal–oral transmission. Attention should also be paid to monitor liver function during the course of COVID-19, especially in patients with higher disease severity.

Keywords: COVID-19; Liver; Severe acute respiratory syndrome coronavirus 2

1. INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported in China, in December, 2019, has posed a critical threat to global public health.[1,2] The World Health Organization (WHO) has recently declared the outbreak of COVID-19 infection an international public health emergency. Lung is considered to be the primary organ of involvement by COVID-19 infection, and most patients with COVID-19 present with typical respiratory symptoms and signs. However, gastrointestinal symptoms and liver injury have also been reported to occur during the course of the disease. In this review, we assess how the digestive system and the liver are affected by COVID-19 using the available evidences to date.

2. GASTROINTESTINAL MANIFESTATIONS OF COVID-19

As SARS-CoV-2 RNA was first detected in stool of the first reported COVID-19 case in the USA, who also presented with the digestive symptoms of nausea, vomiting, and diarrhea,[3] more attentions have been paid to the gastrointestinal manifestations of SARSCoV-2. Digestive symptoms including anorexia, nausea, vomiting, and diarrhea are frequently reported in patients with COVID-19 (Table 1).[4–13] In the currently largest cohort including 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces in China through January 29, 2020, nausea or vomiting and diarrhea were reported in 55 (5%) and 42 (3.8%) patients, respectively.[13]

In the SARS outbreak of 2002-2003, 16% to 73% of patients with SARS had diarrhea during the course of the disease, usually within the first week of illness.[14] In patients with COVID-19, diarrhea is also a common digestive symptom, with the incidence ranging from 1.3% to 29.3% (Table 1). In addition, SARS-CoV-2–induced diarrhea could be the onset symptom in patient with COVID-19.[15] Nevertheless, the incidence of diarrhea varied widely among different reports, suggesting that the criteria for diagnosing diarrhea may differ in different hospitals. Clinicians might underestimate the value of digestive symptom in clinical practice, and it may affect the preliminary diagnostic accuracy.[16]

Pan et al[17] described the clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China. Among the 204 patients with COVID-19 and full laboratory, imaging, and historical data, 99 (48.5%) presented with digestive symptoms as their chief complaint. Patients with digestive symptoms had a variety of manifestations, including anorexia (83.8%), vomiting (0.8%), diarrhea (29.3%), and abdominal pain (0.4%). Compared with patients without digestive symptoms, those presenting with digestive symptoms have a longer time from onset to admission and a worse prognosis. Notably, in 7 (3.4%) cases, there were digestive symptoms but no respiratory symptoms. Based on these findings, clinicians must be aware that digestive symptoms, such as diarrhea, may be a presenting feature of COVID-19 that arise before respiratory symptoms, and on rare occasions may be the only presenting symptom of COVID-19.

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Table 1

Incidence of digestive symptoms and liver injury in patients with SARS-CoV-2 infection

	Patient number	Anorexia, nausea or vomiting	Diarrhea	Liver injury
Huang et al[3]	41	...	1 (3%)	Abnormal AST: 15 (37%)
Chen et al[4]	99	Nausea and vomiting: 1 (%)	2 (2%)	Abnormal ALT: 28 (28%) Abnormal AST: 35 (35%)
Xu et al[5]	62	...	3 (8%)	Abnormal AST: 10 (16.1%)
Wu et al[6]	80	Nausea and vomiting: 1 (1.25%)	1 (1.3%)	Abnormal ALT: 3 (3.75%) Abnormal AST: 3 (3.75%)
Wang et al[7]	138	Anorexia: 55 (39.9%) Nausea: 14 (10.1%) Vomiting: 5 (3.6%)	14 (10.1%)	Significantly higher ALT and AST in ICU cases
Shi et al[8]	81	Anorexia: 1 (1%) Vomiting: 4 (5%)	3 (4%)	Abnormal AST: 43 (53.1%)
Yang et al[9]	52	Vomiting: 2 (4%)	...	Liver dysfunction: 15 (29%)
Mo et al[10]	155	Anorexia: 26 (31.7%) Nausea: 3 (3.7%) Vomiting: 3 (3.7%)	7 (4.5)	Significantly higher AST in refractory cases
Zhou et al[11]	191	Nausea or vomiting: 7 (4%)	9 (5%)	Abnormal ALT: Survivor 24% Non-survivor 48%
Guan et al[12]	1099	Nausea or vomiting: 55 (5%)	42 (3.8%)	Abnormal ALT: 158 (21.3%) Abnormal AST: 168 (22.2%)
Pan et al (AJG)	99	Anorexia: 83 (83.8%) Vomiting: 8 (0.8%)	29 (29.3%)	...

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ICU = intensive care unit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Several reports showed that the SARS-CoV-2 RNA could be detected in the stool of patients with COVID-19, implying that SARS-CoV-2 may be transmitted by the fecal–oral route.[3,18,19] COVID-19 disease in a patient with positive fecal but negative pharyngeal and sputum viral tests has been reported.[20] Wang et al[19] showed that 44 of 153 (29%) patients with COVID-19 were tested positive for the virus in stool. Xiao et al showed that among the 73 hospitalized COVID-19 patients in China, 39 (53.42%) were tested positive for SARS-CoV-2 RNA in stool.[21] The duration of positive stool ranged from 1 to 12 days, and 17 (23.29%) patients remained positive in stool after showing negative in respiratory samples. They performed endoscopic sampling of different parts of the gastrointestinal tract from a patient, and the viral RNA could be detected in esophagus, stomach, duodenum, and rectum. This study provide the direct evidence that gastrointestinal infection of SARS-CoV-2, and the infectious virions may be secreted from the virus-infected gastrointestinal cells.[21]

The mechanism for gastrointestinal tract infection of SARS-CoV is proposed to be the angiotensin-converting enzyme 2 (ACE2) cell receptor.[22,23] SARS-CoV-2, which has the genome sequence of 82% similar to SARS-CoV, may use the same cell entry receptor ACE2, but more efficiently than the 2003 strain of SARSr-CoV.[24] By analyzing endoscopic biopsy samples, Xiao et al[21] showed that ACE2 was rarely expressed in esophageal epithelium, but abundantly distributed in cilia of glandular epithelia, while staining of viral nucleocapsid protein was visualized in the cytoplasm of gastric, duodenal, and rectum glandular epithelial cell, but not in esophageal epithelium. Another study also displayed that ACE2 was highly expressed in the small intestine, especially in proximal and distal enterocytes.[16] The mutual interaction between SARS-CoV-2 and ACE2 might disrupt the function of ACE2 and results in diarrhea.

The possibility of fecal–oral transmission of SARS-CoV-2 emphasized the importance of frequent and proper hand hygiene, especially in areas with poor sanitation. Strict precautions must be observed when handling the stools of patients with COVID-19, and sewage from hospitals should also be properly disinfected. The presence of SARS-CoV-2 in the gastrointestinal tract also raises the concerns of COVID-19 infection in patients with preexisting digestive diseases as well as potential fecal microbiota transplant donors. Nevertheless, the comorbidity spectrum of digestive conditions and its impact on treatment and outcome of COVID-19 remains largely unknown.[25] To prevent SARS-CoV-2 transmission by fecal microbiota transplantation, additional screening methodologies to the current donor screening measures should be performed.[26]

Finally, the gastrointestinal endoscopy departments face significant risk for transmissions of SARS-CoV-2 during endoscopy.[27] In one of the earliest report of COVID-19 in Wuhan, 29% of patients (40 out of 138) were healthcare workers and suggest that the risk of infection to healthcare providers is significant.[8] Possible routes of SARS-CoV-2 transmission during endoscopy examination include person-to-person, respiratory droplets, aerosols generated during endoscopy, and contact with contaminated surroundings, body fluids, and fecal material. The World Endoscopy Organization,[28] the American Society for Gastrointestinal Endoscopy,[29] and the European Society of Gastrointestinal Endoscopy[30] have provided recommendations on the performance of endoscopy during the COVID-19 pandemic.

3. LIVER INJURY IN COVID-19

Liver injury was common in the patients infected by the other two highly pathogenic coronavirus—SARS-CoV and the Middle East respiratory syndrome coronavirus—and associated with the severity of diseases.[31] In patients with COVID-19, several studies have reported the incidence of liver injury (Table 1), indicating that 2% to 11% of patients with COVID-19 had liver comorbidities and 16% to 53% cases reported abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).[32] Guan et al[13] showed that elevated AST levels were observed in 18.2% of patients with nonsevere disease and 39.4% of patients with severe disease, whereas elevated ALT levels were observed in 19.8% of patients with nonsevere disease

and 28.1% of patients with severe disease. Huang et al[4] showed that elevation of AST was observed in 8 (62%) of 13 patients in the intensive care unit (ICU) compared with 7 (25%) of 28 patients who did not require care in the ICU. Wang et al[8] also showed that patients admitted to ICU had significantly higher ALT (35 vs 23, $p = 0.007$) and AST (52 vs 29, $p < 0.001$) levels. These data suggest that liver injury is more prevalent in severe cases than in mild cases of COVID-19.

Liver injury in patients with COVID-19 might be due to viral infection in liver cells or due to other causes such as drug-induced liver injury and systemic inflammation induced by cytokine storm or pneumonia-associated hypoxia.[32] SARS virus has been shown to be present in the liver tissue, although the viral titer was relatively low because viral inclusions were not observed.[33] Nevertheless, a case report of pathological analysis of a patient who died from COVID-19 did not identify viral inclusions in the liver tissue.[34]

The impact of COVID-19 in patients with preexisting chronic liver diseases, such as viral hepatitis, nonalcoholic fatty liver disease, and alcohol-related liver disease, remains to be evaluated. The study from China showed that patients with underlying chronic hepatitis B infection did not have higher disease severity compared with the overall population.[13] Currently there is no report of liver failure in COVID-19 patients with chronic liver diseases, such as chronic hepatitis B or C.

4. CONCLUSION

In this review, we summarized the recent reports of digestive symptoms and liver injury caused by COVID-19. Digestive symptoms are not uncommon in patients with COVID-19, and in some cases digestive symptoms may occur in the absence of any respiratory symptoms. COVID-19 patients with digestive symptoms have worse clinical outcomes and higher risk of mortality compared with those without digestive symptoms. Attention should also be paid to monitor liver function during the course of COVID-19, especially in patients with higher disease severity.

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CLINICAL AT

Effects of Low FODMAP Diet on Symptoms, Fecal Microbiome, and Markers of Inflammation in Patients With Quiescent Inflammatory Bowel Disease in a Randomized Trial

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See Covering the Cover synopsis on page 1.

BACKGROUND & AIMS: There is limited evidence that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) reduces gut symptoms in quiescent inflammatory bowel disease (IBD). We performed a randomized, controlled trial to investigate the effects of a low FODMAP diet on persistent gut symptoms, the intestinal microbiome, and circulating markers of inflammation in patients with quiescent IBD. **METHODS:** We performed a single-blind trial of 52 patients with quiescent Crohn's disease or ulcerative colitis and persistent gut symptoms at 2 large gastroenterology clinics in the United Kingdom. Patients were randomly assigned to groups that followed a diet low in FODMAPs (n = 27) or a control diet (n = 25), with dietary advice, for 4 weeks. Gut symptoms and health-related quality of life were measured using validated questionnaires. Stool and blood samples were collected at baseline and end of trial. We assessed fecal microbiome composition and function using shotgun metagenomic sequencing and phenotypes of T cells in blood using flow cytometry. **RESULTS:** A higher proportion of patients reported adequate relief of gut symptoms following the low FODMAP diet (14/27, 52%) than the control diet (4/25, 16%, P=.007). Patients had a greater reduction in irritable bowel syndrome severity scores following the low FODMAP diet (mean reduction of 67; standard error, 78) than the control diet (mean reduction of 34; standard error, 50), although this difference was not statistically significant ($P = .075$). Following the low FODMAP diet, patients had higher health-related quality of life scores (81.9 ± 1.2) than patients on the control diet (78.3 ± 1.2, $P = .042$). A targeted analysis revealed that in stool samples collected at the end of the study period, patients on the low FODMAP diet had significantly lower abundance of *Bifidobacterium adolescentis*, *Bifidobacterium longum*, and *Faecalibacterium prausnitzii* than patients on control diet. However, microbiome diversity and markers of inflammation did not differ significantly between groups. **CONCLUSIONS:** In a trial of the low FODMAP diet vs a control diet in patients with quiescent IBD, we found no significant difference after 4 weeks in change in irritable bowel syndrome severity scores, but significant improvements in specific symptom scores and numbers reporting adequate symptom relief. The low FODMAP diet reduced fecal abundance of microbes believed to regulate the immune response, compared with the control diet, but had no significant effect on markers of inflammation. We conclude that a 4-week diet low in FODMAPs is safe and effective for managing persistent gut symptoms in patients with quiescent IBD. www.isrctn.com no.: ISRCTN17061468

Keywords: CD; UC; IBS; HR-QOL.

An estimated 35% of patients with inflammatory bowel disease (IBD) experience gut symptoms despite having quiescent disease with minimal objective evidence of gastrointestinal (GI) inflammation.[1] The etiology of these gut symptoms in quiescent IBD is unclear but they are hypothesized to relate to coexistent irritable bowel syndrome (IBS), the legacy of previous GI inflammation on gut function, persistent unidentified low-grade inflammation, or the psychological impact of IBD.[2] These persistent gut symptoms have a significant impact on health-related quality of life (HR-QOL)[3] and pose a treatment dilemma because escalating

Abbreviations used in this paper: **bp, base pair; CD, Crohn's disease; CRP, C-reactive protein; FDR, false discovery rate; FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI, gastrointestinal; GOS, galacto-oligosaccharides; GSRS, GI symptom rating scale; HR-QOL, health-related quality of life; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-SSS, IBS Severity Scoring System; IHMS, International Human Microbiome Standards; ITT, intention-to-treat; KEGG, Kyoto Encyclopedia of Genes and Genomes; MGS, metagenomic species; PP, per protocol; SCFA, short chain fatty acid; SD, standard deviation; SEM, standard error of the mean; UC, ulcerative colitis.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

We performed a randomized trial to investigate the effects of diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) on symptoms not accompanied by inflammation, the fecal microbiome, and circulating markers of inflammation in patients with quiescent inflammatory bowel disease (IBD).

NEW FINDINGS

In comparing outcomes of patients on the low FODMAP diet vs a control diet, we found no significant difference after 4 weeks on change in irritable bowel syndrome severity scores, but significant improvements in specific gut symptom scores and the numbers reporting adequate symptom relief. The low FODMAP diet reduced fecal abundance of microbes believed to regulate the immune response, compared with the control diet, but had no significant effect on markers of inflammation.

LIMITATIONS

This trial included only 52 patients, placed on the diet for 4 weeks. Larger, more long-term studies might be needed.

IMPACT

A 4-week diet low in FODMAPs is safe and effective for managing intestinal symptoms not associated with inflammation in patients with quiescent IBD.

immune-modulating agents is likely to be ineffective. Limited evidence exists to support the pharmacological management of persistent gut symptoms in quiescent IBD.

Dietary fermentable carbohydrates increase small intestinal water through osmotic potential (eg, fructose, mannitol) and colonic gas through microbial fermentation (eg, fructans, galacto-oligosaccharides [GOS]).[4] Randomized, crossover rechallenge trials, which overcome the limitations of masking and confounding in dietary intervention studies, have shown that fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) can induce gut symptoms in both IBS and quiescent IBD.[5,6]

Dietary restriction of FODMAPs (low FODMAP diet) is thought to ameliorate functional gut symptoms by reducing diet-induced luminal water and colonic gas and, consequently, luminal distension, in those with visceral hypersensitivity.[7,8] Randomized, placebo-controlled trials of low FODMAP diet in IBS, delivered through a feeding study or as dietary advice, reported improvement of gut symptoms in 70% and 57% of patients, respectively.[9,10] In IBD, retrospective and prospective uncontrolled studies suggest potential benefit of low FODMAP diet as a therapy for persistent gut symptoms,[11,12] and more recently, a randomized controlled trial reported that gut symptoms improved in 81% of patients with IBD during a low FODMAP diet compared with 46% in control.[13] However, the trial was unblinded, therefore cannot account for the considerable placebo response that occurs in both IBS and IBD,[14] particularly in response to diet interventions.

Low FODMAP diet reduces fermentable substrate in the colon, and in IBS this alters microbiome composition, resulting in reduced Bifidobacteria[9,15] and *Faecalibacterium prausnitzii*[16] abundance. Bifidobacteria abundance in the mucosal microbiome is positively associated with the proportion of interleukin 10 expressing dendritic cells in Crohn's disease (CD).[17] Furthermore, low abundance of *F prausnitzii* is associated with active IBD, and is associated with greater postoperative relapse at 6 months in CD.[18–20] Therefore, the microbiological impact of low FODMAP diet could theoretically have an adverse effect on the mucosal immune response and disease course in IBD, but to date has been investigated in only 1 trial of 9 patients with CD.[21]

Accordingly, clinical trials to establish the therapeutic benefit of low FODMAP diet in managing gut symptoms in IBD must be placebo-controlled and must assess the impact on the microbiome, GI inflammation, and disease activity. To this end, we designed a randomized controlled trial to investigate the effects of low FODMAP dietary advice compared with placebo (sham) dietary advice on persistent gut symptoms, disease activity, GI microbiome, and peripheral T-cell phenotypes in quiescent IBD.

Methods

Study Design and Participants

Patients were recruited from 2 large gastroenterology clinics in London, United Kingdom, in a multicenter, randomized, parallel, single-blinded, placebo-controlled trial. Eligible patients were aged $\geq$18 years, with quiescent CD or ulcerative colitis (UC), experiencing ongoing gut symptoms and were naïve to low FODMAP diet. Quiescent IBD was defined by all of the following: physician global assessment, stable medications, no IBD flare in the previous 6 months, fecal calprotectin $<$250 μg/g, and serum C-reactive protein (CRP) $<$10 mg/L. The threshold for fecal calprotectin was chosen according to evidence proposing optimal sensitivity and specificity for detecting endoscopically quiescent disease.[22] Ongoing gut symptoms were required to meet the Rome III criteria for either diarrhea predominant (IBS-D), mixed subtype (IBS-M), or unsubtyped IBS (IBS-U), functional bloating, or functional diarrhea, experiencing abdominal pain, bloating, and/or diarrhea on $\geq$2 days during the baseline screening week and reporting inadequate relief of GI symptoms.[23]

Patients with dose changes of azathioprine, mercaptopurine, methotrexate, or biologics in the preceding 12 weeks; oral 5-aminosalicylic acid in the preceding 4 weeks; or antibiotics, probiotics, or prebiotics in the preceding 8 weeks were excluded. Patients with pure perianal CD, a current stoma, previous extensive GI resection, or a current stricture were excluded. Patients with established bile acid malabsorption were excluded because gut symptoms relating directly to bile acid malabsorption may not be modifiable by low FODMAP diet. Patients with constipation-predominant symptoms were excluded, because low FODMAP diet could exacerbate this symptom. Patients with self-reported lactose intolerance were included if they continued to experience gut symptoms despite low lactose diet. Patients were excluded if they had significant comorbidities, or if they were pregnant or lactating.

Research ethics committee approval was received from the London Dulwich ethics committee (Reference 15/LO/1684) and the trial was registered on the ISRCTN registry (ISRCTN17061468) before participant recruitment. All authors had access to the study data and reviewed and approved the final manuscript.

Randomization and Masking

A random allocation sequence was prepared online (www.sealedenvelope.com) by an independent researcher using block randomization, with a 1:1 ratio of low FODMAP to placebo sham diet. Randomization was stratified by diagnosis (CD or UC) and fecal calprotectin at screening (≤100 μg/g and 101–249 μg/g). Allocation sequences were sealed in opaque envelopes.

Participants were blinded to diet allocation and informed that both diets would change the types of carbohydrates consumed, but that one was the diet under investigation, whereas the other was a sham diet. The terms "fermentable carbohydrates," "low FODMAP diet," or the mechanisms of the diet were not mentioned to participants.

Study Visits

Patients were identified via gastroenterology clinics and referrals to the dietetic department for the management of gut symptoms in quiescent IBD. Fecal calprotectin and CRP were assessed during screening, and a 7-day food, stool, and GI symptom diary was completed, from which the frequency and severity of gut symptoms were assessed for eligibility. Eligible participants attended a baseline visit, during which questionnaires were completed and stool and blood samples were collected to assess microbiome and immunology. Patients were randomized to follow either low FODMAP or sham dietary advice for 4 weeks and completed a 7-day food, stool, and GI symptom diary in the final week. Finally, all outcomes were reassessed at an end-of-trial visit that was conducted within 3 days of the end of the 4-week period, during which diet allocation was continued.

