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Review

Dietary Modulation of the Gut Microbiome in Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD), which includes ulcerative colitis, and Crohn's disease, is a chronic relapsing-remitting inflammatory state of the gastrointestinal (GI) system. The cause of IBD is multifactorial, encompassing factors of genetics, environment, and the host immune system, initiating a complex interplay of maladaptive host immune responses and subsequent chronic inflammation. Aberrant host immune responses are at least in part due to changes in the commensal microbiome, which can in turn affect the development and progression of IBD. Diet is known to directly affect the composition of the microbiota which in turn affects the host immune system. Herein, we review the impact of dietary macronutrients, notable supplements, and selected dietary interventions on the gut microbiota and its effect on the

microbiome and host metabolism in patients with IBD. Having diet available as an adjunctive, manageable intervention for patients with IBD will remain a promising area of research for the foreseeable future.

Keywords
Diet; inflammatory bowel disease; Crohn's disease; ulcerative colitis; Mediterranean diet; dietary supplements

1. Inflammatory Bowel Disease and the Microbiota

1.1 Introduction

The two main manifestations of IBD are ulcerative colitis (UC), and Crohn's disease (CD). It is estimated there are over 6.8 million individuals affected with IBD worldwide, largely increased from 1990 when the prevalence was 3.7 million [1]. Both the incidence and prevalence of IBD are increasing globally at various rates [2-4]. The etiology of IBD remains elusive yet involves aberrant immune responses to environmental factors, such as dietary antigens. The maladaptive responses are at least in part due to changes in the commensal microbiome, which can in turn affect the development, and progression of IBD. The GI microbiome has been postulated to play a key role in IBD, both as a cause, but also as a propagator of IBD. Clearly, dietary components play a profound role in the function, and composition of the gut microbiota, and thus in the pathogenesis and treatment of IBD.

It is inherently difficult to investigate the complex interactions between dietary components and the microbiota. Several overarching dietary patterns, however, have been investigated in both epidemiological studies and clinical trials. Herein, we examine dietary macronutrients, notable supplements, and selected dietary interventions on the microbiome in patients with IBD and animal models of colitis. We will provide a background on CD and UC, discuss dietary components and their effect on the microbiota in IBD, as well as selected dietary patterns, such as the Mediterranean diet (MD), low fiber diets, and exclusion diets.

1.2 Crohn's Disease

Crohn's disease is characterized by transmural inflammation and skip lesions. While it may occur at any location of the GI tract, roughly 30% of patients have small bowel involvement, most commonly at the terminal ileum. Approximately 20% of patients have disease localized to the colon, and nearly 50% of patients have involvement of the small and large intestine [5]. Individuals with CD often experience periods of symptomatic relapse and remission with variation in disease severity. This typically follows a bimodal pattern at age of onset, with the first peak occurring between 15 and 30 years of age, and the second peak occurring mainly in women between the ages of 60 and 70 [6].

There are many genes at play, most notably the NOD2/CARD15 gene on chromosome 16, which recently has been shown to be associated with ileal involvement and earlier age of onset [7]. Variants at the NOD2 and CDH1 loci confer the largest increase in relative risk of IBD, and have been

associated with UC, specifically [8-10]. However, in non-Caucasian populations, the incidence of IBD does not correlate with NOD2 variation [11]. The pathophysiology involves a multitude of factors including genetic, immunologic, dietary, and infectious. It begins with focal inflammatory infiltrate around intestinal crypts, before progressing to ulceration of the mucosal layer. Non-caseating granulomas soon develop, and inflammation of the entire intestinal wall follows shortly thereafter. Chronic inflammation may lead to strictures and fibrosis of the intestine, increasing the risk for obstruction. Additionally, due to transmural inflammation, enterocutaneous, enterovesical, enterovaginal, and enteroenteric fistulas may occur [6].