Intervention and Control

Low FODMAP and sham dietary advice were provided to all participants by the same research dietician (S.R.C.) with extensive training and experience in delivering low FODMAP diet. The diet involves the restriction of dietary fructans, GOS, lactose, fructose in excess of glucose, and polyols, including sorbitol and mannitol, and is described in detail elsewhere.[24] The selection of an appropriate control group and difficulties in masking intervention and control are challenging in dietary intervention studies, but for research on dietary advice (which most closely mimics clinical practice), "sham" dietary advice is considered gold standard.[25] The sham diet in this trial aimed to provide patients in the control group with an exclusion diet of similar intensity and burden to low FODMAP diet, while not affecting nutrient, fiber or FODMAP intakes. The sham diet has been used successfully in the only randomized, placebo-controlled trial of low FODMAP dietary advice in IBS.[9] Dietary counseling for both low FODMAP diet and sham diet lasted approximately 20 minutes and both groups received written information.

Dietary compliance to both diets was encouraged at weekly telephone contact. Compliance with the diet was assessed at end of the trial using the single question: "During the 4-week trial I have followed the diet…": never/rarely (<25% of the time), sometimes (25%–50% of the time), frequently (51%–75% of the time), or always (76%–100% of the time). For the purposes of per protocol (PP) analysis, compliance was defined as following diet "always" (76%–100% of the time) during the trial.

Outcomes

The primary outcome was the change in IBS Severity Scoring System (IBS-SSS) during the trial, compared between groups. Predefined secondary outcomes included other measures of gut symptoms (total IBS-SSS score, proportion of patients achieving a 50-point IBS-SSS reduction, global symptom question; GI symptom rating scale [GSRS]), disease-specific HR-QOL, stool frequency and consistency, clinical disease activity, inflammatory markers, dietary intake, microbiome composition and function, short chain fatty acid (SCFA) concentrations, and peripheral T-cell phenotype. All predefined secondary outcomes were included in the study protocol before study commencement. Exploratory outcomes included responders defined as achieving at least a 50% reduction in total IBS-SSS score during the trial.

Clinical Outcomes

Gut symptoms were evaluated at baseline and end of trial using the IBS-SSS[26] and the GSRS.[27] The global symptom question was used to assess adequate relief of GI symptoms at end of trial. Disease-specific HR-QOL was assessed using the UK-specific IBD questionnaire.[28] Stool frequency and consistency were measured using the Bristol Stool Form Scale,[29] which has undergone extensive validation.[30]

Disease Activity

At baseline and end of trial, disease activity was assessed using the Harvey-Bradshaw Index for CD[31] and the Partial Mayo Score for UC.[32] Patient-perceived IBD control was assessed in all patients using the IBD Control questionnaire.[33] Fecal calprotectin concentrations were determined using enzyme-linked immunosorbent assay and serum CRP concentrations were determined using a standard assay in the hospital laboratory.

Dietary Intake

Dietary intake was measured at baseline and end of trial using 7-day food records. A nutrient composition database (Nutritics, Dublin, Ireland) was used for assessment of nutrient and fiber intakes, and into a bespoke database to assess FODMAP intake (Monash University, Melbourne, Australia).

Microbiome Composition, Function, and SCFA

A quantitative metagenomic pipeline following the International Human Microbiome Standards (IHMS; http://www.microbiome-standards.org) was used to assess GI microbiome composition and function.[34]

A fresh stool sample was collected at baseline and end of trial and stored immediately on ice. The sample was homogenized and stored at −80°C (IHMS SOP 04 V2). DNA extraction was performed following IHMS SOP 07 V2. DNA was quantitated using Qubit Fluorometric Quantitation (ThermoFisher Scientific, Waltham, MA) and qualified on a

Fragment Analyzer (Agilent Technologies, Santa Clara, CA). The sequencing library was built using 3 μg of high molecular weight DNA (>10 kbp). DNA was sheared into fragments of approximately 150 base pairs (bp) using an ultrasonicator (Covaris, Woburn, MA) and fragment library construction was performed using the 5500 Solid Fragment 48 Library Core Kit (ThermoFisher Scientific). Fragment libraries were sequenced using the Ion Proton Sequencer (ThermoFisher Scientific), generating a minimum of 20 million high-quality reads of 150 bp per library. Gene abundance profiling was performed by mapping high-quality reads to the 9.9 million gene-integrated reference catalog of the human microbiome[35] using Bowtie 2 with a 95% identity threshold.[36] The gene abundance profiling table was generated via a 2-step procedure using METEOR. The gene abundance table was processed for rarefaction and normalization using the MetaOMineR (momr) R package.[37] To decrease technical bias due to different sequencing depth and artifacts of sample size on low abundance genes, read counts were rarefied to 14 million reads per sample by random sampling without replacement. The resulting rarefied gene abundance table was normalized according to the FPKM (fragments per kilobase of exon model per million reads mapped) strategy. Metagenomic species (MGS) are co-abundant gene groups with more than 500 genes corresponding to microbial species.[38] Taxonomical annotation was performed on all genes by sequence similarity using National Center for Biotechnology Information blast N; a species-level assignment was given if >50% of the genes matched the same reference genome of the National Center for Biotechnology Information database (November 2016 version) at a threshold of 95% of identity and 90% of gene length coverage. The remaining MGSs were assigned to a given taxonomic level from genus to superkingdom level, in which more than 50% of their genes had the same assignment level. Microbial gene richness (gene count) was calculated by counting the number of genes detected at least once in a given sample. MGS richness (MGS count) was calculated directly from the MGS abundance matrix.

The functional analysis is led using an MGP pipeline FantoMET (unpublished, 2018). Genes of the catalog were annotated using the Kyoto Encyclopedia of Genes and Genomes (KEGG)82 database. KEGG and Gut Metabolic Modules were reconstructed in each metagenomic species using their pathway structures (and potential alternative pathways).[39] Abundance of each detected module in a metagenomic species corresponds to the abundance of the metagenomic species as described in the method section. Abundance of a given module in a sample is computed as the sum of the abundances of the module in each metagenomic species.

Fecal SCFA concentrations were assessed using a standard gas-liquid chromatography protocol, using the 9890A series gas-liquid chromatography system (Agilent Technologies) and fecal pH was measured using a pH probe (InLab and FE20 FiveEasy Benchtop pH meter; Mettler Toledo, Columbus, OH).

Peripheral T-Cell Phenotype

Blood samples were collected at baseline and end of trial in sodium-heparin vacutainer tubes (BD Bioscience, San Jose, CA) and processed within 3 hours. Whole blood was labeled with fluorescently conjugated monoclonal antibodies to detect CD3 T cells, as well as naïve (CD45RA+) and effector/memory (CD45RA−) CD4 and CD8 T cells, and Vδ2 unconventional T cells. The gut-homing integrin $\alpha4\beta7$ was detected by labeling with anti-$\beta7$.[40,41] The BD FACSCanto II flow cytometer was used to acquire data, the FACS DIVA software (BD Bioscience) was used to collect the data, and Winlist software (Verity, Topsham, ME) was used to analyze the data.

Statistical Analysis

Sample size was calculated based on the primary outcome, with expected values taken from a previous trial in IBS comparing low FODMAP (mean IBS-SSS change −117 points, standard deviation [SD] 86) with sham advice (−44 points, SD 72).[9] With a power of 80% and 2-sided significance of 5%, a sample size of 44 participants was required. Assuming 15% attrition, a sample size of 52 participants (26 per group) was required.

Pre-planned comparisons of the primary (change in IBS-SSS score during trial) and secondary outcomes between the low FODMAP and sham diet at end of trial were performed. Subgroup analysis for UC and CD were pre-planned in the protocol and were conducted for all outcomes. The proportion of participants achieving at least a 50% reduction in total IBS-SSS score during the trial was an exploratory outcome compared between the diet groups.

Data on gut symptoms, HR-QOL, disease activity, inflammatory markers and peripheral T-cell phenotype were analyzed by intention-to-treat (ITT), followed by PP, the latter consisting of patients who completed the trial, did not violate protocol, and were "always" compliant with dietary intervention. Data on microbiome composition and SCFA concentrations are presented for the PP population.

Clinical variables, SCFA, and T-cell phenotype data were compared between groups at end of trial using analysis of covariance, with corresponding baseline values as a covariate, and are therefore presented as estimated marginal mean (standard error of the mean [SEM]). Categorical variables, presented as number (%), were compared between groups using the χ^2 or Fisher's Exact Test. Statistical analysis was performed using SPSS Version 24.0 (IBM, Chicago, IL).

Differences in gut microbial alpha and beta diversity between low FODMAP and sham diet were calculated using Mann-Whitney tests, whereas comparisons of taxonomical and functional composition were assessed using likelihood ratio tests. Microbiome composition was analyzed using 2 approaches. First, an untargeted analysis of the relative abundance of all characterized bacteria (a total of 616 species and strains) was performed. Then, a targeted analysis of the specific species and strains of interest with regard to the low FODMAP diet or IBD was performed. P values were adjusted for multiple comparisons using the Benjamini Hochberg approach for both the untargeted and targeted analyses. Microbiome bioinformatics was performed using R version 1.0.136 (Vienna, Austria). Differences are stated as statistically significant where $P \leq .05$.

Results

Recruitment occurred between February 2016 and May 2017. Of 155 screened participants, 103 were ineligible

(Supplementary Figure 1). Fifty-two patients were randomized to low FODMAP (n = 27) and sham diets (n = 25). All 52 randomized patients were included in the ITT analysis. Six participants were withdrawn; 2 withdrew consent during the trial (1 in each group), 1 became pregnant (sham diet), 2 commenced steroids due to an IBD flare (1 in each group), and 1 commenced antibiotics for an unrelated infection (low FODMAP diet). Of the 46 patients completing the trial, 3 were noncompliant with the diet, leaving 43 participants (21 low FODMAP diet, 22 sham diet) in the PP analysis.

Baseline characteristics are displayed in Table 1. There were no differences in IBD characteristics between diet groups. However, participants in low FODMAP group were younger (33, SD 11 years) than in the sham diet (40, SD 13 years, $P = .031$). There was a greater proportion of participants of white ethnicity in the low FODMAP (25/27, 92%) than the sham group (19/25, 76%, $P = .029$).

Adverse Events

There were 6 adverse events during the trial. Two participants had an IBD relapse (1 in each group) and 1 commenced antibiotics unrelated to IBD (low FODMAP). All 3 participants were withdrawn from the trial because of meeting exclusion criteria. One participant reported a worsening of abdominal pain lasting 2 days that resolved (sham diet). Flu-like symptoms and sinusitis were reported (1 in each group), both of which were unrelated to the diet. No serious adverse events were recorded.

Table 1. Baseline Demographic and IBD Characteristics of the Study Groups

Variable	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*
Age (*yr*)	33 (11)	40 (13)	**.031**
Male, n (%)	10 (37)	13 (52)	.278
Body mass index (kg/m^2)	24 (3)	25 (4)	.526
Ethnicity, white, n (%)	25 (92)	19 (76)	**.029**
Rome III criteria, n (%)			.150
IBS-Diarrhea predominant	10 (37)	5 (20)	
IBS-Mixed subtype	2 (7)	2 (8)	
IBS-Unsubtyped	0 (0)	1 (4)	
Functional bloating	15 (56)	13 (52)	
Functional diarrhea	0 (0)	4 (16)	
Baseline IBS-SSS score	222 (76)	227 (81)	.847
CD, n (%)	14 (52)	12 (48)	.781
Time since diagnosis, *yr*	7 (8)	11 (11)	.187
Montreal classification			
Crohn's disease location, n (% of CD)			.773
Ileal	4/14 (29)	2/12 (17)	
Colonic	4/14 (29)	4/12 (33)	
Ileocolonic	6/14 (42)	6/12 (50)	
CD behavior, n (% of CD)			.949
Nonstricturing, nonpenetrating	9/14 (64)	8/12 (66)	
Stricturing	3/14 (21)	2/12 (17)	
Penetrating	2/14 (14)	2/12 (17)	
Perianal disease, n (% of CD)	4/14 (29)	3/12 (25)	1.000
UC extent, n (% of UC)			.403
Proctitis	6/13 (46)	3/13 (23)	
Left-sided	4/13 (31)	7/13 (54)	
Extensive	3/13 (23)	3/13 (23)	
Medication, n (%)			
Mesalamine	12 (44)	11 (44)	.974
Thiopurine	9 (33)	12 (48)	.282
Infliximab	10 (37)	4 (16)	.087
Adalimumab	2 (7)	4 (16)	.411
Vedolizumab	0 (0)	1 (4)	.481
Methotrexate	2 (7)	1 (4)	1.000
Clinical symptoms			
Total IBS-SSS score, mean (SD)	222 (76)	227 (81)	.847
Stool frequency, mean (SD)	1.8 (1.3)	2.1 (1.0)	.282
Stool consistency, proportion normal stools (type 3, 4, 5), mean (SD)	66 (29)	64 (32)	.869

NOTE. Continuous variables are presented as mean (SD) and were compared between groups using unpaired *t*-test, and categorical variables are presented as n (%) and were compared between groups using χ^2 test. Bold text indicates statistically significant *P* values ($P \leq .05$).

Table 2. IBS Severity Scoring System Scores, Global Symptom Question, and Stool Frequency and Consistency at End of Trial

	All participants			UC			CD		
	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*	Low FODMAP diet (n = 13)	Sham diet (n = 13)	*P*	Low FODMAP diet (n = 14)	Sham diet (n = 12)	*P*
Change in IBS-SSS score, mean (SEM)	−67 (12)	−34 (13)	.075	−77 (15)	−29 (15)	**.031**	−55 (99)	−42 (43)	.515
Total IBS-SSS score, mean (SEM)	158 (12)	190 (13)	.075	135 (15)	183 (15)	**.031**	170 (96)	208 (95)	.515
Pain severity	22 (3)	30 (3)	.098	20 (4)	29 (4)	.123	24 (22)	32 (20)	.475
Days of pain (days)	36 (5)	38 (5)	.781	31 (6)	35 (6)	.645	36 (37)	48 (37)	.871
Bloating severity	23 (3)	34 (3)	**.021**	21 (4)	31 (4)	.113	22 (20)	39 (17)	.071
Satisfaction with bowels	39 (3)	47 (4)	.103	31 (5)	45 (5)	.068	52 (18)	43 (26)	.487
Impact on life	38 (3)	41 (3)	.521	34 (4)	41 (4)	.199	36 (25)	46 (25)	.799
IBS-SSS 50% reduction, n (%)	9 (33)	1 (4)	**.012**	4 (31)	0 (0)	.096	5 (36)	1 (8)	.170
Adequate relief, n (%)	14 (52)	4 (16)	**.007**	7 (54)	2 (15)	.097	7 (50)	2 (17)	.110
Stool frequency (per d), mean (SEM)	1.7 (0.1)	2.1 (0.1)	**.012**	1.8 (0.1)	2.0 (0.1)	.501	1.7 (0.1)	2.1 (0.1)	**.019**
Stool consistency									
Daily BSFS score, mean (SEM)	4.3 (0.2)	4.4 (0.2)	.606	4.0 (0.2)	4.4 (0.2)	.191	4.6 (0.2)	4.4 (0.2)	.673
Stool consistency, proportion normal stools (Type 3, 4, 5), mean proportion (SEM)	65 (5)	69 (5)	.478	66 (6)	73 (6)	.487	63 (6)	65 (7)	.815

NOTE. Continuous variables are presented as estimated marginal mean (SEM) and were compared between groups using an analysis of covariance with the corresponding baseline values as a covariate, and categorical variables are presented as n (%) and were compared between groups using χ^2 test. Bold text indicates statistically significant *P* values ($P \leq .05$).
BSFS, Bristol Stool Form Scale.

Gut symptoms and HR-QOL

There was a greater reduction in total IBS-SSS score following low FODMAP (−67, SEM 12) compared with sham diet (−34, SEM 13), although the difference was not statistically significant ($P = .075$) (Table 2). There was a significantly lower score for bloating severity (IBS-SSS) following low FODMAP (23, SEM 3) than sham diet (34, SEM 3, $P = .021$). The PP analysis showed similar results to the ITT analysis for all IBS-SSS outcomes. The exploratory analysis revealed that significantly more participants achieved a 50% reduction in IBS-SSS following low FODMAP (9/27, 33%) than sham diet (1/25, 4%, P=.012) (Table 2).

Predefined subgroup analyses of UC (n = 26) and CD (n = 26) were performed for all clinical outcomes (Table 2). In UC, there was a significantly greater reduction in IBS-SSS score following low FODMAP compared with sham diet ($P = .031$), as well as a significantly lower end-of-trial IBS-SSS score ($P = .031$). In CD, there was no difference in change in IBS-SSS score following low FODMAP compared with sham diet ($P = .515$), or in end-of-trial IBS-SSS score ($P = .515$).

Significantly more patients reported adequate relief of gut symptoms following low FODMAP (14/27, 52%) than sham diet (4/25, 16%, $P = .007$). There were no differences in the proportion of patients reporting adequate relief between low FODMAP and sham diet in the subgroup analysis of UC (7/13, 54% vs 2/13, 15%, $P = .097$) or CD (7/14, 50% vs 2/12, 17%, $P = .110$).

The severity of flatulence, as measured using the GSRS, was significantly lower during low FODMAP (0.9, SEM 0.1) compared with sham diet (1.2, SEM 0.1, $P = .035$); however, no other symptoms, including abdominal pain, were different between groups (Supplementary Table 1). Significantly lower daily stool frequency was reported following low FODMAP (1.7, SEM 0.1) than sham diet (2.1, SEM 0.1, $P = .012$), but there was no difference in the proportion of stools of normal consistency (types 3–5) between low FODMAP (65% normal consistency, SEM 5%) and sham diet (69%, SEM 5%, P=.478) (Table 2).

Total IBD questionnaire score was significantly greater (indicating better HR-QOL) following low FODMAP (81.9, SEM 1.2) than sham diet (78.3, SEM 1.2, $P = .042$). Specifically, the Bowel II domain score (effects of GI symptoms on HR-QOL) was significantly greater following low FODMAP (76.5, SEM 2.0) than sham diet (70.0, SEM 2.1, $P = .031$).

Disease Activity

At baseline, most participants had CRP <5 mg/L (50/52, 96%) and fecal calprotectin <100 μg/g (43/52, 83%).

In CD, there was no difference in Harvey-Bradshaw Index score between low FODMAP (3.2, SEM 0.4) and sham diet (3.4, SEM 0.5, $P = .814$) at end of trial. In UC, there was no difference in Partial Mayo score between low FODMAP (0.2, SEM 0.2) and sham diet (0.2, SEM 0.2, $P = .951$). The IBD-control score demonstrated greater patient-perceived control of IBD following low FODMAP (88.3, SEM 4.3) compared with sham diet (74.3, SEM 4.5, $P = .028$); these differences were seen specifically in UC (94.2, SEM 6.6 vs 71.3, SEM 6.6, $P = .022$) but not in CD (81.4, SEM 5.2 vs 79.1, SEM 5.7, $P = .768$).

Importantly, there was no difference in end-of-trial fecal calprotectin between low FODMAP (60.0 μg/g, SEM 9.4) and sham diet (59.6 μg/g, SEM 9.8, $P = .976$) or in serum CRP concentration between low FODMAP (2.0 mg/L, SEM 0.3) and sham diet (1.6 mg/L, SEM 0.3, $P = .246$).

Further fecal calprotectin concentration data (including UC and CD subgroup analyses and baseline compared with end-of-trial comparisons) are presented in Supplementary Table 2.

Dietary Intake and Compliance

In low FODMAP and sham diet groups, 24 (88%) of 27 and 25 (100%) of 25 participants reported following the diet "always" (76%–100% of the time) ($P = .230$). In support of high levels of self-reported compliance, intakes of fructans, GOS, lactose, excess fructose, sorbitol, and mannitol were significantly lower in the low FODMAP compared with sham diet (Supplementary Table 3).

Seven-day food diaries revealed significantly lower energy, protein, fat, sugars, calcium, phosphorus, and iodine intake in low FODMAP compared with sham diet (Supplementary Table 3). There were no significant differences in intakes of any other nutrients between diet groups.

Microbiome Composition, Function, and SCFA

An average of 22,690,418 sequencing reads of 150 bp were obtained for each sample, with an average 14,310,652 reads mapping uniquely to the gene catalog (67% of reads).

There was no difference in gene count, species count, phyla distribution, or any index of α-diversity or β-diversity between diet groups at end of trial (Figure 1*A–D*).

Of 616 species present in more than 5% of subjects, the abundance of 29 species (4.7%) was significantly affected ($P \leq .05$) by the diet (untargeted microbiome analysis) (Figure 2). None of these remained significant when adjusted for multiple comparisons. In the targeted microbiome analysis (Table 3), relative abundance of total Bifidobacteria was not significantly different between low FODMAP and sham diet ($P = .073$); however, *Bifidobacterium longum* ($P = .005$, $Q = .017$) and *Bifidobacterium adolescentis* ($P = .003$, $Q = .017$) were significantly lower, and *Bifidobacterium dentium* abundance was higher ($P = .035$, $Q = .096$) following the low FODMAP diet. Abundance of total *F prausnitzii* species was significantly lower following low FODMAP compared with sham diet ($P = .038$). However, no *F prausnitzii* strains were significantly lower and, interestingly, *F prausnitzii* SL3/3-M21/2 was higher following low FODMAP compared with sham diet (Table 3).

Differences in microbial abundance in the UC and CD subgroup analyses are presented in the Supplementary Table 4.

The metabolic potential of the microbiome was assessed using functional metagenomics. The abundance of 34 KO (KEGG orthology) groups were significantly different

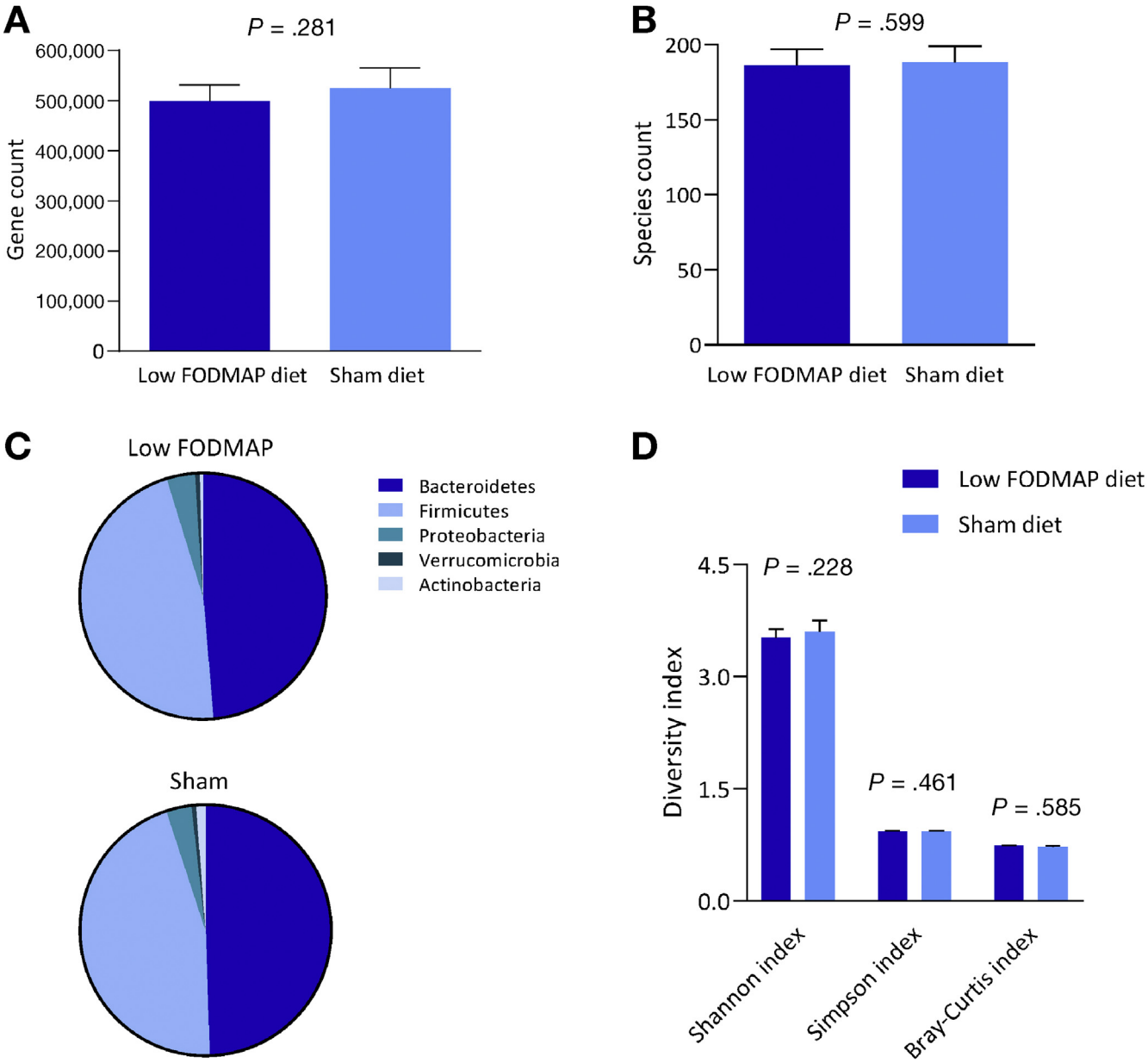

Figure 1. Alpha and beta diversity and phyla distribution at end of trial. (*A*) Microbial gene richness. (*B*) Microbial species richness. (*C*) Phyla distribution. (*D*) Shannon index, Simpson index, and Bray-Curtis index.

($P \leq .05$) between low FODMAP and sham diet groups (Figure 3). Among the modules significantly higher in abundance following low FODMAP compared with sham diet were cellobiose transport system and propionate production, and among modules lower in abundance were lactose and galactose degradation pathways and glutamate transport system and the putative zinc/manganese transport system. None of these remained significant following false discovery rate (FDR) correction.

There were lower fecal concentrations of total SCFA following low FODMAP (398 mg/100 g feces, SEM 37) compared with sham diet (505 mg/100 g feces, SEM 36, $P = .049$) in the PP population. In UC, total SCFAs were significantly lower following low FODMAP (386 mg/100 g feces, SEM 53) than sham diet (553 mg/100 g feces, SEM 55, $P = .041$); however, in CD there was no difference between diet groups (409 mg/100 g feces, SEM 51) and sham diet (463 mg/100 g feces, SEM 46, $P = .453$). Individual SCFA concentrations and fecal pH in the ITT and PP populations, and in UC and CD, are provided in the Supplementary Table 5.

Peripheral T-Cell Phenotype

There were no differences in absolute numbers or proportions of circulating naïve or effector/memory CD4 and CD8 T-cell subsets, or in cells within these subsets expressing $\alpha 4\beta 7$, between diet groups at the end of the trial (Supplementary Table 6). Although there was no difference in the total number of Vδ2 T cells between groups, there

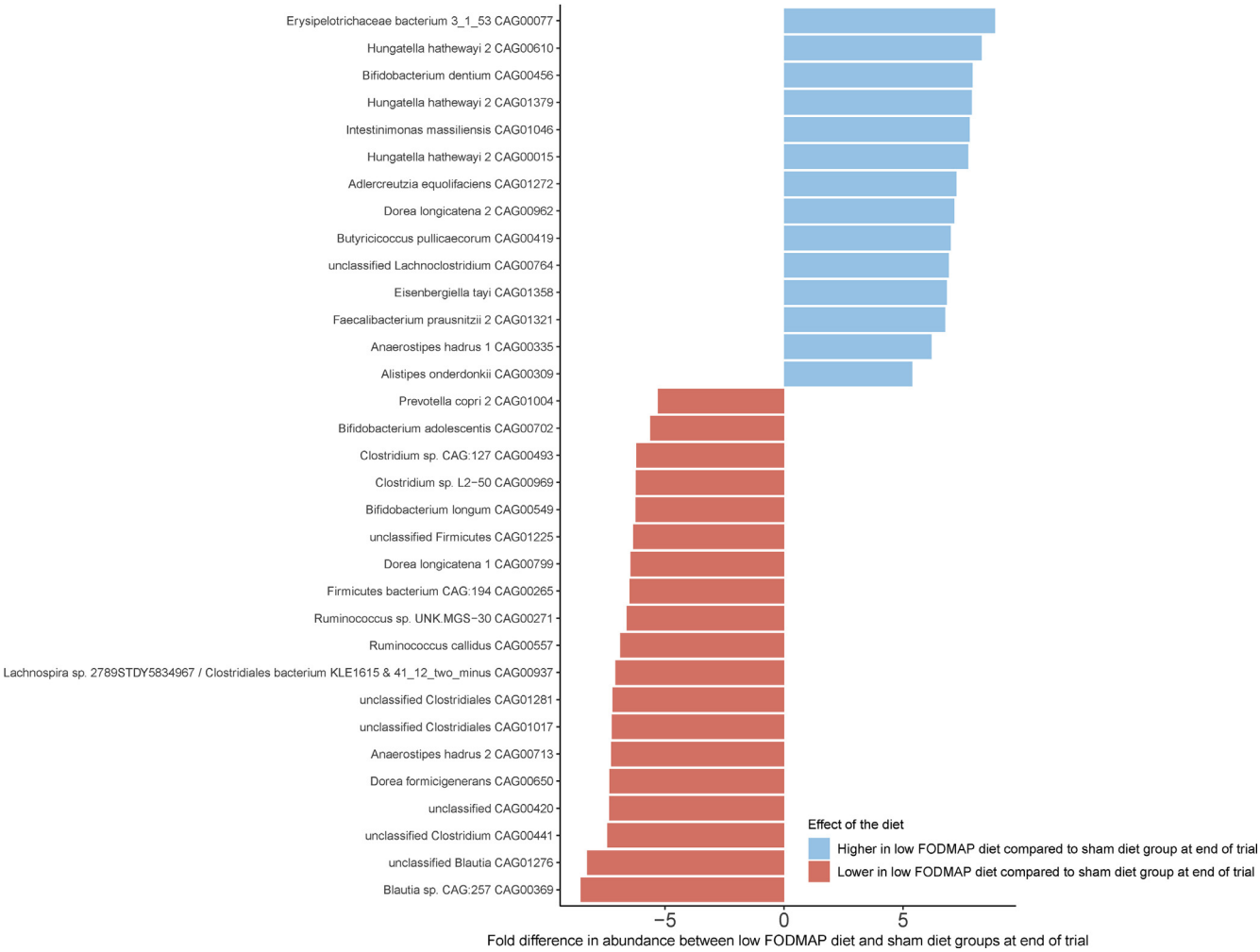

Figure 2. Untargeted microbiome analysis: fold difference in abundance of 33 species that were significantly different ($P < .05$) between diet groups at end of trial. None of these remained significant after FDR correction

were significantly fewer $\alpha4\beta7$ positive Vδ2 T cells following low FODMAP compared with sham diet (Supplementary Table 6).

Discussion

This is the first randomized, placebo-controlled trial demonstrating that low FODMAP dietary advice improves aspects of gut symptoms and HR-QOL in patients with quiescent IBD compared with sham dietary advice. Low FODMAP diet did not alter overall microbiome diversity or any species or strains on an untargeted analysis, although it altered some immune-regulatory components of the GI microbiome during a targeted analysis. Nonetheless, there was no impact on clinical disease activity or markers of inflammation.

The finding of no significant difference in change in IBS-SSS despite higher rates of adequate relief following low FODMAP diet contrasts with a recent trial in IBS that reported a significant reduction in IBS-SSS but no difference in adequate relief.[9] The effectiveness of low FODMAP diet in the current trial confirms the findings of a nonblinded randomized controlled trial in IBD in which more patients responded to low FODMAP diet than the normal diet group,[13] although the IBS-SSS response rate to low FODMAP diet in the current trial was significantly lower, which likely relates to the lack of blinding in the previous trial.

The subgroup of patients with UC, but not CD, reported a significantly greater reduction in IBS-SSS score after low FODMAP compared with sham diet. Differing efficacy of drug[42] and dietary[43] interventions has been demonstrated between CD and UC previously, and may be explained by differing disease pathophysiology and location. Furthermore, patients with CD are more likely to have intestinal inflammation not detected through fecal calprotectin,[44] which could have abrogated GI symptom responses to the diet. This subgroup analysis, although planned a priori, should be interpreted with caution because the trial was not powered for this comparison.

As expected from the proposed mechanism of action of low FODMAP diet, and consistent with previous studies in both IBS and IBD,[9–10,13,15] the greatest impact was on bloating and flatulence. Interestingly, abdominal pain was not different between diet groups following the diet. Unlike

Table 3. Targeted Microbiome Analysis: Relative Abundance of *Bifidobacteria* Species and *Faecalibacterium prausnitzii* Strains Between Diet Groups at End of Trial

	Low FODMAP diet (n = 21)	Sham diet (n = 22)	*P*	*Q*-value
Bifidobacteria (total)	8.63^{-7} (4.41^{-7})	3.19^{-6} (3.59^{-6})	.073	-[a]
Bifidobacterium adolescentis	1.99^{-7} (2.78^{-7})	2.55^{-6} (5.48^{-6})	**.003**	**.017**
Bifidobacterium longum	1.24^{-7} (1.81^{-7})	6.95^{-7} (1.03^{-6})	**.005**	**.017**
Bifidobacterium animalis	1.87^{-9} (8.59^{-9})	1.00^{-8} (4.58^{-8})	.746	.768
Bifidobacterium bifidum	6.77^{-8} (1.35^{-7})	1.79^{-7} (3.38^{-7})	.066	.146
Bifidobacterium breve	2.39^{-8} (1.09^{-7})	2.21^{-9} (1.09^{-7})	.768	.768
Bifidobacterium dentium	1.68^{-8} (5.23^{-8})	4.72^{-9} (1.75^{-8})	**.035**	.096
Bifidobacterium pseudocatenulatum	3.55^{-8} (1.17^{-7})	1.48^{-7} (4.42^{-7})	.473	.651
Faecalibacterium prausnitzii (total)	1.12^{-5} (1.42^{-5})	1.65^{-5} (1.35^{-5})	**.038**	-[a]
F prausnitzii A2-165	2.33^{-6} (1.93^{-6})	2.81^{-6} (2.81^{-6})	.186	.341
F prausnitzii SL3/3-M21/2	1.52^{-6} (2.08^{-6})	1.35^{-6} (1.68^{-6})	**.003**	**.017**
F prausnitzii L2-6	3.61^{-6} (4.26^{-6})	1.30^{-6} (1.32^{-6})	.750	.768
F prausnitzii cf. KLE1255	2.68^{-6} (3.48^{-6})	3.41^{-6} (3.89^{-6})	.310	.488

NOTE. All data are presented as mean (SD) relative abundance and were compared between groups adjusted for baseline abundance and end-of-trial stool consistency. Bold text indicates statistically significant *P* values ($P \leq .05$).
[a]Total Bifidobacteria and *F prausnitzii* abundance were not adjusted for multiple comparisons because these were analyzed separately at the genus level.

IBS, there is only limited evidence that abdominal pain in quiescent IBD relates to luminal distension.[45] Furthermore, at trial entry, 62% of participants fulfilled functional bloating or functional diarrhea criteria, but not IBS, and therefore had minimal abdominal pain.

In both the untargeted and targeted microbiome analyses, the abundance of fecal *B longum*, *B adolescentis,* and total *F prausnitzii* were lower following low FODMAP compared with sham diet, in agreement with the findings of some previous IBS trials,[9,16] but in contrast with a previous trial in which no changes in these bacteria were demonstrated in a small (n = 9) subgroup of patients with CD following low FODMAP diet.[21] Following adjustment for multiple comparisons, these findings remained significant in only the targeted microbiome analysis, as a result of fewer comparisons. These microbial alterations are likely a result of changes in colonic fermentable substrate; Bifidobacteria preferentially ferment fructans and GOS, whereas *F prausnitzii* indirectly use them through cross-feeding.[46]

The reduction in Bifidobacteria and *F prausnitzii* during low FODMAP diet are of potential concern, as these bacteria have immune-regulatory effects, including consistent

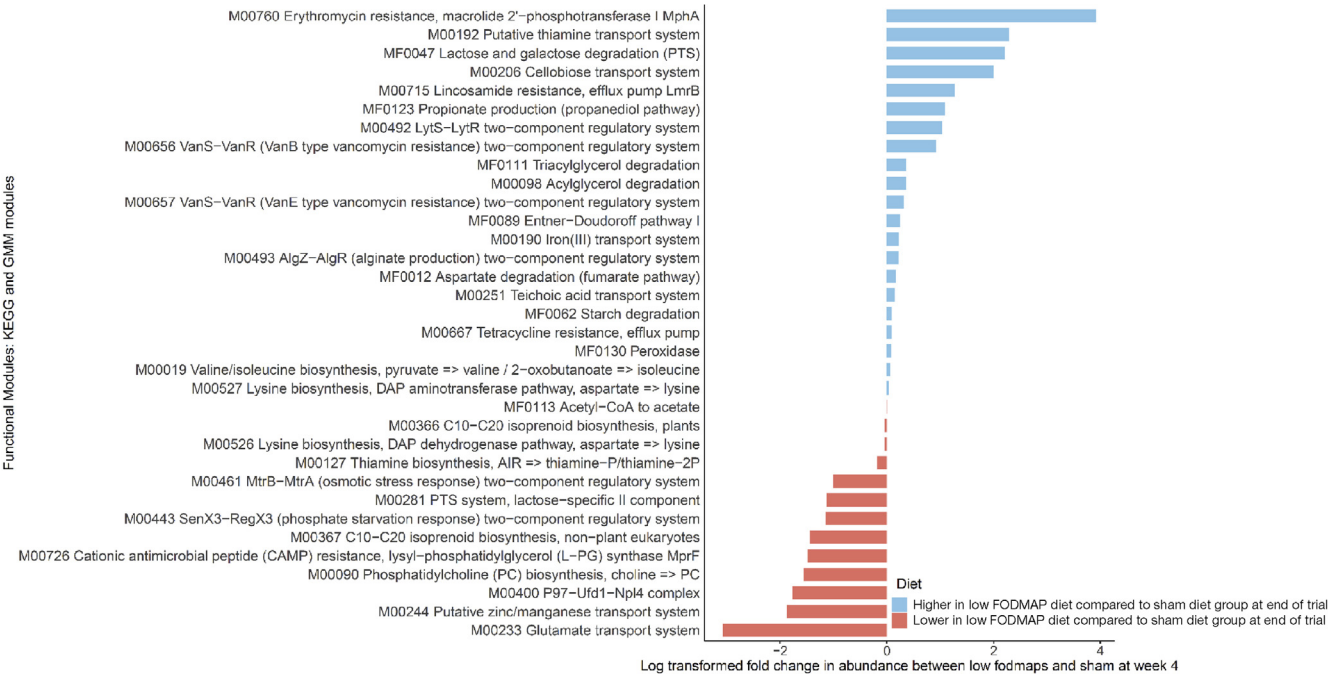

Figure 3. Fold difference in abundance of 34 functional modules with significantly different ($P < .05$) abundance between diet groups at end of trial. None of these remained significant after FDR correction.

evidence that Bifidobacteria and *F prausnitzii* increase peripheral blood mononuclear cell interleukin 10 production in vitro.[18,47] Furthermore, *F prausnitzii* is associated with lower postoperative CD recurrence.[18] Despite this, there were no detrimental effects of low FODMAP diet on fecal calprotectin or CRP. The lower proportion of $\alpha 4\beta 7+$ V$\delta 2+$ T cells following low FODMAP diet may relate to variability in and the possible effect of thiopurine exposure on V$\delta 2+$ T-cell numbers between individuals,[48] because there was no difference in absolute numbers of this T-cell subgroup between diet groups.

The lack of effect of low FODMAP diet on inflammation, despite microbiome alterations, may be explained in several ways. First, much of the evidence of immune-regulatory effects of *F prausnitzii* relate to strain A2-165,[18,49] which was not different between diet groups. Second, other GI bacteria, such as *Roseburia intestinalis* and *Lactobacillus* species, also exert immune-modulatory effects and were not altered by the diet.[47,50] Finally, the impact of longer-term restriction on inflammation in IBD is unknown because trial duration was 4 weeks.

Abundance of hydrogen-consuming *Adlercreutzia equolifaciens* was higher following low FODMAP compared with sham diet, confirming findings in IBS.[51] An emerging hypothesis is that low FODMAP diet may reduce luminal gas through both reduced fermentation and increased abundance of hydrogen-consuming bacteria; however, this requires confirmation.

The reduced SCFA concentrations in UC specifically may be explained by differences in baseline microbiome composition between UC and CD[52] and also the greater GI symptom responses to low FODMAP diet in UC. Furthermore, because the colon is the site of SCFA generation, the degree of colonic disease involvement may contribute to differences in SCFA generation between CD and UC. It is tempting to speculate that the UC microbiome possesses greater saccharolytic potential, which is thus more likely to respond to reduced fermentable substrate with a decline in GI symptoms and a concomitant decline in SCFA. However, this requires confirmation in studies powered to detect differential effects of the diet in UC and CD.