1.3 Ulcerative Colitis

Ulcerative colitis is the other major type of IBD, and the more common form worldwide. It follows a bimodal distribution, with the first incidence peak occurring around 20 to 30 years of age, and the second peak occurring around 50 to 80 years of age [12]. It is characterized by continuous mucosal inflammation beginning in the rectum and extending proximally throughout the colon. Inflammatory infiltrate, primarily consisting of lymphocytes, invade the lamina propria and crypts of Lieberkühn, leading to crypt branching, and abscess formation. This further progresses to ulceration of the mucosa and submucosa, loss of normal vascular pattern, friability, bleeding, and granulation tissue [6, 12, 13].

Genetic susceptibility is the most significant risk factor, with family history encompassing 8% to 14% of patients, and leading to four times the risk of developing UC [13]. Additionally, it is hypothesized that genetically susceptible individuals who develop the disease undergo alterations in gut microbiota thereby affecting mucosal immunity. Ulcerative Colitis is strongly associated with primary sclerosing cholangitis and poses an increased risk for colorectal carcinoma with 5% of patients developing colon cancer [6, 12, 14].

1.4 IBD and the Microbiome: Dysbiosis

The microbiota of each person is unique with significant variability of taxa between persons. The intestinal microbiota comprises a multitude of phyla, the most common of which are *Bacteroidetes, Firmicutes, Proteobacteria,* and *Actinobacteria* [15, 16]. Diet is known to directly influence the composition of these phyla into distinct phenotypes, which directly affects the host immune system. Given the gut microbiota acts symbiotically to produce energy substrates, facilitate host metabolism, as well as modulate the host immune system. Specifically, the microbiota helps to modulate host immunity by protecting against pathogens.

The significant inter-individual variation in the microbiome composition can be attributed to multiple factors that affect development of the 'normal' microbiome. Several prenatal and childhood factors (childhood exposome), including amniotic fluid microbial composition, cesarean section versus vaginal delivery, breast versus formula feeding, and diet and local environment during childhood, are all associated with variation in composition of commensal flora [17]. Additional work has also demonstrated several phenotype associations in addition to childhood exposome, including diet, current exposome, socioeconomic factors, and general state of health [18]. Of the phenotype groups, diet seems to have a greater associative effect on commensal microbial composition than socioeconomics, general medical factors, and current and childhood exposomes [18].

The microbiome and the host have a mutual symbiotic relationship where the host provides a diet rich in nutrients, while the gut microbiome can affect many physiologic mechanisms and cascade pathways. More importantly, evidence has shown that certain microbiome antigens play an immune-mediated destructive or protective role in inducing the differentiation of mucosal CD4+ T cells into T-helper 1 cells, T-helper 17 (Th17) cells, or T-regulatory (Treg) cells [19]. The balance of Th17 and Treg cells, which is characterized by levels of pro-inflammatory and anti-inflammatory cytokines, is critical for the host's intestinal homeostasis, and is directly affected by the normal gut microbiota content. Moreover, the mucosal immune cells act in concert with the intestinal barrier to maintain a balanced flora. A misbalanced flora, or dysbiosis of the flora, can result in damage to the intestinal microbial barrier.

Dysbiosis encompasses a change in the composition of the commensal microbiome as compared to those of healthy individuals. It has been viewed as a risk factor in the pathogenesis of many GI diseases including GI reflux disease, peptic ulcer disease, infections, and various cancers [20-22]. Describing changes in the gut microbiome taxonomy generally includes describing changes in the composition of the major phyla *Bacteroides* and *Firmicutes*. The ratio of these phyla has important influence in maintaining normal intestinal homeostasis, expressed as the *Firmicutes/Bacteroidetes* (F/B) ratio [23]. It is generally accepted that decreases in the F/B ratio have been associated with IBD [23]. *Bacillus, Clostridium, Enterococcus, Lactobacillus*, and *Ruminicoccus* are the most common genera in the *Firmicutes* phylum. Whereas in the phylum *Bacteroidetes*, the most common genera include *Bacteroides, Parabacteroides,* and *Prevotella*.

Specific alterations in the genera have been associated with IBD. For instance, *Fecalibacterium prausnitzii, Clostridium,* and *Bacteroides* have been associated with a decreased abundance in IBD [24, 25]. On the contrary, *Escherichia coli, Fusobacterium,* and *Veillonella* have been associated with an increased abundance in patients with IBD [24, 25]. Further, these changes and modulations in the genera composition were associated with disease activity in patients with IBD. In a study comparing active UC and inactive UC, there was a significant difference in the abundance of *Firmicutes* [26]. In the study, there was similarly a significant difference in those with severe CD as compared to mild to moderate CD [26]. The equilibrium of the gut microbiota with the host is highly important to overall systemic physiology, intestinal barrier integrity, and host immunity. Next, we will discuss how dietary components can directly affect the composition of the intestinal microbiota.

2. Dietary Macronutrients and the Gut Microbiota

2.1 Fats

Dietary fats play essential and critical roles in metabolism, cell function, and comprise cell membranes. Dietary fatty acids can be classified into saturated fatty acids and unsaturated fatty acids. Unsaturated fatty acids include monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). PUFAs can be further classified into omega-3 (n-3) and omega-6 (n-6) fatty acids. The intake of dietary fats has significant and varied effects on the immune system through changes in gut microbiota composition and changes in paracellular permeability by interacting with epithelial cells directly [27]. Evidence supports proliferative changes in the colonic microbiome lead to cytokine production, with a subsequent effect on the host immune system.

Key players in the inflammatory pathways include Toll-like receptors (TLRs) and NF-κB. Activation of NF-κB leads to the production of pro-inflammatory cytokines [28]. PUFAs inhibit the NF-κB

pathway through protectins. The influence of dietary PUFAs on inflammation may be due to increased endotoxemia as evidence supports a direct correlation between plasma endotoxin levels and dietary fat intake, affecting epithelial gut permeability [29]. These changes are demonstrated in germ-free mouse models colonized by dysbiotic flora and with high fat microbiota transfers. Several studies on murine and human models have demonstrated several possible etiologies-increased endotoxemia [30], increased gut permeability [31], and a shift in the gut microbiota composition [32].

The F/B ratio, as discussed previously, influences intestinal homeostasis [23]. High fat (HF) diets have been shown to induce changes in both murine models and human trials [33]. HF diet changes in animal and human models were characterized by a decrease in *Bacteroides,* and an increase in *Firmicutes*, a possible hallmark for obesity [23]. These changes in taxonomy affect the gut metabolome and modulate the expression of tight junctions in the mucosal gut barrier [33, 34]. The microbiota of mice fed a HF diet were transferred to germ-free mice, with a notable increase in body fat. The microbiota of obese individuals, and of those fed a HF diet, are characterized by a decrease in *Bacteroides* and an increase in *Firmicutes* [23, 33]. Depletion of *Bacteroides* results in dysbiosis via depletion of short-chain fatty acids. HF diets induce a pro-inflammatory state, decrease microbial diversity, promote intestinal colonization with pathobionts, exacerbate colitis severity in murine models, and are associated risk factors in patients with IBD [29, 35-42].

The effect of dietary fatty acids on microbiota changes differ according to the type as each type has varied effects on the immune system and inflammatory cascades. MUFAs, n-6 PUFAs, and n-3 PUFAs each play a different role in IBD pathogenesis [43].

2.2 MUFAs and PUFAs

The different roles of n-3 and n-6 PUFAs are demonstrated by their metabolism by-products. The metabolism of n-6 and n-3 fatty acids results in different effects on inflammatory cascades. Although there is some disagreement, effects of n-3 PUFAs on inflammation are generally considered anti-inflammatory, whereas n-6 PUFAs are pro-inflammatory [44]. N-3 PUFAs include eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6). PUFAs are important constituents in cell membranes and phospholipid bilayers. Increasing intake of PUFAs modifies cell membranes by increasing EPA and DHA [45]. By influencing the cell membrane constituents, PUFAs influence the function of cells involved in inflammation as well as alter the microbiome composition.