The analysis revealed differing abundance in numerous microbial genomic functional pathways between diet groups at end of trial. The abundance of acetyl-CoA to acetate pathway was lower following low FODMAP diet, in line with lower fecal acetate concentrations (Supplementary Information). Although fecal propionate concentrations were not affected by diet, the abundance of propionate production pathway was greater following low FODMAP diet.

A major strength of this trial is that low FODMAP dietary advice was compared with sham dietary advice, providing the first placebo-controlled evidence of effectiveness in IBD. Unlike feeding studies, which are ideal for proof-of-concept, the current trial methodology assessed the effectiveness of a dietary intervention as used in clinical practice. This trial also represents the first use of metagenomic sequencing providing a comprehensive assessment of GI microbiome composition and functional potential following low FODMAP diet. Furthermore, this is the first assessment of the effects of low FODMAP diet on immune function in IBD.

The trial design did not permit blinding of the investigator to treatment allocation. Furthermore, the observed alterations in certain nutrient intakes following low FODMAP diet, as demonstrated in previous low FODMAP diet trials,[53,54] may be confounders in interpreting the effects of low FODMAP diet in this trial. Finally, although not all patients fulfilled the IBS criteria at baseline, the IBS-SSS was chosen for gut symptom assessment because it encompasses the predominant symptoms of IBS (abdominal pain/altered bowel habit), functional bloating (bloating/distension), and functional diarrhea (altered bowel habit).

Quiescent IBD was defined, in part, as having fecal calprotectin $\leq$250 μg/g, as this has been shown to have optimal sensitivity and specificity for the identification of quiescent IBD.[22] Theoretically, this may have resulted in recruitment of some participants with very mildly active disease. However, only 16 (31%) of 52 had a fecal calprotectin above 50 μg/g and 9 (17%) of 52 above 100 μg/g at enrollment, thus likely having minimal effects on trial outcomes.

In conclusion, the first randomized, placebo-controlled dietary advice trial of low FODMAP diet in quiescent IBD reports improvement in some GI symptoms and HR-QOL. Despite a decline in Bifidobacteria and *F prausnitzii* abundance, the diet did not adversely affect disease activity. Therefore, we propose that a 4-week low FODMAP diet with expert advice and intensive follow-up is safe and effective in the management of persistent gut symptoms in quiescent IBD, but caution should be taken in longer-term use.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.09.024.

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Acknowledgments
Author contributions: SRC and KW were grant holders; SRC, JOL, AJS, MCL, PMI, and KW conceived and designed the study; SRC, PMI, and JOL recruited participants; SRC collected, collated, and analyzed the data; KW supervised data analysis; SRC and KW interpreted the data; SRC, AJS, and NEM performed flow cytometry and analysis; SF, SBI, NM, NP, HR, NG, FL, and SDE advised on and performed metagenomic sequencing and bioinformatics analysis; SRC wrote the manuscript; KW performed extensive editing of the manuscript; all authors reviewed and approved the final manuscript for submission.

Conflicts of interest
These authors disclose the following: Kevin Whelan and Miranda C. Lomer are the co-inventors of a mobile application to assist patients following the low FODMAP diet. Kevin Whelan has received consultancy fees from Danone, and a research grant from Clasado. The remaining authors disclose no conflicts.

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Supplementary Methods

Microbiome Composition and Function

The gene abundance profiling table was generated via a 2-step procedure using METEOR. First, reads uniquely mapping to a gene in the catalog were attributed to their corresponding genes. Second, reads mapped to multiple shared genes in the catalog were attributed according to the ratio of the unique mapping counts of the genes.

The 9.9 million–gene catalog was constructed by clustering 1436 MGS from 1267 human gut microbiome samples, as previously described.[1] MGS abundances were estimated as the mean abundance of the 50 genes defining a robust centroid of the cluster.

Supplementary Results

Gut Symptoms

The incidence of moderate or severe GI symptoms and 7-day severity of symptoms (as assessed using the GSRS) is presented in Supplementary Table 1. There were no differences between the diet groups in the incidence or severity of any symptoms, except for lower flatulence severity following low FODMAP compared with sham diet

Dietary Intake

Daily intakes of energy, protein, fat, sugars, calcium, phosphorus, and iodine were significantly lower following the low FODMAP compared with sham diet at end of trial (Supplementary Table 2).

There were no differences in the proportion of patients meeting national macronutrient, micronutrient and fiber recommendations between the low FODMAP and sham diet groups at end of trial, or between baseline and end of trial in either diet group (data not shown).

Microbiome Composition and SCFA

Supplementary Table 3 displays the relative abundance of the bacterial species or strains that were significantly different between the diet groups at end of trial in the untargeted UC and CD subgroup microbiome analyses.

There were no differences in α-diversity or β-diversity between the diet groups in UC or CD (data not shown).

There were no differences in concentrations of individual fecal SCFAs between diet groups at end of trial in the ITT population (Supplementary Table 4). However, in the PP population, there were significantly lower concentrations of total SCFAs following low FODMAP diet compared with sham diet (Supplementary table 4). Specifically, fecal acetate was significantly lower following low FODMAP diet compared with sham diet.

In patients with UC on the low FODMAP diet, compared with sham diet, there were lower concentrations of acetate (209 mg/100 g, SD 109 vs 328 mg/100 g, SD 154, $P = .037$), butyrate (66 mg/100 g, SD 40 vs 111 mg/100 g, SD 75, $P = .050$) and valerate (6 mg/100 g, SD 4 vs 13 mg/100 g, SD 10, $P = .044$) in the PP population. In patients with CD, there was a significantly lower end-of-trial isobutyrate concentration following the low FODMAP diet (7 SD 3 mg/100 g) compared with the sham diet (11 mg/100 g, SD 3, $P = .024$). There were no differences in the concentrations of any other individual SCFA in patients with CD in the PP population (data not shown).

Peripheral T-Cell Phenotype

There were no differences in proportion of T cells expressing $\alpha4\beta7$ between diet groups in patients with UC. In CD there were significantly fewer naïve CD4+ T cells (58.2%, SEM 4.5% vs 79.8%, SEM 5.7%; $P = .008$), naïve CD8+ T cells (62.6%, SEM 4.0% vs 76.4%, SEM 4.9%; $P = .042$) and effector/memory CD8+ T cells (59.5%, SEM 3.0% vs 70.3%, SD 3.7%; $P = .036$) expressing $\alpha4\beta7+$ on low FODMAP compared with sham diet.

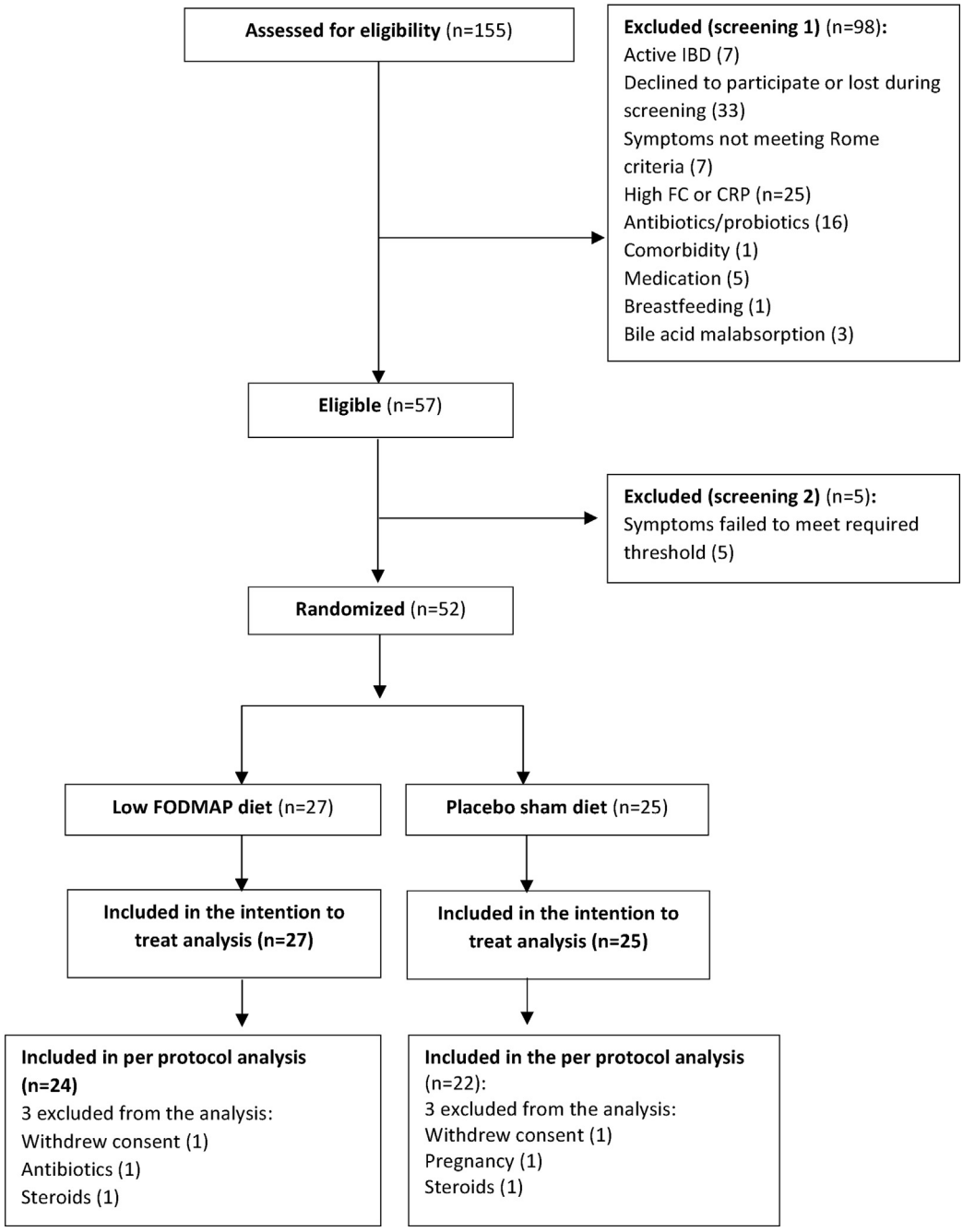
Fecal Calprotectin Between Baseline and End of Trial

There was no difference in fecal calprotectin concentrations between low FODMAP and sham diet groups at end of trial in either the CD (61.2 μg/g SEM 6.3 vs 68.4 μg/g SEM 6.8, $P = .448$) or the UC (55.9 μg/g SEM 18.2 vs 54.2 μg/g SEM 18.2, $P = .950$) subgroups.

There were no differences in fecal calprotectin at baseline compared with end of trial in low FODMAP or sham diet groups, and the same was true for the UC and CD subgroups (Supplementary Table 6).

Supplementary Reference

1. Nielsen HB, Almeida M, Juncker AS, et al. Identification and assembly of genomes and genetic elements in complex metagenomic samples without using reference genomes. Nat Biotechnol 2014;32:822.



Supplementary Figure 1. CONSORT diagram of participant flow through the trial.

Supplementary Table 1. Incidence and Severity of GI symptoms, as measured by the GSRS, at end of trial

	Incidence of moderate or severe symptoms[a]			Severity of GI symptoms[b]		
Symptom	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*
Pain	1.5 (0.3)	1.1 (0.3)	.220	0.9 (0.5)	0.7 (4.5)	.243
Heartburn	0.3 (0.1)	0.2 (0.1)	.514	0.2 (0.5)	0.1 (0.3)	.344
Acid regurgitation	0.3 (0.1)	0.2 (0.1)	.359	0.2 (0.5)	0.2 (0.5)	.504
Nausea	0.5 (0.1)	0.3 (0.1)	.283	0.3 (0.5)	0.3 (0.5)	.335
Gurgling	0.7 (0.2)	0.8 (0.2)	.858	0.6 (0.5)	0.6 (0.5)	.995
Bloating	1.4 (0.3)	1.7 (0.3)	.595	0.9 (0.5)	0.9 (0.5)	.628
Belching	0.2 (0.1)	0.5 (0.1)	.141	0.4 (0.5)	0.5 (0.5)	.312
Flatulence	1.4 (0.3)	2.1 (0.4)	.152	0.9 (0.5)	1.1 (0.6)	**.035**
Constipation	0.5 (0.2)	0.6 (0.2)	.768	0.3 (0.5)	0.3 (0.5)	.513
Diarrhoea	0.4 (0.1)	0.5 (0.1)	.507	0.2 (0.5)	0.3 (0.5)	.214
Loose stools	0.9 (0.2)	0.9 (0.2)	.914	0.5 (0.5)	0.5 (0.5)	.981
Hard stools	0.1 (0.1)	0.3 (0.1)	.293	0.2 (0.4)	0.2 (0.5)	.656
Urgency	0.9 (0.2)	0.8 (0.2)	.756	0.6 (0.5)	0.5 (0.5)	.635
Incomplete evacuation	0.7 (0.2)	0.5 (0.2)	.592	0.5 (0.5)	0.4 (0.5)	.166
Tiredness	2.3 (0.3)	2.0 (0.4)	.692	1.1 (0.5)	1.0 (0.5)	.694
Overall symptoms	1.2 (0.5)	1.7 (0.7)	.439	1.0 (0.5)	1.1 (0.5)	.493

NOTE. Data are presented as estimated marginal mean (SEM) and groups were compared using analysis of covariance with baseline values as a covariate.
[a]Number of days on which each symptom was reported at moderate or severe during the final week of the diet.
[b]Average severity across 7 days: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

Supplementary Table 2. Baseline Compared With End-of-Trial Fecal Calprotectin Concentrations in the Low FODMAP and Sham Diet Groups in All Patients and the UC and CD Subgroups

	All patients (low FODMAP n = 27, sham n = 25)			UC (low FODMAP n = 13, sham n = 13)			CD (low FODMAP n = 14, sham n = 12)		
	Baseline	End of trial	*P*	Baseline	End of trial	*P*	Baseline	End of trial	*P*
Low FODMAP (*μg/g*)	54.8 (84.8)	53.3 (84.8)	.857	21.9 (69.7)	10.9 (30.7)	.087	22.8 (66.1)	35.2 (26.8)	.674
Sham (*μg/g*)	70.9 (117.3)	66.9 (106.4)	.727	25.2 (67.3)	28.6 (67.7)	.721	22.8 (52.5)	15.9 (87.8)	.929

NOTE. Data are presented as median (interquartile range) and were compared between baseline and end of trial using a Wilcoxon signed rank test.

Supplementary Table 3. Daily Intake of Nutrients and FODMAPs in the Diet Groups at End of Trial (7-day Average Intakes)

	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*
Energy (*kcal/d*)	1697 (47)	1918 (49)	**.002**
Protein (*g/d*)	74 (2)	83 (2)	**.008**
Fat (*g/d*)	68 (4)	80 (4)	**.035**
Saturated fat (*g/d*)	24 (1)	27 (2)	.102
Carbohydrate (*g/d*)	180 (6)	197 (6)	.058
Starch (*g/d*)	116 (4)	117 (5)	.841
Sugars (*g/d*)	63 (4)	76 (4)	**.022**
Fiber, AOAC (*g/d*)	17.8 (0.8)	19.2 (0.9)	.249
Calcium (*mg/d*)	692 (39)	911 (41)	**<.001**
Iron (*mg/d*)	10.9 (0.6)	12.0 (0.6)	.170
Zinc (*mg/d*)	9 (1)	10 (1)	.470
Sodium (*mg/d*)	1532 (85)	2195 (89)	**<.001**
Potassium (*mg/d*)	2938 (148)	3034 (154)	.658
Phosphorus (*mg/d*)	1140 (36)	1312 (37)	**.002**
Magnesium (*mg/d*)	290 (13)	297 (13)	.709
Iodine (*μg/d*)	124 (15)	176 (16)	**.022**
Selenium (*μg/d*)	59 (4)	57 (4)	.823
Vitamin A (*μg/d*)	1358 (207)	1328 (215)	.921
Vitamin C (*mg/d*)	90 (7)	75 (8)	.166
Vitamin D (*μg/d*)	6.4 (0.4)	6.3 (0.4)	.818
Vitamin B_9 (folate) (*μg/d*)	229 (12)	257 (12)	.110
Vitamin B_{12} (cobalamin) (*μg/d*)	6.0 (0.9)	5.6 (0.9)	.782
FODMAPs			
Fructans (*g/d*)	1.3 (0.2)	2.9 (0.2)	**<.001**
GOS (*g/d*)	0.4 (0.1)	0.8 (0.1)	**<.001**
Lactose (*g/d*)	5.6 (1.0)	10.9 (1.1)	**.001**
Excess fructose (*g/d*)	0.5 (0.2)	1.4 (0.2)	**.001**
Sorbitol (*g/d*)	0.1 (0.1)	0.6 (0.1)	**.001**
Mannitol (*g/d*)	0.1 (0.0)	0.3 (0.0)	**.002**

NOTE. Data are presented as estimated marginal mean (SEM) and groups were compared using analysis of covariance with baseline values as a covariate.
AOAC, Association of Official Analytical Chemists.

Supplementary Table 4. Untargeted Microbiome Analysis: Relative Abundance of Species and Strains That Were Significantly Different Between the Diet Groups ($P \leq .05$) at End of Trial in Patients With UC and CD