A large majority of the gut microbiota belongs to the phyla *Bacteroidetes* and *Firmicutes*, as well as the genera *Lactobacillus* and *Bacteroides*. The type of dietary fat is a major driver of these phyla and genera structures. In one study exploring the differences in the microbiota of murine models fed differing fat diets, the microbiota of the fish oil diet had higher levels of *Lactobacillus* as compared to those fed a lard diet [46]. The species *Lactobacillus* has been linked to reduced gut inflammation in IBD [35]. N-3 PUFA supplementation produces a positive impact on gut microbiota through changes in its common genera as evidenced in a recent randomized, open-label, crossover trial [47]. The study was 8 weeks in duration and supplementation consisted of 4 grams of mixed EPA/DHA supplementation with a washout period of 3 months. The study demonstrated a reversible increased abundance of several genera, including *Bifidobacterium*, *Roseburia*, and *Lactobacillus* with the n-3 PUFA interventions, all of which are butyrate-producing bacteria. No statistically significant changes were observed in the F/B phyla ratio. Butyrate-producing bacteria have been

linked to favorable effects due to short-chain fatty acid (SCFA) production by the microbiota and restoration of epithelial barrier integrity in patients with IBD [48-50].

Other studies have considered whether certain ratios of fatty acids have more favorable effects on microbiome changes in an effort to optimize immune function. An increased n-6/n-3 ratio and a correlation to an increased incidence of IBD have been noted in several studies [51, 52]. One study demonstrated an increased risk of developing UC in patients with high n-6 PUFA intake and a reduced risk with n-3 PUFA intake [51]. In a prospective study of women enrolled in the Nurses' Health Study cohorts, comprised of 269 incident cases of CD, and 338 incident cases of UC, greater intake of n-3 PUFAs was associated with a lower risk of UC.

An optimal ratio of n-3 to n-6 PUFAs is desirable as the former is associated with benefit in patients with IBD, and the latter with risk. One such study examined the relationship between multiple oil blends, to include both MUFAs and PUFAs [53]. The authors sought to investigate how multiple oil blends affect the intestinal microbiota in 25 persons after 1 month of treatment. The treatments included three diets with differing MUFA:PUFA ratios. The study demonstrated microbiota shifts at the lower taxonomical levels rather than at the phyla level, but the effect was more pronounced in the obese subjects. The MUFA-rich treatments increased the populations of *Prevotella* and *Parabacteroides*, and decreased *Isobaculum*. The two PUFA-rich diets favored an increase in *Isobaculum*. These genera have not been well studied so their function in an increased capacity has not been elucidated. However, these results suggest a profound effect of BMI on treatment effect in gut microbiota at lower taxonomical levels.

Higher BMI has been associated with a greater abundance of *Firmicutes*, and a lesser abundance of *Bacteroidetes* in phyla ratios. Moreover, a recent study investigating the influence of a fish oil enriched diet on intestinal tissues, taken from patients with IBD, found a significantly increased ratio of interleukin-1ra (the receptor antagonist of IL-1) resulting in a decrease in the pro-inflammatory IL-1 activation [54]. *Bifidobacteria, Lactobacilli, Prevotella spp.,* and *Roseburia spp.*, all known to be beneficial gut bacteria, were significantly increased whereas harmful gut bacteria were significantly decreased.

In summary, most studies indicate a beneficial effect of dietary n-3 PUFAs on the gut microbiome. Dietary n-3 PUFAs have shown to affect gut integrity, improve epithelial barrier function, optimize the F/B ratio, and increase the abundance of butyrate-producing bacteria thus favoring anti-inflammatory activity.

2.3 Omega-3 Supplementation in IBD

Supplementation of n-3 fatty acids has been employed in multiple RCTs in an attempt to replicate its perceived effectiveness in ameliorating inflammation. In a Cochrane meta-analysis, n-3 PUFA supplementation was suggested to aid in the maintenance of remission in CD [55]. It also noted an inverse relationship between n-3 consumption and the risk of IBD. However, when analyzing several of the larger studies to exclude inherent bias, the authors concluded n-3 PUFA supplementation was unlikely to be effective for the maintenance of remission in CD and was not better than placebo for preventing relapse [52]. In summary, dietary fish oil-derived n-3 PUFAs may affect disease outcomes in a beneficial manner for those with IBD. However, there is clearly a need for further study to better characterize how n-3 PUFAs may improve biomarkers, clinical outcomes, and restore a homeostatic microbiome.