	UC				CD			
Genus or species	Low FODMAP diet (n = 13)	Sham diet (n = 11)	*P*	*Q*-value	Low FODMAP diet (n = 8)	Sham diet (n = 11)	*P*	*Q*-value
Bifidobacterium adolescentis	1.52^{-7} (2.65^{-7})	1.72^{-7} (2.79^{-6})	**.004**	.592	2.73^{-7} (3.02^{-7})	3.31^{-6} (7.19^{-6})	.216	.690
Bifidobacterium longum	1.60^{-7} (2.18^{-7})	7.21^{-7} (1.13^{-6})	**<.001**	.115	6.53^{-8} (7.46^{-8})	6.73^{-7} (9.83^{-7})	.201	.682
Faecalibacterium prausnitzii								
SL3/3-M21/2	1.30^{-6} (1.93^{-6})	1.55^{-6} (1.47^{-6})	**.017**	.592	1.87^{-6} (2.39^{-6})	1.17^{-6} (1.90^{-6})	**.031**	.654
A2-165	2.38^{-6} (2.02^{-6})	2.97^{-6} (2.35^{-6})	.563	.806	2.26^{-6} (1.91^{-6})	2.66^{-6} (3.29^{-6})	.094	.654
L2-6	3.76^{-6} (4.67^{-6})	1.68^{-6} (1.19^{-6})	.356	.693	3.37^{-6} (3.79^{-6})	9.56^{-7} (1.39^{-6})	.443	.752
KLE1255	3.63^{-6} (4.14^{-6})	4.43^{-6} (3.81^{-6})	.562	.806	1.13^{-6} (8.88^{-7})	2.48^{-6} (3.89^{-6})	**.025**	.654
Ruminococcus sp. UNK.MGS-30	0.00 (0.00)	5.14^{-7} (9.13^{-7})	**.024**	.592	0.00 (0.00)	0.00 (0.00)	.393	.729
Ruminococcus bicirculans	8.78^{-7} (2.18^{-6})	2.97^{-6} (5.15^{-6})	**.005**	.592	1.40^{-6} (2.58^{-6})	1.05^{-6} (1.97^{-6})	.984	.993
Ruminococcaceae unclassified CAG00957	2.19^{-8} (7.21^{-8})	1.44^{-8} (3.49^{-8})	**.010**	.592	1.63^{-9} (4.61^{-9})	1.31^{-7} (4.10^{-7})	.475	.768
Clostridium sp. AT4	4.91^{-7} (1.44^{-6})	5.35^{-8} (9.36^{-8})	**.015**	.592	1.02^{-7} (2.10^{-7})	1.31^{-7} (3.51^{-7})	.596	.849
Clostridium unclassified CAG00441	3.44^{-8} (3.72^{-8})	7.92^{-8} (1.31^{-7})	.107	.592	2.63^{-8} (1.89^{-8})	5.95^{-8} (1.30^{-7})	**.009**	.563
Clostridium bolteae	1.01^{-6} (2.99^{-6})	3.87^{-8} (4.40^{-8})	**.049**	.592	5.41^{-8} (2.71^{-7})	2.04^{-7} (2.71^{-7})	.800	.966
Clostridium citroniae	8.52^{-8} (1.03^{-7})	3.21^{-8} (3.29^{-8})	.799	.927	1.01^{-7} (1.03^{-7})	4.90^{-8} (6.40^{-8})	**.001**	.311
Clostridium sp. KLE 1755	9.04^{-8} (1.55^{-7})	2.80^{-8} (5.72^{-8})	.201	.597	2.40^{-7} (2.70^{-7})	1.62^{-7} (4.46^{-7})	**.035**	.654
Clostridiales unclassified CAG01017	0.00 (0.00)	7.73^{-8} (1.25^{-7})	.075	.592	1.17^{-8} (2.20^{-8})	4.98^{-8} (1.28^{-7})	**.049**	.654
Clostridiales unclassified CAG01281	2.42^{-8} (8.05^{-8})	1.57^{-8} (3.90^{-8})	**.006**	.592	4.44^{-10} (1.26^{-9})	1.33^{-7} (4.39^{-7})	.087	.654
Roseburia intestinalis CAG00291	5.09^{-6} (8.80^{-6})	4.71^{-6} (8.35^{-6})	**.028**	.592	2.98^{-6} (6.09^{-6})	6.39^{-7} (1.37^{-6})	.300	.726
Roseburia intestinalis CAG01369	4.94^{-6} (8.59^{-6})	4.42^{-6} (7.70^{-6})	**.032**	.592	2.90^{-6} (5.94^{-6})	5.92^{-7} (1.27^{-6})	.307	.726
Roseburia unclassified CAG00869	7.95^{-8} (1.50^{-7})	5.65^{-8} (6.71^{-8})	.649	.871	4.14^{-8} (8.93^{-8})	1.45^{-7} (2.47^{-7})	**.043**	.654
Flavonifractor sp. 2789STDY5834895	1.40^{-7} (1.55^{-7})	1.52^{-7} (1.71^{-7})	**.018**	.592	2.44^{-7} (5.96^{-7})	4.12^{-7} (5.54^{-7})	.148	.654
Prevotella unclassified CAG00517	5.62^{-8} (2.03^{-7})	3.24^{-8} (1.03^{-7})	**.018**	.592	0.00 (0.00)	1.37^{-6} (4.53^{-6})	.335	.726
Prevotella sp. CAG:520	8.29^{-7} (2.99^{-6})	4.38^{-7} (1.39^{-6})	**.018**	.592	0.00 (0.00)	6.59^{-7} (2.19^{-6})	.148	.654
Eubacterium ventriosum	3.01^{-7} (5.45^{-7})	4.69^{-8} (7.85^{-8})	**.021**	.592	3.74^{-8} (1.01^{-7})	3.86^{-7} (5.64^{-7})	**.043**	.654
Eubacterium hallii	2.02^{-7} (2.57^{-7})	1.66^{-7} (1.62^{-7})	.369	.694	5.35^{-8} (6.15^{-8})	1.73^{-7} (1.57^{-7})	**.036**	.654
Catenibacterium mitsuokai	6.12^{-9} (2.21^{-8})	3.45^{-7} (1.09^{-6})	**.024**	.592	1.25^{-7} (3.53^{-7})	0.00 (0.00)	.311	.726
Barnesiella intestinihominis	3.49^{-6} (5.64^{-6})	1.99^{-6} (2.93^{-6})	**.024**	.592	2.73^{-6} (3.36^{-6})	3.97^{-6} (5.50^{-6})	.638	.862
Firmicutes unclassified CAG00808	9.75^{-8} (2.04^{-7})	1.62^{-8} (4.34^{-8})	.886	.958	2.63^{-8} (3.74^{-8})	4.77^{-8} (1.01^{-7})	**.012**	.654
Firmicutes bacterium CAG:194	0.00 (0.00)	2.02^{-7} (4.02^{-7})	**.036**	.592	0.00 (0.00)	4.25^{-7} (1.41^{-6})	.402	.729
Bacteroides xylanisolvens	2.57^{-6} (6.30^{-6})	1.66^{-6} (2.11^{-6})	.481	.771	1.43^{-5} (2.43^{-5})	2.58^{-6} (4.99^{-6})	**.009**	.563
Bacteroides cellulosilyticus	1.46^{-7} (3.71^{-7})	1.59^{-8} (3.06^{-8})	**.038**	.592	6.14^{-8} (1.74^{-7})	5.69^{-7} (1.10^{-6})	.247	.706
Parabacteroides distasonis	7.40^{-6} (1.61^{-5})	1.15^{-6} (9.61^{-7})	.798	.927	3.99^{-6} (3.84^{-6})	3.25^{-6} (3.22^{-6})	**.007**	.563
Candidatus gastranaerophilales bacterium HUM_2	1.16^{-6} (2.86^{-6})	2.07^{-7} (6.55^{-7})	**.032**	.592	5.99^{-7} (1.69^{-6})	6.49^{-7} (2.11^{-6})	.219	.693
Coprobacter secundus	2.03^{-8} (4.44^{-8})	3.65^{-8} (7.37^{-8})	**.046**	.592	1.80^{-7} (3.06^{-7})	2.63^{-8} (8.74^{-8})	.195	.682
Coprobacter fastidiosus	5.85^{-8} (1.37^{-7})	9.51^{-8} (1.95^{-7})	.951	.975	3.04^{-9} (6.17^{-9})	2.57^{-7} (4.49^{-7})	**.027**	.654
Dorea longicatena 1	3.61^{-7} (5.35^{-7})	6.77^{-7} (9.24^{-7})	.634	.860	1.19^{-7} (7.84^{-8})	5.72^{-7} (5.70^{-7})	**.001**	.311
Dorea longicatena 2 CAG00962	2.61^{-7} (6.72^{-7})	8.13^{-8} (1.16^{-7})	**.009**	.592	3.93^{-8} (5.78^{-8})	1.27^{-7} (3.23^{-7})	.353	.727
Dorea formicigenerans	3.03^{-7} (2.85^{-7})	3.49^{-7} (2.13^{-7})	.512	.785	1.00^{-7} (6.40^{-8})	2.02^{-7} (1.86^{-7})	**.005**	.453
Dorea sp. CAG:105	1.21^{-8} (1.92^{-8})	2.66^{-8} (3.73^{-8})	.924	.973	1.12^{-8} (1.60^{-8})	2.13^{-8} (2.16^{-8})	**.021**	.654
Hungatella hathewayi 2 CAG00015	2.50^{-8} (2.60^{-8})	3.83^{-9} (9.37^{-9})	**.052**	.592	2.56^{-8} (3.91^{-8})	9.46^{-9} (1.22^{-8})	**.021**	.654

Supplementary Table 4. Continued

Genus or species	UC				CD			
	Low FODMAP diet (n = 13)	Sham diet (n = 11)	*P*	*Q*-value	Low FODMAP diet (n = 8)	Sham diet (n = 11)	*P*	*Q*-value
Blautia unclassified CAG00235	1.74^{-7} (4.60^{-7})	9.77^{-9} (2.87^{-8})	.108	.592	8.91^{-10} (2.52^{-9})	5.31^{-8} (9.61^{-8})	**.024**	.654
Anaerostipes hadrus	1.80^{-6} (5.47^{-8})	3.92^{-7} (3.28^{-7})	.209	.597	1.48^{-7} (1.19^{-7})	6.37^{-7} (6.58^{-7})	**.005**	.453
Haemophilus parainfluenzae CAG00950	9.40^{-8} (1.32^{-7})	4.06^{-8} (7.41^{-8})	.715	.901	1.24^{-7} (2.52^{-7})	2.49^{-8} (5.14^{-8})	**.002**	.311
Haemophilus parainfluenzae CAG01056	6.50^{-7} (1.08^{-6})	3.58^{-7} (6.93^{-7})	.542	.798	9.61^{-7} (2.14^{-6})	1.94^{-7} (3.77^{-7})	**.033**	.654
Streptococcus thermophilus	4.93^{-8} (6.58^{-8})	1.59^{-8} (2.31^{-8})	.245	.628	2.81^{-9} (7.95^{-9})	6.21^{-8} (1.48^{-7})	**.019**	.654
Massiliomicrobiota CAG00816	5.65^{-8} (1.75^{-7})	3.22^{-9} (7.35^{-9})	.318	.660	0.00 (0.00)	8.64^{-9} (1.45^{-8})	**.025**	.654
Fusicatenibacter saccharivorans	1.26^{-6} (1.29^{-6})	1.00^{-6} (1.07^{-6})	.704	.901	4.67^{-7} (2.90^{-7})	1.76^{-6} (1.73^{-6})	**.027**	.654
Eisenbergiella tayi	1.24^{-7} (3.02^{-7})	7.64^{-9} (1.36^{-8})	.075	.592	2.28^{-7} (4.92^{-7})	1.69^{-8} (4.08^{-8})	**.019**	.654
Adlercreutzia equolifaciens	1.75^{-7} (2.18^{-7})	6.69^{-8} (7.42^{-8})	.471	.762	2.76^{-8} (2.74^{-8})	5.54^{-8} (6.39^{-8})	**.003**	.447
Alistipes onderdonkii	9.11^{-7} (1.25^{-6})	4.06^{-7} (1.06^{-6})	**.015**	.592	1.29^{-5} (2.68^{-5})	2.18^{-6} (4.41^{-6})	.336	.726
Intestinimonas massiliensis	1.08^{-7} (2.57^{-7})	1.71^{-9} (5.42^{-9})	**.023**	.592	2.17^{-8} (3.66^{-8})	1.11^{-7} (2.41^{-7})	.128	.654
Lachnoclostridium unclassified CAG00764	3.36^{-7} (6.64^{-7})	5.11^{-8} (9.28^{-8})	**.022**	.592	1.37^{-7} (2.56^{-7})	2.17^{-7} (3.47^{-7})	.307	.726
Unclassified CAG00420	2.69^{-8} (5.38^{-8})	7.54^{-8} (1.63^{-7})	**.024**	.592	1.43^{-8} (2.85^{-8})	5.85^{-8} (1.17^{-7})	.128	.654

NOTE. Data are presented as mean (SD) relative abundance and were compared between groups adjusted for baseline abundance and end of trial stool consistency. None of these species were significantly different between diet groups after FDR correction.

Supplementary Table 5. Total and Individual SCFA Concentrations in the ITT and PP Analysis

	ITT analysis			PP analysis		
	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*	Low FODMAP diet (n = 21)	Sham diet (n = 22)	*P*
Total SCFA	398 (192)	556 (245)	.080	366 (174)	536 (251)	**.049**
Acetate	232 (117)	323 (138)	.073	213 (109)	313 (140)	**.044**
Butyrate	67 (42)	92 (58)	.102	62 (40)	86 (60)	.094
Propionate	76 (41)	108 (71)	.190	69 (36)	104 (71)	.138
Valerate	7 (5)	11 (8)	.169	7 (4)	10 (8)	.164
Isobutyrate	7 (3)	9 (6)	.142	6 (3)	9 (6)	.084
Isovalerate	10 (5)	13 (9)	.468	9 (4)	13 (9)	.304
pH	6.7 (0.6)	6.4 (0.6)	.329	6.7 (0.6)	6.5 (0.6)	.409

NOTE. Data are presented as estimated marginal mean (SEM) and were compared between groups using an analysis of covariance with baseline values as a covariate.

Supplementary Table 6. T-cell Subset Analysis: Proportion of Each Population Expressing $\alpha4\beta7+$ and Absolute Number of $\alpha4\beta7+$ Cells at End of Trial

	Low FODMAP diet (n = 27)	Sham diet (n = 23)	*P*
Naïve CD4+			
Proportion (%)	67.1 (2.9)	74.0 (3.2)	.116
Absolute	333,815 (4024)	279,761 (4466)	.377
Effector/memory CD4+			
Proportion (%)	38.7 (1.2)	41.1 (1.3)	.164
Absolute	166,034 (1634)	164,934 (1821)	.965
Naïve CD8+			
Proportion (%)	68.9 (2.5)	74.6 (2.7)	.135
Absolute	225,275 (2486)	172,076 (2759)	.163
Effector/memory CD8+			
Proportion (%)	63.6 (2.3)	69.9 (2.3)	.054
Absolute	81,845 (8812)	80,040 (9803)	.894
Vδ2+			
Proportion (%)	71.6 (2.0)	79.1 (2.2)	**.017**
Absolute	30,535 (3897)	31,140 (4419)	.377

NOTE. Data are presented as estimated marginal mean (SEM) and were compared between groups using an analysis of covariance with baseline values as a covariate.

nutrients

MDPI

Article

Impact of FODMAP Content Restrictions on the Quality of Diet for Patients with Celiac Disease on a Gluten-Free Diet

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Abstract: Restrictive diets as gluten-free (GFD) or reduced in Fermentable, Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAP) are used to improve gastrointestinal (GI) symptoms in sensitive individuals. Aiming at comparing the nutritional quality and effects of a regular GFD regimen (R-GFD) and a low-FODMAP GFD (LF-GFD), in 46 celiac patients with persistent GI symptoms we conducted a randomized, double-blind intervention-controlled study. Patients received a personalized diet, either a strict GFD (n = 21) or a LF-GFD (n = 25) for 21 days. A validated food-frequency questionnaire before intervention and a 7-day weighed-food record after the intervention assessed the diets. Patients were 41.1 ± 10.1 years (mean ± SD), 94% women, with mean BMI 21.8 ± 2.9 kg/m^2. On day 21, patients on R-GFD still showed poor nutritional adequacy compared to dietary recommendations, with decreased energy intake, even though an improvement in carbohydrates and folates was observed (all $p < 0.025$). In both groups, intake of iron, calcium, vitamin D, sodium and folates did not meet daily recommendations. As expected, consumption of legumes and grains was lower and that of fruits was higher in the LF-GFD group than in the R-GFD one (all $p < 0.05$). The nutritional quality of both diets was not different. When restrictive diets are useful to improve the persistent GI symptoms, careful nutritional surveillance and counseling is mandatory.

Keywords: gluten-free diet; FODMAP; diet quality; nutritional adequacy; celiac disease

1. Introduction

The exclusion of dietary gluten is the only currently accepted treatment for gluten-related disorders [1], as Celiac Disease (CD). This is an autoimmune condition triggered by gluten, affecting mainly the small intestine in genetically susceptible individuals and exhibiting broad clinical

manifestations [2]. The withdrawal of gluten from the diet implies the exclusion of all food containing wheat, rye, barley, spelta, and hybrids such as triticale. Although restrictive, the gluten-free diet (GFD) should be rich in nutrients with an adequate balance in macro- and micronutrients, including natural and processed gluten-free foods, easily accessible and at an affordable price [3]. Because the GFD that celiac patients maintain as treatment must be strict, permanent and maintained lifelong, it often results in a high burden on social life and health related quality of life [4,5], favoring poor compliance [6].

GFD is safe and effective. In most patients, it improves histological lesions, blood biochemistry, clinical manifestations and decreases the risk of complications [7]. However, some patients do not show complete clinical remission despite following strict GFD; these patients report persistent gastrointestinal symptomatology resembling Irritable Bowel Syndrome (IBS) [8]. Studies restricting fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) intake has proved efficacious for IBS management [9]. FODMAP are poorly absorbed short-chain carbohydrates, including fructose, lactose, polyols, fructans, and galacto-oligosaccharides [10]. We were first to report potential benefits of FODMAP restriction in celiac patients on GFD and with persisting functional gastrointestinal symptoms [11]. We showed that a short-term low-FODMAP diet improves gastrointestinal symptomatology and psychological health, enhancing patients' well-being. Another study has reported consistent results when evaluating the combination of both diets in the treatment of Non-Celiac Gluten Sensitivity (NCGS), showing significant clinical and psychological symptom improvements in these patients [12].

Both GFD and low-FODMAP diets are characterized by an important restriction of food categories (i.e., grains in GFD and plant-based foods in low-FODMAP diet (LFD) and applying them together may have harmful nutritional consequences. Calcium and short-chain carbohydrates intake has been reported to be reduced in patients on a low-FODMAP diet [13]; however, a recent study showed that nutritional adequacy was not deteriorated in patients following a low-FODMAP diet even after a long time (18 months) [14]. On the other hand, higher fat, sugar, and energy content is often reported in the diet of CD patients, as a consequence of the gluten-free foods composition [15]. A lower intake of micronutrients such as magnesium, iron, zinc, manganese, and folate have also been reported in CD patients [3,16,17]. Aiming at improving our knowledge in this area, in this present study, we aimed at comparing the nutritional quality of the regular GFD (R-GFD) and a short-term low-FODMAP GFD (LF-GFD) regimen, in celiac patients already on GFD.

2. Materials and Methods

This study involved CD patients participating in a randomized, double-blind intervention-controlled study (previously registered at ClinicalTrials.gov with ref. no. IDNCT02946827), which assessed the effect of a GFD combined with a LFD on GI symptoms, as previously described [11]. Patients were 41.1 ± 10.1 (mean ± SD) years of age, mainly women (94%) with a mean body-mass index of 21.8 ± 2.9 kg/m^2. Inclusion criteria were: adults (18 to 60 years old), treated with GFD for at least a year, with negative plasma tissue transglutaminase values and IBS-like symptoms (functional gastrointestinal disorders according to the Rome III criteria) [18], with a global well-being score < 4 assessed by a visual analogue scale. Exclusion criteria were: low adherence to GFD as evaluated by the Celiac Dietary Adherence Test [19]; refractory CD, as evaluated by i) small intestinal biopsy to assessed the persistence of intestinal atrophy while on GFD and ii) an interview by a trained nutritionist, who assessed patients' adherence to the diet; individual intolerance to disaccharides lactose and fructose as evaluated by hydrogen test; a history of previous nutritionist evaluation or nutritional treatment for IBS dietary management; IBS pharmacological therapy; abdominal surgery; and type-2 diabetes. CD was diagnosed by positive serological tests -anti endomysium antibodies and anti-tissue transglutaminase antibodies- and duodenal histological abnormalities that followed the modified Marsh classification (following the American College of Gastroenterology clinical guidelines) [20]. The patients were recruited at the Center for Prevention and Diagnosis of Celiac Disease of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan. The Institutional Review Board of the University of Milan reviewed

and approved the study protocol (Project Identification Code 744_2015bis). All patients fulfilling the inclusion criteria and agreeing to participate were enrolled. A signed written informed consent was obtained from all patients prior to incorporation to the protocol.

2.1. Intervention Diets

A personalized GFD adjusted to match the daily requirements of energy, macronutrients, and micronutrients was calculated for each patient by a trained nutritionist, who was not involved in the patients' management. In each case, an in-depth GFD review and food education regarding GFD and LFD (in the LF-GFD group) was provided to the patient; then a structured 21-day dietary plan was given to the participants, which excluded all sources of dietary gluten. This plan included daily meals and specific foods/beverages. After the initial explanation, the nutritionist addressed doubts related to the dietary plan via e-mail or telephone thereafter. Changes in FODMAP dietary content included dietary counseling on how to start changing FODMAP consumption towards LFD. The FODMAP content of the R-GFD and LF-GFD included a median amount (interquartile range) of 21.8 (18.5–22.5) and 3.7 (3.0–4.12) g/day, respectively, as previously described [11,21,22]. Compliance to and doubts on the dietary plan were assessed ten days later by telephone call or e-mail by a nutritionist. On day 14, patients were instructed to record their daily consumption in a 7-day weighed food diary and return it completed on day 21. At this time, a second nutritional interview was carried out by the same nutritionist that assessed the dietary data during the intervention period.

2.2. Nutritional Assessment

Diets' characteristics were assessed at twice: before the intervention started (through a validated food-frequency questionnaire (FFQ)) and at the end of the intervention period (by means of the 7-day weighed food diary where the dietary information was recorded between day 14 and 21). The FFQ was administered by a trained nutritionist, who obtained information about food consumption during the previous year.

2.3. Dietary Evaluation at Baseline

The electronic version of the EPIC FFQ, developed for northern-central Italy and specifically adapted for the celiac population (including 188 food items), was used to establish the usual intake of food and beverages consumed during the year prior to this study [17]. In the questionnaire, each respondent was asked to indicate the number of times any given food/beverage was consumed (per day, week, month, or year). Participants selected an image of a food portion (a pre-defined standard portion was used when no image was available) to quantify the portion size. This instrument does not ask about the frequency of intake and dosages of commonly consumed dietary supplements. The nutritional composition of food items listed in the EPIC FFQ was modified as described previously [17] to include the recipes of composite gluten-free foods and generic gluten-free commercial foods. Complex foods were split into their ingredients, and the gluten-free products with the closest ingredient composition was used. In doing so, definition of an appropriate alternative of gluten-free food was based mainly on energy and carbohydrates composition. For the modified EPIC FFQ 24 foods containing gluten were replaced with 24 gluten-free foods. An ad-hoc computer program (Nutritional Analysis of Food Frequency Questionnaire) developed by the Epidemiology and Prevention Unit of the IRCCS Foundation, National Cancer Institute of Milan, was used to convert the questionnaire's dietary data into the frequencies of consumption and mean daily quantities of foods (grams per day), energy, and nutrients consumed. The food items contained in the FFQ were grouped into the same food groups identified for the 7-day weighed food diary, based on the similarities in the nutrient profile and culinary usage.