2.4 Carbohydrates

Carbohydrates serve as a key source of nutrition for the microbiota as well as the host. Carbohydrates can be categorized as digestible and non-digestible. Digestible carbohydrates include both mono- and disaccharides as well as starches. Non-digestible carbohydrates are mainly found as components of dietary fiber. In general, high sugar diets are associated with an increased risk of UC and CD [56]. Large epidemiological studies have defined an association between both refined sugar and artificial sweeteners with IBD incidence [51]. A high sugar diet can alter the gut microbial composition and diminish SCFAs, a proposed mechanism to exacerbate colitis [56]. The proposed mechanism suggests as different carbohydrates are digested, an imbalance in intestinal absorption is created in the lumen, leading to growth of specific pathobionts [57]. In patients with IBD, carbohydrate malabsorption is a common observation and lends support to high carbohydrate diets favoring dysbiosis [36, 57-59].

2.5 Short-Chain Fatty Acids

Fiber consists of soluble and insoluble fiber. Although non-digestible carbohydrates do resist digestion, they are able to provide the body with energy through fermentation. For instance, fiber can be fermented into SCFAs by the gut microbiota to produce carbon and energy. The SCFAs produced by gut bacteria are acetate, propionate, and butyrate. When SCFAs are produced by the gut microbiota, through a variety of anti-inflammatory local effects, they protect the host and have beneficial effects on energy metabolism. Butyrate and other SCFAs have anti-inflammatory effects that improve host immunity, mainly though promotion of optimal intestinal barrier function and integrity. Consequently, a lack of fiber may compromise intestinal barrier function and perpetuate IBD, the mechanism of which is still to be completely understood.

The gut microbiome in patients with IBD is associated with a depletion of SCFA-producing bacteria as evidenced in fecal and mucosal samples [56]. Among the dominant butyrate-producing taxa, the *Ruminococcaceae* and *Lachnospiraceae* families of the *Firmicutes* phylum have been noted to be depleted in those with IBD, as well as *Faecalibacterium prausnitzii,* and *Roseburia hominis* [60, 61]. In IBD, other notable alterations have been noted in *Eubacterium*, *Roseburia*, *Anaerostipes*, and *Coprococcus spp* [62, 63]. Research suggests a key genetic microbial inability to produce butyrate or a significant decrease of which is involved in IBD pathogenesis [62].

2.6 SCFA Supplementation in IBD

SCFAs have been employed in multiple RCTs with various delivery methods in an attempt to ameliorate IBD-related inflammation [64-69]. In a recent RCT, the authors sought to evaluate the colonic-delivery formulation of butyrate, and its effect on the fecal microbiota [68]. The study was designed as a double-blinded placebo-controlled study of 49 patients with IBD. Patients were randomized to receive microencapsulated sodium-butyrate or placebo for 2 months. Prior to treatment, patients with CD had a lower abundance of *Feacalibacterium, Akkermansia,* and *Lachnospiraceae* as compared to healthy controls. After treatment, in patients with CD, there was an increase in butyrogenic colonic bacteria *Butyricicoccus*. In patients with UC, there was a notable increase in *Lachnospiraceae spp*. However, the authors did not find any difference in terms of clinical outcome or disease activity. The authors also noted limitations of the study to include a small

sample size, and the majority of the patients were not in active UC or CD. However, the study concluded oral butyrate did modulate the composition of the microbiome to more favorable ratios and increased SCFA production. This study establishes a possible directed intervention to optimizing outcomes in IBD through SCFA supplementation or butyrogenic bacteria.