2.4. Dietary Evaluation at the End of Intervention

The total food and beverage consumption was assessed using the 7-day food diary, filled on days 14–21 [23]. At baseline and on the day 14 visit, the participants were instructed by a nutritionist on how to record all foods consumed and the dairies were reviewed by the nutritionist with the patient on day 21 to clarify doubts. These food diaries were sent to the Department of Food and Drug of the University of Parma for processing. Nutrient intake was calculated by means of a Microsoft Access application (version 2003, Microsoft Corp., Redmond, WA, USA) linked to the European Institute of Oncology's food database, which covered the nutrient composition of 900+ Italian foods [24], integrated with the nutrient composition of 60 gluten-free foods available in the Italian market [25]. When a food recorded by the participant was not be found in the database, an alternative food was appropriately chosen based on its similarities in energy and nutrient composition. The output consisted of the daily intake of energy and nutrients for each patient. The food items of interest for this study were grouped into the following categories: pasta, bread (including crackers and salted snacks), cereals (including corn, quinoa, buckwheat, and rice), fruits, vegetables, legumes, potatoes, sweeteners (honey, saccharin, fructose, barley malt syrup) and sweets (including biscuits, sweet snacks, breakfast cereals, ice-cream, candies, and chocolate), dried fruits, lipids (oil and fats), dairy products (including milk, yogurt, cream, cheese), eggs, fish meats, soft drinks, juices, coffee/tea, and alcoholic beverages. For each patient, the mean daily intake of each food category was calculated. Nutrient, adequacy was calculated against the Recommended Dietary Allowances (RDA). For each nutrient, adequacy was considered if the calculated nutrient intake was at least equal or higher than the respective daily RDA for that nutrient, according to the Institute of Medicine, National Academies, USA [26]. The adequacy of the energy intake was calculated as the energy intake relative to the estimated energy expenditure, (i.e., (energy intake/energy expenditure) × 100).

2.5. Statistical Analysis

Data were described as median ± Standard Deviation (SD) or median (inter-quartile range), depending on the parametric or non-parametric distribution of variables. The data distribution was assessed by graphical inspection and the Shapiro–Wilk test. The X^2-test or Fisher's exact two-tailed test were used for nutrient adequacy comparison between the baseline and last-week intervention within groups. The independent sample Student's *t*-test was used to compare nutritional intake and adequacy of critical nutrients between groups at the last week of intervention. The non-parametric Wilcoxon rank-sum test was used to evaluate differences regarding the food groups consumption at the last week of intervention. A 5% significance level was used, and the software packages STATA® v. 13.1 (StataCorp LLC, College Station, TX, USA) and GraphPad Prism v. 6 (GraphPad Software, La Jolla, CA, USA) were used for analysis and figures processing.

3. Results

Nutritional Adequacy of Consumed Diets Compared to Macro- and Micronutrients Recommendations

Nutritional composition and adequacy to daily nutrient recommendations of 46 celiac disease patients GFD (n = 21) or a LF-GFD (n = 25) were analyzed, in Table 1 both groups are shown. In the R-GFD group, at baseline there was excess energy intake and poor compliance of carbohydrates (9/21 subjects) and fat (7/21 subjects) recommendations. For micronutrients, the lowest degree of adequacy was observed for vitamin D, folate, calcium, iron, sodium and potassium (Table 1). Changes in diet sufficiency during the last week of intervention were evaluated, revealing a significant decrease in energy adequacy ($p = 0.0001$) and an improvement in the adequacy of carbohydrates ($p = 0.025$). Regarding micronutrients, the only significant difference found was in folates, with better achievement of daily recommendations at the end of the intervention ($p = 0.009$, Table 1).

Table 1. Nutritional composition of diets and nutritional adequacy of macro and micronutrients against the daily recommendations in both groups.

	R-GFD Group				LF-GFD GRoup					
	Baseline (*n* = 21)	**Adequacy †**	**End of Intervention (*n* = 21)**	**Adequacy †**	**Baseline (*n* = 25)**	**Adequacy †**	**End of Intervention (*n* = 25)**	**Adequacy †**	***p* Value R-GFD ‡**	***p* Value LF-GFD ‡**
Energy, kcal ††	2212.4 ± 511.7	111.9 ± 30.0	1556.2 ± 220.4	78.8 ± 14.3	1837.0 ± 481.5	91.5 ± 27.8	1578.0 ± 238.9	78.9 ± 17.6	**0.0001**	**0.048**
Protein, %	13.8 ± 2.6	19 (90.4)	15.6 ± 2.2	21 (100.0)	16.2 ± 2.7	25 (100.0)	16.8 ± 3.3	24 (96.0)	0.147	0.999
Carbohydrate, %	44.4 ± 8.2	9 (42.8)	49.3 ± 4.5	17 (80.9)	41.2 ± 7.1	5 (20.0)	50.4 ± 3.8	23 (92.0)	**0.025**	**0.0001**
Fat, %	39.4 ± 6.3	7 (33.3)	35.7 ± 4.1	8 (38.0)	42.4 ± 6.2	2 (8.0)	33.9 ± 3.8	18 (72.0)	0.747	**0.0001**
Dietary fiber, g	26.0 ± 8.4	13 (61.9)	24.2 ± 10.8	7 (33.3)	21.0 ± 5.7	10 (40)	21.9 ± 8.8	8 (32.0)	0.064	0.556
Thiamin, mg	0.9 ± 0.2	8 (38.0)	0.9 ± 0.2	5 (23.8)	0.9 ± 0.2	5 (20.0)	0.9 ± 0.2	6 (24.0)	0.317	0.733
Riboflavin, mg	1.5 ± 0.4	19 (90.4)	1.5 ± 0.4	17 (80.9)	1.6 ± 0.6	21 (84.0)	1.4 ± 0.3	23 (92.0)	0.663	0.667
Niacin, mg	19.5 ± 3.8	20 (95.2)	19.6 ± 4.7	19 (90.4)	20.0 ± 6.7	20 (80.0)	20.6 ± 6.8	20 (80.0)	0.990	0.990
Vitamin B6, mg	2.0 ± 0.4	21 (100.0)	1.9 ± 0.4	21 (100.0)	2.1 ± 0.7	24 (96.0)	1.9 ± 0.3	25 (100.0)	-	0.990
Vitamin C, mg	120.5 ± 46.5	17 (80.9)	146.0 ± 82.7	19 (90.4)	138.9 ± 92.2	22 (88.0)	207.4 ± 107.0	24 (96.0)	0.663	0.609
Vitamin E, mg	12.7 ± 4.1	9 (42.8)	14.0 ± 2.7	7 (33.3)	11.8 ± 4.0	5 (20.0)	13.6 ± 2.3	7 (28.0)	0.525	0.508
Vitamin D, g	2.9 ± 1.1	0 (0)	2.3 ± 1.1	0 (0)	3.5 ± 3.0	1 (4.0)	2.7 ± 2.4	0 (0)	-	0.990
Folate, g	261.2 ± 68.6	0 (0)	331.8 ± 126.7	7 (33.3)	274.1 ± 89.1	1 (4.0)	290.3 ± 96.0	4 (16.0)	**0.009**	0.349
Calcium, mg	804.6 ± 391.3	3 (14.2)	599.7 ± 198.8	0 (0)	879.8 ± 434.8	7 (28.0)	601.2 ± 170.5	2 (8.0)	0.072	0.066
Iron, mg	11.0 ± 3.0	3 (14.2)	10.8 ± 3.6	2 (9.5)	10.4 ± 3.0	5 (20.0)	11.0 ± 3.2	9 (36.0)	0.990	0.208
Phosphorus, mg	1244.9 ± 374.6	20 (95.2)	1002.4 ± 209.5	18 (85.7)	1239.7 ± 454.9	24 (96.0)	1019.2 ± 205.9	24 (96.0)	0.606	0.990
Sodium, mg	2455.8 ± 846.0	2 (9.5)	4056.5 ± 1146.5	2 (9.5)	1861.8 ± 540.6	4 (16.0)	4243.5 ± 1374.5	3 (12.0)	0.990	0.684
Potassium, mg	3193.8 ± 697.4	0 (0)	2937.1 ± 750.9	0 (0)	3122.7 ± 957.6	1 (4.0)	3186.7 ± 772.7	2 (8.0)	-	0.990
Zinc, mg	9.7 ± 2.3	17 (80.9)	8.8 ± 1.7	15 (71.4)	9.5 ± 3.3	17 (68.0)	8.6 ± 1.7	14 (56.0)	0.719	0.382

Data are expressed as mean ± SD for the absolute intake of nutrients, and as frequency and (percentage) for their adequacy level; † For each nutrient, adequacy was achieved if the calculated nutrient intake was at least equal or higher than the respective nutrient daily Recommended Dietary Allowance (RDA), according to the Institute of Medicine, National Academies, USA. [26]; †† The energy adequacy was calculated as the energy intake relative to the estimated energy expenditure: (energy intake/energy expenditure) × 100. For protein, carbohydrates, and fat adequacy, RDA is 10%–35%, 45%-65%, and 20%-35% of the energy intake. ‡ For comparison of nutrients adequacy between baseline and the end of intervention, a chi-square or Fisher's exact test was used. Numbers in bold highlight significant differences between groups. R-GFD: Regular gluten-free diet; LF-GFD: low-FODMAP gluten-free diet.

At baseline, the same analysis in the LF-GFD group showed adequate energy and protein sufficiency but poor compliance to carbohydrates and fat recommendations. In both groups, a low proportion of patients complied to the micronutrient adequacy of vitamin D, folates, vitamin E, iron, sodium, potassium and calcium. Dietary adequacy changed in the last week of intervention with lower energy adequacy ($p = 0.048$) and improvement in carbohydrates and fat adequacy (both $p = 0.0001$); there were no changes in the adequacy of evaluated micronutrients in the last week of intervention (Table 1).

At the end of the intervention period, comparison of the nutritional intake composition between the two groups showed similar daily intake of macronutrients and micronutrients, except for higher intake of animal protein ($p = 0.037$), cholesterol ($p = 0.011$), and vitamin C ($p = 0.033$) in the LF-GFD group than in R-GFD group (Table 2). The level of adequacy of critical nutrients folates, iron, calcium, and vitamin D intake was below the daily recommendations in both groups (Figure 1), with iron adequacy tending to increase in the LF-GFD group over the intervention period ($p = 0.081$).

Table 2. Comparison of nutritional daily intakes between the R-GFD and LF-GFD groups at the end of intervention [1].

	R-GFD (*n* = 21)	**LF-GFD (*n* = 25)**	***p* Value**
Energy, kcal	1556.2 ± 220.4	1578.0 ± 238.9	0.750
Energy adequacy, %	78.8 ± 14.3	79.0 ± 20.2	0.959
Total protein, g	59.6 ± 10.9	65.7 ± 17.3	0.154
Protein, % of energy	15.6 ± 2.2	16.8 ± 3.3	0.133
Animal protein, g	36.3 ± 9.4	44.2 ± 15.4	0.037
Vegetal protein, g	23.1 ± 7.0	21.2 ± 5.1	0.311
Total carbohydrate, g	190.9 ± 31.4	198.4 ± 32.7	0.431
Carbohydrate, % of energy	49.3 ± 4.5	50.4 ± 3.8	0.376
Total fat, g	62.1 ± 11.7	59.6 ± 11.0	0.463
Fat, % of energy	35.7 ± 4.1	33.9 ± 3.8	0.123
Cholesterol, mg	148.3 ± 35.0	178.4 ± 42.6	0.011
Dietary fiber, g	24.2 ± 10.8	21.9 ± 8.8	0.433
Thiamin, mg	0.9 ± 0.2	0.9 ± 0.2	0.820
Riboflavin, mg	1.5 ± 0.4	1.4 ± 0.3	0.741
Niacin, mg	19.6 ± 4.7	20.6 ± 6.8	0.573
Vitamin B6, mg	1.9 ± 0.4	1.9 ± 0.3	0.637
Vitamin C, mg	146.0 ± 82.7	207.4 ± 107.0	0.033
Vitamin E, mg	14.0 ± 2.7	13.6 ± 2.3	0.642
Vitamin D, g	2.3 ± 1.1	2.7 ± 2.4	0.477
Folate, g	331.8 ± 126.7	290.3 ± 96.0	0.225
Calcium, mg	599.7 ± 198.8	601.2 ± 170.5	0.978
Iron, mg	10.8 ± 3.6	11.0 ± 3.2	0.874
Phosphorus, mg	1002.4 ± 209.5	1019.2 ± 205.9	0.786
Sodium, mg	4056.5 ± 1146.5	4243.5 ± 1374.5	0.617
Potassium, mg	2937.1 ± 750.9	3186.7 ± 772.7	0.274
Zinc, mg	8.8 ± 1.7	8.6 ± 1.7	0.695

[1] Data are shown as mean ± SD. *p*-value for comparison between the groups using independent samples *t*-test. R-GFD: Regular gluten-free diet, LF-GFD: Low-FODMAP gluten-free diet.

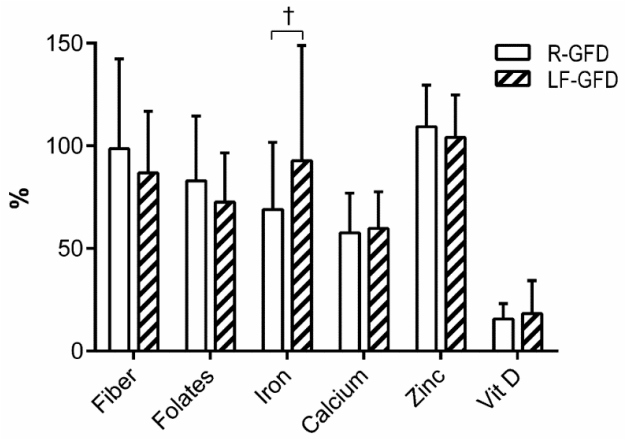

Figure 1. Adequacy level of critical nutrients between groups against the dietary recommendations. Data as mean ± SD. † Adequacy: [nutrient intake/nutrient daily recommendation (RDA)] × 100. Independent samples *t*-test: † $p = 0.081$. R-GFD: Regular gluten-free diet, LF-GFD: Low-FODMAP gluten-free diet.

At the end of the intervention period, evaluation of relevant food groups was performed by quantifying the consumption of relevant food groups (Figure 2). Overall, comparison of most food groups showed no differences between diets; especially, dairy products, eggs and meats consumption did not differ between groups However, in the LF-GFD group there was a trend to have higher bread consumption whereas legumes consumption was significantly lower ($p = 0.008$) and consumption of fruits was higher and grains lower than R-GFD (both $p < 0.05$, Figure 2).

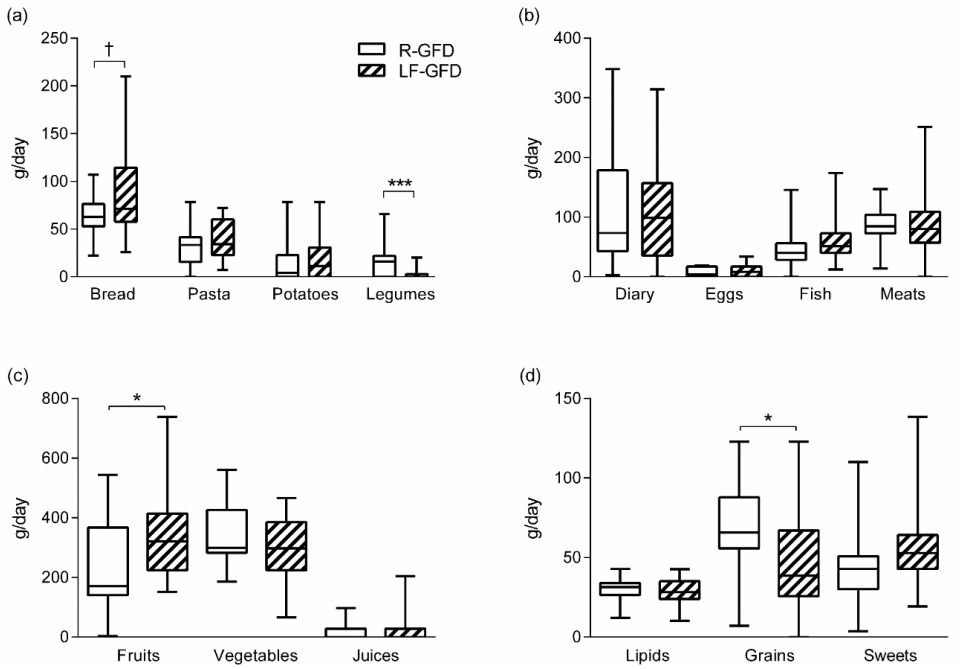

Figure 2. Food categories consumption between the groups at the end of intervention. Data as median. (horizontal line), interquartile range (p25-p75, box), and minimum and maximum (whiskers). (**a**–**d**) show to different food classifications. Wilcoxon's Rank Sum Test: * $p < 0.05$; *** $p = 0.0008$; † $p = 0.098$. R-GFD: Regular gluten-free diet; LF-GFD: Low-FODMAP gluten-free diet.

4. Discussion

In this study, we evaluated celiac patients with persistent gastrointestinal symptoms that followed either R-GFD or a diet that additionally restricted FODMAPs content. Nutrient adequacy in patients

on R-GFD was poor when compared to dietary recommendations and it did not improve when a low-FODMAP diet was implemented. When comparing both types of diet at the end of the intervention period, slight differences were detected with regard to intake of animal protein, cholesterol, and vitamin C. When restricting FODMAP content, food groups consumption showed the expected changes, mainly a lower intake of legumes and grains and a higher fruit consumption compared to the R-GFD group. As a whole, our results show low nutritional quality of the GFD regimen and that the exclusion of FODMAP-rich foods from the diet does not worsen its nutritional quality. Both diets can be used as an alternative treatment for selected patients who continue with persistent symptomatology when following GFD.

The adherence to GFD by CD patients was considered to be nutritionally adequate when retrospective evaluated along the years [27]. Currently, several reports point out that patients on GFD should be continuously monitored to detect and prevent nutritional deficiencies that may develop in some individuals as well as affecting the practice of GFD [28–30]. It is widely agreed that the adverse nutritional impact of CD is related to the duration of the untreated state of the disease, the extension, and location of the mucosal lesions, and the degree of malabsorption of specific nutrients [31]. In this study, we evaluated the intake of some critical nutrients as proposed by others [3], showing that nutritional adequacy was achieved for zinc and fiber while was not for iron, folates, calcium, vitamin D, potassium and sodium. It is worth noting that nutritional supplements consumption was not included in our dietary analysis. We also observed that the group receiving R-GFD regimen showed some differences at the end of our intervention, as compared with their baseline assessment. After the overall evaluation and reinforcement of GFD on day 14, the diet quality improved as they reduced the energy intake and improved compliance to carbohydrates recommendations, a relevant issue considering the current scenario of overweight/obesity observed in several celiac patients [32].

The importance of nutritional quality of GFD has been more and more emphasized over the last decades. One study [33] showed an increased BMI after GFD initiation together with a higher (almost doubled) percentage of overweight subjects while they were on GFD. The authors speculated that this may be a consequence of incorrect eating habits, influenced by expensive commercial gluten-free products with poor nutritional quality and high-fat content [33]. In this study, post-intervention improvements (after 21 days on R-GFD) showed that folates intake also increased, suggesting that follow-up and reinforcement of dietary indications are essential to improve macro- and micronutrients intake. Therefore, a patient's periodic monitoring with a trained nutritionist for prescribing and guiding GFD is of paramount importance [3].

FODMAP dietary restriction improved the persistent symptoms in our celiac patients that were already on GFD [11]. The physiological principle that supports FODMAP restriction is based on the fact that the incomplete hydrolysis/absorption short-chain carbohydrates in the small intestine reach the colon and are fermented by the microbiota, generating increased intestinal water and colonic gas [34]. However, it has been reported that FODMAP exclusion may lead to nutritional inadequacy celiac disease [35].

The resulting big question then is whether restriction of FODMAP in patients that are already on GFD may deteriorate nutrients intake. Results of this study show that this was not the case; after implementing the low-FODMAP diet there were no significant differences in energy or macronutrients intake as compared with R-GFD. Instead, there was an increase in animal protein, cholesterol, and vitamin C at the end of the intervention period as compared with R-GFD. However, comparing the energy and macronutrients intake pre- and post-intervention in the LF-GFD group, there was a significant decrease in the energy intake, a change that did not differ from the behavior of the R-GFD group. This issue has already been described in previous studies that report a lower carbohydrate and energy intake in subjects following a low-FODMAP diet as compared with their pre-intervention usual diet [36,37]. However, it has also been shown that the energy and macronutrient intake after a low-FODMAP diet was not different from their usual control diet [38].

Although GFD has some nutritional deficiencies, in this study we only found a trend for better adequacy of the iron intake in LF-GFD in comparison with the patients on R-GFD.

The analysis of the food groups shows the expected results regarding the food restriction in a low-FODMAP diet. However, such a restriction of specific foods is subject to the re-challenge phase. As part of the re-challenge phase-specific dietary triggers must be identified, and well-tolerated foods are re-introduced. The role of a nutritionist is crucial to assist patients in identifying specific dietary triggers, in reducing the level of dietary restriction, and increasing the prebiotic intake [39]. The re-challenge supports the re-introduction of a greater variety of foods by making food choices more flexible, arriving at one's personal version of a modified LFD [40]. Our results also emphasize that these patients should be managed by a specialized nutritionist, who should educate, control and follow the restrictive diets (R-GFD and LF-GFD), ensuring that nutritional adequacy is reached and maintained [4] and that the impact on patients' quality of life due to the restrictive diet is as low as possible.

Our study has some limitations that we would like to mention. First, we studied a relatively small sample of patients with CD and both dietary treatments were conducted during a rather short period of time. Further studies should evaluate the effect of FODMAP restriction in CD patients during a longer term. Second, the use of a structured 21-day diet plan that included daily meals and specific foods/beverages, which was designed individually for each patient, could clearly impact the composition of the diets as opposed to what patients might select them when instructed to follow the basic rules of such diets. Therefore, the findings may not reflect real-world practice where patients choose their own meals within the confines of the instructed diet. However, this allowed us ensuring that patients effectively consumed foods according to planned quantity and quality, and better compliance with the designed diets. Third, we used different methods for the assessment of food intake (FFQ and 7-day food diary) in our patients. This differential approach was chosen as the use of FFQ allowed us to evaluate patients' usual dietary pattern while the 7-day food diary evaluated food intake during the last week of the intervention period, allowing us to acutely evaluate food intake under both diets.

5. Conclusions

This study demonstrates that patients with CD fail to meet relevant nutritional recommendations and shows an overall low diet quality. A three-week low-FODMAP diet/GFD, when applied by a specialized nutritionist, does not significantly impact on nutrient intake as compared with a regular GFD regimen and helps mitigating persistent gastrointestinal symptoms. However, this study applied the two diets and evaluated their effect only for 21 days. Further studies are necessary to confirm our results in long-term studies. When a low-FODMAP diet is prescribed to celiac patients on GFD, they must be supervised and periodically assessed by a specialized nutritionist. This will help improving the patients' nutritional state and his/her quality of life.

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nutrients

MDPI

Review

Nutrition, IBD and Gut Microbiota: A Review

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Abstract: Inflammatory bowel disease (IBD) is a chronic relapsing–remitting systemic disease of the gastrointestinal tract, characterized by an inflammatory process that requires lifelong treatment. The underlying causes of IBD are still unclear, as this heterogeneous disorder results from a complex interplay between genetic variability, the host immune system and environmental factors. The current knowledge recognizes diet as a risk factor for the development of IBD and attributes a substantial pathogenic role to the intestinal dysbiosis inducing an aberrant mucosal immune response in genetically predisposed individuals. This review focused on the clinical evidence available that considers the impact of some nutrients on IBD onset and the role of different diets in the management of IBD and their effects on the gut microbiota composition. The effects of the Specific Carbohydrate Diet, low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet, gluten free diet, anti-inflammatory diet and Mediterranean diet are investigated with regard to their impact on microbiota and on the evolution of the disease. At present, no clear indications toward a specific diet are available but the assessment of dysbiosis prior to the recommendation of a specific diet should become a standard clinical approach in order to achieve a personalized therapy.

Keywords: inflammatory bowel disease; nutrition; diet; gut microbiota; microbiome

1. Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a heterogenous set of inflammatory diseases, mediated by the immune system, which affect the gastrointestinal tract.

The two main IBD manifestations are Crohn's Disease (CD) and ulcerative colitis (UC). CD may affect any area of the gastrointestinal tract and its involvement is transmural; colonoscopy findings include skip lesions, cobblestoning, ulcerations and strictures. UC generally occurs only in the colon and involves the mucosa and submucosa only; classically described colonoscopy findings are pseudopolyps and continuous areas of inflammation [1,2].

It is estimated that approximately 3 million people (1.3%) in the US population suffers from IBD [3]. A similar estimate has been provided for Europe [4] with annual direct and indirect costs in the range of billions USD [3,4].

In North America incidence rates for CD range from 0 to 20.2 per 100,000 persons/years and from 0 to 19.2 per 100,000 persons/years for UC. Prevalence ranges from 25.9 to 318.5 cases per 100,000 persons for CD and from 37.5 to 248.6 cases per 100,000 persons for UC. Similarly, in Europe, incidence rates for UC range from 0.9 to 24.0 per 100,000 persons/years and from 0.0 to 11.5 per 100,000 persons/years for CD. Prevalence of UC varies from 2.4 to 294 cases per 100,000 persons, whereas the prevalence of CD

ranges from 1.5 to 213 cases per 100,000 persons [5]. In Asia, South America and southern and eastern Europe, the prevalence of IBD is, on average, lower [5,6].

Both incidence and prevalence of IBD are increasing worldwide, and especially in regions usually displaying lower rates, such as Asia and South America [4,5]; furthermore, people migrating to countries displaying high IBD prevalence have a propensity to develop IBD [7] and this is especially true for their first-generation offspring [8].

The etiology of IBD is still not completely understood. Yet, several studies support the hypothesis that its onset is due to a combination and interplay of genetic factors, immune dysregulation and environmental triggers [9,10]. Genetic analysis, which will be discussed in detail in a dedicated section, has led to the discovery of over 230 genes predisposing to IBD [11]. Meaningfully, most of these IBD susceptibility genetic polymorphisms are associated with host mucosal barrier function and are involved in host–microbiome interactions [12–17]. These findings support the hypothesis that alterations of the gut microbiome are essential in triggering chronic inflammation and not merely a consequence [18,19]. Further evidence supporting the pivotal role of gut microbiome in the onset of IBD [18] is that CD and UC patients often present a characteristic dysbiosis [20–25]; fecal microbiota transplantation seems to induce remission in active UC [26]; the use of antibiotics and probiotics induce and maintain the remission of IBD [27–29]; depletion of commensal microbes can result in impaired mucosal healing, chronic mucosal inflammation and colitis [30].

The current theory concerning IBD pathogenesis is that a chronic intestinal inflammation is consequent to an aberrant mucosal immune response that affects genetically predisposed individuals, whose intestinal microbiome undergoes pathologic alterations [18]. Environmental factors, in fact, appear to be pivotal in triggering the onset of the disease given a genetical background predisposing the subject to developing the disease; such a conclusion stems from the observation that the concordance of IBD among monozygotic twins <50% as well as the fact that penetrance of IBD-predisposing gene variants in the general population is incomplete [31–34]. The role of environmental factors has also been inferred by the analysis of trends in epidemiologic data. The greater incidence and prevalence of IBD in North America and US, as well as the increased risk of IBD for people who emigrate in such regions, and that of their offspring, support a correlation between incidence of IBD and living according to a "Western" lifestyle [9,35]. Main environmental factors, beyond geographical location, that modulate the onset of IBD appear to be diet, smoking, alcohol and drugs (such as nonsteroidal anti-inflammatory drugs and oral contraceptives) [36]. Smoke, alcohol and drugs are supposed to contribute to IBD onset because they may both alter the intestinal epithelial barrier properties [7,9] and have an influence on the microbiota composition [37,38]. Yet, mechanisms underlying such correlation are still not well understood—possibly involving, concerning smoke, molecular pathways for oxidative stress induction and hypoxia, alterations in the composition of mucin and intestinal tight junctions, and changes in acid-base balance [37,39] and, concerning alcohol, mainly its effect on the immune system [38,40], and possibly on gut microbiome [41] even if epidemiological studies on alcohol as a risk factor for IBD have sometimes failed to find a significant correlation [38,42].

Based on the above considerations, the purpose of this review is to give further insights on the relationships between nutrition, microbiome and inflammatory bowel diseases. In particular, we focused on various nutritional approaches, specific food components and microbiome to identify a possible link between them that could influence the evolution of IBD, with the aim of determining a personalized diet for patients affected by UC or CD. To this end, the present investigation takes into account what has emerged from the last 10 years of literature focused on nutritional approaches, microbiome and IBD.

2. IBD, Genetics and Epigenetics

The genetic component has a strong influence in the susceptibility of IBD, as studies demonstrated that up to 12% of IBD patients have a family history of IBD [11,43,44]. Until now, genome-wide association studies (GWAS) have identified more than 230 single nucleotide polymorphisms (SNPs)

associated with IBD [11,45–47]. Among the chromosomes, 110 loci related to the development of IBD have been specifically associated with CD and UC, meaning that the diseases share the same mechanistic pathways such as those involved in the innate immunity (NOD2, IRGM and IL-23 pathway) [48]. The genetic risk locus having the strongest association with IBD is NOD2, which in particular, on chromosome 16 is associated with CD [49,50]. NOD2 codes for a pattern recognition receptor that is pivotal in the host-microbe immune response. NOD2, a cytosol protein, is expressed in monocytes, macrophages, gut epithelial cells (including Paneth cells), and lamina propria lymphocytes, including T cells [51–54]; it binds the muramyl dipeptide (MDP), a portion of a bacterial cell wall peptidoglycan. Upon binding, assembly of NOD2 oligomer induces activation of NF-κB and MAPK and hence transcription of inflammatory cytokines [55,56]. Impaired NOD2 response to microbiome changes may favor changes in the homeostasis between the host immune system and the microbiome, resulting in increased risk of developing IBD [57]. CD patients with NOD2 mutations also display Paneth cells with altered morphology and diminished secretion of α-defensins, antimicrobial peptides also contributing to the homeostasis between the host immune system and the gut microbiome [58]. Mutations of NOD2 may therefore also alter this pathway, finally contributing to establishing both dysbiosis and inflammation [59]. The exact mechanisms by which NOD2 plays a role in IBD onset are still not clearly defined; these observations, yet, strongly suggest that polymorphism at the NOD2 locus modulates host response to the gut microbiome [11]. The risk variant for IBD located in the nucleotide oligomerization domain containing protein 2 gene (NOD2), has the highest odd risk (OR) of 3.1 in CD. Notably, all other SNPs identified have lower ORs. Other genetic variants identified in several genes such as ATG16L1, LRRK2, and IRGM have been associated with increased risk of IBD. These are all linked to autophagy, a process cells activate to clear cytosolic debris and damaged organelles, possibly involved in the response to intracellular pathogens [60–62], whose possible link to IBD is yet to be clarified [63,64]. Again, genetic variants may involve an augmented risk of IBD through alteration of the epithelial barrier function, thinning of the mucus layer, and unfolding of protein due to endoplasmic reticulum stress (genes such as MUC19, ITLN1, FUT2, and XBP1) [65,66].

Recent research has also highlighted a role of epigenetic modification—that is, DNA methylation and noncoding RNAs—in the onset and course of IBD [67–70]. Genetic variants associated with IBD show, as said, incomplete penetrance, and homozygote twins develop IBD in less than 50% of cases [31–34] leading to the conclusion that environmental factors play a role as risk factors for IBD incidence. Some environmental factors might modulate the risk of developing IBD by epigenetic modifications [69,71]. At present, evidence of epigenetic modifications in patients affected by IBD exists in the differential expression of specific microRNAs (miRNAs) in the colonic mucosa samples of IBD patients compared to control patients [68] and the presence of specific miRNA in the peripheral blood and tissue of IBD patients [72]. miRNAs are also involved in the differential regulation of cytokines following the immune response to bacteria invasion [73]. miRNAs are small noncoding RNA molecules of approximately 22 nucleotides, secreted by microvescicles in a cell-to-cell communication system and are deputed to regulate multiple target genes or signaling pathways. In the last decade, many studies focused on the emerging role of miRNAs in the development of diseases as well as potential biomarkers for diseases [74]. It has been demonstrated that dysregulation of miRNAs in Th17 cells is implicated in IBD, and that, even if the amount of miRNAs does not change between active IBD and remission IBD, the specific miR-16, miR-21 and miR-223 are highly expressed in IBD with active disease compared to patients with IBD in remission [69,74]. Differences in DNA methylation have been described in UC and CD patients; however, results are not robust and consistent enough to establish a causal-link with gene expression in IBD. In an elegant study by Taman et al., some patterns of hypo- or hyper-methylation have been reconducted to the pathogenesis of CD [75]. These data seem to be supported also by the evidence in a large pediatric IBD population, where specific epigenetic variations in the intestinal epithelium might influence the progression of the disease and might gain prognostic value as biomarkers for the disease [76]. Microbiota influences the activation of some genes associated

with hypomethylated active regulatory regions, thus inducing the expression of genes associated with colitis and IBD [77].

3. IBD and Microbiota

The human gut microbiota is estimated to contain 500–1000 different bacterial species, as well as fungi and viruses [78], with a number of micro-organisms estimated at 1018 CFU/g, ten times greater than that of the cells of the whole human body. The total amount of genes of the microbiota is estimated to be one hundred times greater than that of the human genome [79]. The intestinal microbiome acts symbiotically to produce vitamins, repress expansion of pathologic organisms and facilitate digestion of dietary substrates, all the while being in constant contact with the host immune system, which it modulates [18]. By competing with pathogens for nutrients and by producing bacteriocin, short-chain fatty acids (SCFA), namely butyrate, acetate and propionate, and hydrogen peroxide, the gut microbiota effectively defends the host against bacterial infections [80–84].

The gastrointestinal microbiota shows a gradient in quantity and diversity from the stomach to the colon, with a limited number of species inhabiting the stomach because of its acidic environment, while increasing in number and diversity from the small to the large intestine. The number of species in the gut has been estimated to be between 500 and 1000 [78]; however, the most represented bacterial phyla (90%) consist of four types: *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria* [21,78]. The microbiota composition seems to be dictated by the first inoculum the newborn receives during childbirth, with some differences occurring between natural and cesarean delivery, and between subsequent breast- or formula-feeding [11,85]. After cessation of breast feeding, the reduction of immunoglobulin A (IgA) passage from the mother induces changes in the microbiome, for example, the increase of *Firmicutes* and *Bacteriodetes* [86]. During the first one to three years of life, the immune system and gut microbes develop a dependency relationship, leading to establishment of the host–microbiome homeostasis [87–89] destined to remain stable unless there is an occurrence of an illness, the use of antibiotics or considerable changes in diet [90,91].

The microbiota benefits from the mutualistic association with the human body, seeing as though the human intestine is a nutrient-rich environment; however, host diet, lifestyle, hygiene or antibiotic consumption induce rapid and constant changes in gut microbiota composition. The microbiome therefore can change rapidly as a result of variation in the composition of the microbiota.

IBD is clearly associated with intestinal dysbiosis. Changes in the microbiome have a pivotal role in determining the onset of the pathology, when the genetic background of the individual makes him/her predisposed and other concomitant environmental factors intervene [18].

Results of studies aimed at characterizing the microbiota of patients suffering from IBD, even sometimes with checkered results, indicate a generalized decrease in biodiversity, measured by an appropriate parameter—alpha [18]—as well as a reduction in specific taxa including *Firmicutes* and *Bacteroidetes*, *Lactobacillus* and *Eubacterium* [20–25]. IBD patients also present a reduction in species producing butyrate [92], a short chain fatty acid positively modulating intestinal homeostasis [93,94] and reducing inflammation [95].

A concomitant taxonomic shift, with a relative increase in *Enterobacteriaceae*, including *Escherichia coli* and *Fusobacterium* has also been observed [96]. Joossens et al. (2011) observed in CD patients increased *Ruminococcus gnavus* and decreased *Bifidobacterium adolescentis, Dialister invisus, Faecalibacterium prausnitzii*, alongside an unspecified member of *Clostridium cluster XIVa* [97]. Overall, there is a consensus for a reduction in the total number of species and a decrease in diversity of the microbiota in IBD.

In an elegant study by Lloyd-Price et al. (2019) [98], 132 IBD patients were recruited to identity their molecular profiles and to evaluate microbial activity during the course of the disease. Authors observed a functional dysbiosis in the gut microbiome during flairs of the disease with impaired microbial transcription and, concerning the composition of microbiota, facultative anaerobes were increased at the expense of obligate anaerobes.

4. Nutrients

The following paragraphs will address the impact of fats, proteins, carbohydrates and fibers on the onset of IBD and how they can influence the progression of the disease. As far as we know, the incidence of IBD is raised when the Western diet becomes popular, in particular in those countries where it was previously at low-incidence, such as southern Europe and Asia, resulting in the speculation that the nutritional approach might be correlated to the development of the disease [99].

4.1. Fats

The casual relationship between a high fat intake diet (HFD) and IBD was first hypothesized when an increase in incidence of CD was observed following the introduction of margarine in Europe at the beginning of the 20th century [100] and later in studies on the Japanese population, correlating fat consumption and incidence of CD and UC [101,102]. This association is now well-established, on the basis of different case-control diet studies and an HFD is regarded as a certain risk factor for developing IBD. More in-depth studies highlight a different impact on disease pathogenesis of different types of fats; particular attention has been paid to the different role of ω-3 and ω-6 polyunsaturated essential fatty acids (PUFA) with several studies demonstrating that ω-3 PUFA is anti-inflammatory, whereas ω-6 PUFA is pro-inflammatory and a balanced ratio of ω-3 to ω-6 PUFA is essential for homeostasis [103]. Indeed, Western diets usually involve a high ω-6 to ω-3 ratio, leading to a greater probability of developing IBD [101,104].

Other fats involved in increasing the risk of developing IBD are long-chain triglycerides (LCT), that prompt intestinal lymphocyte proliferation and up-regulate pro-inflammatory mediators [105]. Medium chain triglycerides (MCT), instead, suppress production of interleukin-8 (IL-8)—a neutrophil attractant mediator overexpressed in the mucosa of IBD patients [106,107]—and are therefore anti-inflammatory [9].

Increased risk consequent to HFD diet may be due both to increased intestinal permeability and to the alteration of the intestinal microbiota. Indeed, most healthy subjects following an HFD diet for one month had their plasma endotoxins levels increase, even if they did not develop inflammation [108]. The mechanism underlying increased permeability may involve under-expression of occludins, some proteins forming epithelial tight junctions [9]. Animal studies clearly show that the HFD diet alters the microbiota, favoring pathobiont expansion [109–111], similar to those observed in IBD patients [112].

4.2. Proteins

Recent studies connect high protein intake with changes in IBD incidence, suggesting high protein intake from different sources, including red meat, fish, eggs, milk, cheese, nuts may be also a factor modulating IBD incidence [9]. A prospective two-year survey of 67.581 middle-aged women showed that animal protein from fish or meat, excluding those from eggs or dairy, was correlated to increased IBD development [113]. An additional prospective study on the clinical course and relapse of UC patients showed that high meat intake was associated with a significantly increased risk of relapse [114]. Yet, other studies, on a large number of patients, failed to find an association between high protein intake and increased UC incidence [115]. Mechanisms underlying the role of proteins as a factor modulating the onset of IBD remain largely unknown [9]. It has been speculated that animal protein degradation in the gut may produce substrates favoring the expansion of pathobionts, or SCFAs modulating the function of enterocytes [95,114].

In particular, some metabolites coming from protein fermentation, such as ammonia and total sulfide, seems to be increased in UC patients when compared to healthy subjects [116]. As biological consequences, the mucus layer undergoes remodeling in terms of loss of cell and mucus increasing paracellular permeability. Other metabolites, deriving from normal protein degradation, can be considered harmful in such conditions of altered microbiota and gut inflammation:

1. phenolic compounds, the products of aromatic amino acids fermentation by *Bacteriodetes* spp and some *Firmicutes* (phenylacetic acid, phenols, indoles and *p*-cresol), have an in vitro damaging effect on the mucosal barrier function that depend, in vivo, on the presence of other nutrients
2. *N*-nitroso compounds have carcinogenic potential via DNA alkylation
3. polyamines (putrescine, spermidine and spermine) might affect the expression of a particular cotransporter for monocarboxylates such as lactate, pyruvate, leucine and many others, which contribute to the regulation of central metabolic pathways and insulin secretion
4. the metabolism of nitric oxide (NO), deriving from arginine, produces prooxidant species in IBD
5. unabsorbed bile acids influence the balance between acid sensitive/tolerant bacteria shifting toward the latter [116].

Noteworthy, polyamines are also exploited by several pathogens such as *Shigella flexneri*, *Streptococcus pneumoniae*, *Salmonella enterica*, *Helicobacter pylori* to increase their virulence [117].

When considering protein fermentation, of particular relevance are the effects on the matrix produced by the mucus barrier. The mucosal matrix plays a fundamental protective role in the gut, balancing the microbiota and preventing harmful bacteria from contacting the intestinal epithelium. In UC patients the mucus layer is thinner than in healthy subjects, displaying altered mucin composition, such as altered *O*-glycosylation of MUC2, the main mucin secreted. Mucins of affected subjects have impaired glycosylation, sialylation and sulfation that in remission phases can shift to normal levels [118]. *Ruminococcus torques* is particularly active in mucin degradation. Conversely, CD patients present increased MUC2 expression and reduced sulfation and glycosylation altering mucus viscoelastic properties during acute inflammation.

Taken together, these observations pinpoint IBD mucins alterations, due to increased rates of pathogen colonization and to their metabolism, as strongly impacting the worsening of the disease.

4.3. Carbohydrates

Carbohydrates show a different absorption profile within the intestine according to their degree of polymerization [9]. The small intestine hydrolyzes and absorbs simple sugars (glucose, fructose, sucrose and starch) while the microbial species in the large intestine degrade fructooligosaccharides and galactooligosaccharides, together with inulin. Insoluble fibers are not digested and increase the bulk of the feces [9,119].

Early studies in the late 1970s first suggested carbohydrates could be a risk factor for CD [120]; later, several studies highlighted a correlation between high sugar and low fiber intakes with IBD, and especially with CD incidence, with a different effect of different carbohydrates [121,122]. A possible mechanism underlying the effects of carbohydrates on gut microbiota is an imbalance in intestinal absorption leading to differential sugar profiles being available in the intestinal lumen, favoring the overgrowth of specific pathobionts [9]. This hypothesis is consistent with the observation that fructose malabsorption and lactose intolerance are associated with IBD [123] and with observations on animals showing that high carbohydrates intake favors dysbiosis [124]. Such observations have led to the formulation of several low- or selective-carbohydrate intake diets (see following paragraph).

Low fiber intake has also been associated with increased IBD incidence [7,100,104,121,122]. Fibers are fermented within the colon, where they promote bacterial diversity, preserve mucosal barriers and prompt the production of SCFA that, in turn, positively modulate intestinal homeostasis [93,94] and reduce inflammation [95]. As said, IBD patients show a decrease in butyrate producing bacterial species, as well as a decreased expression of butyrate transporters [92,125].

5. Dietary Additives

Food additives are used to preserve and enhance food quality and improve the taste of processed foods. They can be coating and coloring substances, fillers or stabilizers. In recent years, attention has been given to the effects of dietary additives in the evolution of inflammatory bowel diseases [126]. It has

been speculated that elements, such as carrageenan, are a source of sulfur for sulfate-reducing bacteria (SRB) such as *B. wadsworthia*. The hydrogen sulfide (H_2S) generated has been shown to have detrimental inflammatory effects in the colon, including DNA damage. Emulsifiers, detergent-like molecules as carboxymethylcellulose and polysorbate-80, are widely present in processed foods. They might induce damage in the mucus layer with ensuing alteration in the microbiome and worsening of colitis in animal experimental models [127,128]. Other agents are maltodextrin, used as filler or thickener (it affects gut microbiota, impairs mucus layer and can be involved in necrotizing enterocolitis), noncaloric artificial sweeteners largely present in many common beverages (induce dysbiosis and mucosal inflammation), inorganic nanoparticles, food colorants such as titanium dioxide (it has been shown to induce intestinal inflammation and to increase oxidative stress in mice) and antimicrobial agents (damage intestinal microvilli and impair intestinal epithelial barrier) [126].

6. IBD and Diets

The scenario outlined in the previous paragraphs, underlines how IBD incidence and course depend on the interplay between genetic predisposition and exposure to different environmental factors, including food intake, with certain food components possibly exerting a negative effect, while others possibly exerting a positive one. Given this scenario, an increasing interest has been given to diet as an easily modifiable environmental factor and, therefore, as a possible preventive or treatment option for IBD [99]. Indeed, IBD patients themselves attribute more importance to diet in affecting their symptoms, than to pharmaceutical treatment [129].

6.1. The Specific Carbohydrate Diet (SCD)

The Specific Carbohydrate Diet (SCD) was developed in the 1920s as a treatment for the celiac disease and given the positive results of its application in treating UC [130] was later proposed as an approach for managing IBD [131]. SCD, to be followed for one year during active flares and then for one additional year (and later resumed if symptoms reappear), involves excluding more complex carbohydrates, on the basis that when they reach the colon, being still undigested, they cause fermentation and overgrowth of bacteria and yeasts, switching the microbiome toward a pro-inflammatory profile, finally causing IBD [132,133]. Simple (mono-) saccharides are, instead, included. Allowed foods include unprocessed meats, most fresh vegetables and fruits, all fats and oils, aged cheeses and lactose-free yogurt. Prohibited foods include milk, grains, soft cheeses and non-honey sweeteners [99]. When re-switching to an uncontrolled diet, reintroduction of prohibited food occurs one food type at a time.

6.2. The Low FODMAP Diet

The low FODMAP diet involves, similar to SCD, a reduction in poorly absorbed and highly fermentable carbohydrates (monosaccharides, disaccharides, oligosaccharides and polyols), with the difference that monosaccharide intake is favored in SCD, while it is discouraged in FODMAP; the premise underlying the two diets is similar, i.e., that carbohydrates that are poorly absorbed may lead to large intestine dysbiosis, inflammation, fermentation, water secretion and lumen distension [134–136]. Foods high in FODMAPs that should therefore be excluded in the low FODMAP diet include high-lactose dairy, excess fructose vegetables/fruits and food rich in fructans/galactans and polyols. Low, regulated consumption of foods with moderate FODMAPs is allowed. Low FODMAPs foods such as dairy free from lactose, low fructans and galactans from vegetables and low fructose are allowed. At the beginning of this nutritional approach, patients should follow an initial 4–6 weeks of strict FODMAP diet adherence, followed by subsequent re-introduction of FODMAPs while monitoring symptoms, with the aim of reaching a FODMAP consumption that still manages symptoms [137]. The FODMAP diet should be followed under oversight of a dietitian, to avoid risk of micronutrient deficiencies or, worse, malnutrition [99].

6.3. The Gluten-Free Diet

The gluten-free diet has a clear role in managing celiac disease, involving elimination of gliadin. Allowed foods include gluten-free grains from corn and rice, fresh poultry or meat, fruits, vegetables and dairy; this diet has also been practiced by subjects suffering from non-celiac gluten sensitivity (NGCS), that is, individuals showing improvement of IBS-like symptoms when eliminating gluten, even if lacking of the genetic and immunological features defining the celiac disease [99,138,139]. How this diet may benefit IBD patients is less clear [99]. A possible mechanism may involve the inactivation of the immune system by amylase-trypsin inhibitors (proteins found in wheat and commercial gluten) and/or wheat germ agglutinin, as in NGCS [139–141], but gliadin might also increase intestinal permeability, translocation of bacteria and immune response interfering with epithelial tight junctions [142]. Further, the gluten-free diet also involves low FODMAPs consumption, with the consequent possible benefits already outlined for that approach [139,140]. Again, the gluten-free diet should be undertaken under supervision of a competent specialist because of its potential implications, including micronutrient and dietary fiber deficiencies [143].

6.4. The Anti-Inflammatory Diet

The anti-inflammatory diet is based on the aim of reducing inflammation by intake of anti-inflammatory phytonutrients and spices and omega-3 polyunsaturated fatty acids (from fish). The individual is advised to daily intake fruits and vegetables, providing anti-inflammatory compounds like vitamins B3, B6, E, C, beta-carotene as well as zinc and magnesium. Animal proteins are allowed but plant proteins from legumes are recommended [99]. A practical application has been provided by Olendzki et al. [144] who developed an anti-inflammatory diet for IBD patients, called nutritional regimen for IBD (IBD-AID). This diet differs from SCD as it allows for consuming some grains, gluten and probiotic foods, aimed at addressing some of the deficiencies of SCD and involves taking omega-3 fatty acids while decreasing total and saturated ones. The regimen develops into four phases with different food categories and texture [144].

6.5. The Mediterranean Diet

The Mediterranean diet is somewhat similar to the anti-inflammatory one as it involves intaking phytonutrients, unsaturated fats such as olive oil replacing saturated and trans-fatty acids, omega-3 polyunsaturated fats, vegetables, high-fiber whole grains, nuts and low intake of red meats [145]. Adherence to this diet has been correlated to a decrease in inflammatory markers [146,147]. This diet appears promising as a possible strategy to tackle IBD as evidence exists [104], when considering pre-illness diets, that high fruit and fiber diets protect against CD, and a great vegetable intake prevents the develop of UC, while high intake of meats, omega-6 fatty acids, polyunsaturated fatty acids, and total fats are associated with increased incidence of CD and UC. Different to other dietary approaches, the Mediterranean diet is less prone to expose the patient to nutritional deficiencies [99,145].

6.6. Other Nutritional Interventions

Other nutritional interventions rely on observations of different IBD incidence rate according to exposition to different food components. For example, given the anti-inflammatory effect of ω-3 PUFA outlined in Section 4, ω-3 PUFA have been investigated as supplementing agents possibly allowing to manage IBD; indeed, several reports showed that supplementation of ω-3 PUFA decreases inflammatory parameters but has no effect on disease activity or relapse rates [148–151]. Furthermore, two clinical trials on the supplementation with ω-3 PUFA showed mixed results for UC and concluded that supplementation cannot prevent CD relapse [152,153]. Instead of mere supplementation, results of another investigation indicate that a different approach, by balancing ω-3 and ω-6 PUFA, could be more effective, as IBD patients with a unitary ω-3/ω-6 ratio showed a higher remission rate [154,155]. Similarly, the observation that long chain triglycerides (LCT) rich diets increase IBD incidence, suggests that

low-LCT diets might be effective in inducing IBD remission [156,157]. However, more clinical evidence is needed to determine if fats with anti-inflammatory effects may be therapeutically advantageous in IBD [9].

7. Diets Effectiveness and Impact on Microbiota

Considering the mechanisms of action underlying how the different diets outlined in the section might be effective in managing or even treating IBD, two main—and interconnected—action modalities emerge: a possible direct modulation of inflammation or immune response and a positive effect on the microbiota/microbiome, with the latter based on knowledge about gut microbiota composition and metabolism, on the degradation pathways of different food components and on the observation that diet seems to have a crucial influence on microbiota composition and function both when switching from a vegetarian to an animal-food based diet [158,159] and from a high-fat/low fiber to a low-fat/high fiber diet [160].

7.1. The Specific Carbohydrate Diet (SCD)

In a survey of 50 subjects affected by IBD and self-treating with the SCD, the clinical remission was observed in 66% of patients after about 10 months following the nutritional regimen. Furthermore, numerous subjects were able to discontinue corticosteroid therapy [161]. The authors specifically indicate changes in intestinal microbiome they previously observed as a contributory mechanism explaining the positive results they observed [161]. An anonymous online survey completed by 417 adult patients suffering of IBD (47% CD, 43% UC, and 10% indeterminate colitis) and following the SCD, showed that 33% and 42% of patients experienced symptomatic remission after 2 and 6–12 months of diet, respectively [162]. Among the outcomes self-assessed by patients, abdominal pain was improved as well as improvements regarding diarrhea, blood in the stool, limitations of activities and weight loss. Of note, concerning the impact of SCD on the microbiota and microbiome, twelve pediatric patients aged 10 to 17 with mild to moderate IBD and subjected to SCD diet for 12 weeks underwent significant clinical improvement; the authors observed a distinctive dysbiosis for each individual in most pre-diet microbiomes ending in significant changes in microbiota composition after dietary switch. Interestingly, changes were not consistent in all patients (with contrasting results regarding even microbial diversity, where some patients showed increasing post-diet diversity, others showed a decrease) [163].

A case report of a young lady with a UC diagnosis and assuming SCD, showed that the diet successfully improved all UC symptoms and induced a dramatic variation of the microbiome. Prior to the SCD regimen, the most abundant species were *Fusobacterium ulcerans* and *Viellonella dispar*. In that study, the microbiota of the case subject was compared to that obtained from three healthy subjects with no restriction diet. None of the species *Fusobacterium ulcerans* and *Viellonella dispar* were found in the control subjects, where instead the dominating species were *Bacteriodeaceae, Ruminococcaceae* and *Lachnospiraceae*. After two weeks of diet, the patient's microbiome showed a decrease of *Fusobacterium ulcerans* alongside a marked increase of many *Enterobacteriaceae* species [164].

In another trial, six subjects with CD compared to two healthy controls, were treated with SCD or low residue diet for thirty days. Fecal samples were evaluated at day 1 and day 30. At baseline, the results, consistent with previous findings, showed a reduced microbial diversity in CD patients. The most increased classes were *Clostridia* and *Gammaproteobacteria* and some species of the *Phylum Bacteriodetes*, while *Clostridium lactifermentans* was reduced. After the SCD regimen, the microbial diversity increased with a high prevalence of nonpathogenic species of the clostridia family. However, no clinical significant improvement was observed [165].

On the whole, robust data—especially on adults—are lacking, and prospective investigations, possibly through comparative case-control studies, are warranted to get an in-depth understanding of how the SCD may impact the microbiota and the microbiome [99].

7.2. The Low FODMAP Diet

Concerning the low FODMAP diet, meaningful results have been achieved when using it as a tool to manage symptoms of irritable bowel symptoms (IBS) [166]; such findings are interesting considering that more than 30% of IBD patients also suffer from concomitant IBS [167,168]. When 89 adult IBD patients (28 CD, 61 UC) in clinical remission or with mild-to-moderate disease were randomized to undergo for 6 weeks either a normal diet or a low FODMAP, a significant improvement was observed in terms of quality of life and in terms of reduction of IBS-like symptoms [169]. These findings have been recently corroborated by Bodini et al, who observed an amelioration of the disease alongside a quality of life increase in 26 IBD subjects undergoing a low FODMAP diet compared to IBD subjects under a standard diet in a 6-week period [170].

Serial FODMAP challenges in a randomized, double-blind, placebo-controlled, crossover, re-challenge trial concerning IBS-like symptomatic IBD patients in remission showed that, contrary to galacto-oligosaccharides and sorbitol, the intake of fructans worsened gastrointestinal symptoms in patients with IBD compared to placebo [171]. Low FODMAPs diet in a small randomized, controlled, crossover trial on quiescent CD patients showed improvement in overall gastrointestinal symptoms; 9 patients were randomized to 21 days of low or high FODMAP diets with ≥21-day washout in between. Five-day fecal samples were collected at the end of each diet and analyzed for calprotectin, pH, SCFA and bacterial abundance and symptoms were recorded daily. SCFA, pH and total bacterial abundance remained unaltered; the relative abundance was higher for butyrate-producing *Clostridium cluster XIVa* and mucus-associated *Akkermansia muciniphila* and was lower for *Ruminococcus torques* during the high compared with low FODMAP diet. No effects were observed in calprotectin but the severity of the symptoms was worsened with the high FODMAP diet [172].

Yet, while it is currently accepted that IBD patients may be treated for their IBS-like symptoms according to a low FODMAP approach, little is known concerning how this diet may impact the underlying inflammation [99].

7.3. The Gluten-Free Diet

Herfarth and colleagues studied the prevalence of a gluten-free diet and the improvement of clinical symptoms in patients with IBD [173]. They considered 1.647 patients in a cross-sectional study, finding that 0.6% of them had a co-diagnosis of celiac disease and 4.9% reported NCGS. About 20% of the subjects had previously adhered to a gluten-free diet and 8.2% were currently following it; about 66% of patients who had followed the gluten-free diet reported improvement of intestinal symptoms and about 38% reported less severe and frequent IBD flares. Yet another large prospective study involving 1254 patients, most not being diagnosed with celiac disease, found no significant differences between patients adhering to a gluten-free diet and those who did not, concerning disease activity, hospitalization, surgery, or complication [174]. This study found a variation in the microbiota of patients adhering to the gluten-free diet; in fact, alpha diversity analysis tended to be higher in those affected by CD and following a gluten-free diet than in CD patients following a regular diet, with the lowest species richness observed in patients eating meat >4 days per week; in UC patients, the gluten-free group tended to have the lowest species richness, with a trend for the highest species richness in patients eating meat >4 days per week. The authors also observed significant differences in the operational taxonomic units (OTUs) between diet types in CD patients, where several representatives of the phyla *Bacteroidetes* and *Firmicutes* were significantly correlated with regular diet patients when compared to the those adhering to the gluten-free one; they did not observe similar differences in UC ones [174].

7.4. The Anti-Inflammatory Diet (AID)

Olendzki et al., who developed the IBD-AID diet, published a study concerning 11 IBD patients who were refractive to pharmacological treatment or had not adequately controlled symptoms [144].

All 11 patients reported an improvement in symptoms and could reduce medications. At present, no other data, either concerning inflammatory markers or microbiome modifications, are available concerning this diet [99].

7.5. The Mediterranean Diet

Results from clinical and translational research on the Mediterranean diet point to its possible meaningful use in managing IBD, and thus additional studies could have the potential to add further insights to the field [99]. Concerning published data, it was observed that 153 Italian healthy subjects were investigated for their dietary habits and their gut microbiota was assessed, and high-level adherence to a Mediterranean diet was found to beneficially impact the gut microbiota and associated metabolome [175]. These studies provided the first concrete evidence for the interconnection between Mediterranean dietary patterns, gut microbiota and microbial metabolites as they observed that the consumption of fruit, vegetables and legumes by subjects with satisfactory adherence to the Mediterranean diet was associated with an increase in fecal SCFA levels, an effect that was likely boosted by bacteria belonging to both the *Firmicutes* and *Bacteroidetes* capable of degrading carbohydrates not digestible by the host. When eight adult patients suffering from CD followed the Mediterranean diet for 6 weeks, their transcriptome analysis showed a change in expression of more than 3000 genes; changes in the intestinal microbiota, although not significant, showed a trend towards normalization [176] with an increase in the expression of *Bacteroidetes* (17.89% to 18.74%), *Clostridium cluster IV* (19.2% to 21.86%) and *Clostridium cluster XIVa* (26.78% to 28.79%) and a decrease in the abundance of *Proteobacteria* (5.93% to 5.48%) and *Bacillaceae* (4.65% to 4.21%).

The Mediterranean diet has a high amount of fiber, thus can be unsuitable for patients during flares of the disease but it is highly recommended after remission, with appropriate adjustments. In fact, the use of pulses, containing soluble fibers, has a prebiotic effect promoting the growth of microbial species that produce propionic and butyric acid which decrease inflammatory cytokines expression. Vegetables can be consumed both cooked and uncooked and broccoli especially seems to prevent relapse in CD patients [177]. Fruits can be treated with a juice extractor, to eliminate fibers and the minerals and vitamins contained are involved in the immunomodulation, as well as olive oil and bluefish which have anti-inflammatory effects.

8. Conclusions

The individual nutritional status is crucial to one's overall well-being and is one of the fundamental factors ensuring the appropriate function of the immune system.

By ensuring an adequate intake of nutrients during both flairs and remission phases of the disease, the nutritional approach truly influences the management of IBD.

The evaluation of the last decade's most relevant literature on the association between nutrition, IBD and microbiome shows that IBD is clearly associated with intestinal dysbiosis and that, at present, no specific nutritional regimen is effective for all CD and UC patients.

The role of many nutrients for developing IBD has been demonstrated; furthermore, several studies have showed that, in IBD patients, specific diets either negatively or positively influence disease symptoms. This effect seems to be associated with a variation in the gut microbiota.

Understanding how to modulate the composition and metabolism of gut microbiota through a nutritional approach could be a strategy to control the disease. The therapeutic goal is to achieve the remission of the disease and, possibly, to maintain an optimal homeostasis and prevent any relapse through a specific and individualized diet.

The hypothesis that nutrition might contribute to achieving and maintaining the remission of the disease is at the same time challenging and attractive. Future perspectives should include investigating the correlation between nutrients and microbiome through appropriate, well-designed and targeted clinical studies.

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