2.7 Protein

Dietary proteins are derived from many different foods and represent a significant component in both animal and plant products. Animal-based proteins differ from plant-based proteins in terms of amino acid composition, nutritional value, bioavailability, quality, and quantity. Animal-based proteins tend to have a higher level of bioavailability and essential amino acids but also more saturated fat. High protein intake, mainly animal protein such as meat or fish but not eggs or dairy, is associated with an increased risk of UC and CD [70, 71]. Animal-derived foods have consistently been associated with higher abundances of *Firmicutes, Ruminococcus* and pathways favoring endotoxin synthesis [72].

Consumption of certain amino acids has been studied in terms of immunomodulation, and pro- and anti- inflammatory cascades. Whereas consumption of glutamine, arginine, histidine, tryptophan, and threonine has been demonstrated in murine colitis models to improve clinical and biochemical markers [73-81]. High consumption of branched-chain amino acids (BCAAs) has been associated with oxidative stress while low consumption has an anti-inflammatory effect [82-84]. Moreover, consumption of certain amino acids may lead to dysbiosis and worsening of colitis [85].

3. Noteworthy Dietary Supplements and the Gut Microbiota: Curcumin, Vitamin D, and Polyphenols

3.1 Curcumin

Curcumin, found in the Indian spice turmeric, has long been purported to have anti-inflammatory medicinal properties [86]. Its antioxidant properties are largely due to potent inhibition of NF-κB activation and inhibition of TNF-mediated actions [87-90]. In the microbiome, its effects have been investigated in murine models as well as human models as to protect gut barrier integrity and increase species diversity [91, 92]. In one study, curcumin supplementation ameliorated endotoxemia induced by a HF diet in rat models [93]. Another study illuminated how curcumin can increase the abundance of butyrate-producing bacteria, which led to improved gut barrier integrity [91]. The study found a significant increase in the species *Clostridium*. Another study found curcumin to increase the relative abundance of *Lactobacillales* [94].

In human models, a double-blinded, randomized pilot study used turmeric, curcumin, or a placebo (turmeric tablets contained 1000 mg turmeric root and the curcumin tablets contained 1000 mg of curcumin) for a total of 8 weeks and determined subsequent changes in the gut microbiota community architecture [92]. Among the individual participants, microbiome species diversity did increase although patterns in increase were not uniform among the subjects. Although both turmeric and curcumin altered the gut microbiota in a similar pattern. The authors describe the subjects in terms of “responders” and “non-responders.” The “responders” had an increase in *Clostridium spp., Bacteroides spp., Citrobacter spp., Cronobacter spp., Enterobacter spp., Enterococcus spp., Klebsiella spp., Parabacteroides spp.,* and *Pseudomonas spp*. The authors

postulated that these results suggest individual response to curcumin dependent on host characteristics. In previous studies [51], host BMI was a significant factor in phyla shift dynamics, although the authors did not comment on this characteristic. The results suggest subject-to-subject variation in response dynamics. These studies support the anti-inflammatory and antioxidant effects of curcumin, and their effect on the microbiome through down regulation of pro-inflammatory cytokines.

3.2 Curcumin Supplementation in IBD

In a randomized, placebo-controlled, double-blinded study, curcumin was given in combination with mesalamine to patients with mild to moderate UC [95]. The treatment group consisted of mesalamine and curcumin capsules (3 g/day) whereas the placebo group consisted of mesalamine and an identical placebo. Clinical remission rates were significant in the group with curcumin (53.8% versus 0%; P = 0.01). In addition, clinical response (65.3% versus 12.5%; P < 0.001), and endoscopic remission (38% versus 0%; P = 0.043) were also found to be significant as compared to mesalamine and placebo. The study demonstrates the efficacy of curcumin as an adjuvant treatment to standard therapy. These findings have been replicated and validate that the adjunctive use of curcumin with mesalamine versus the use of mesalamine alone in the treatment of UC increased the odds of clinical remission by threefold [96]. Studies have also demonstrated that curcumin has the ability to significantly improve rates of maintenance of remission in patients [97]. A recent meta-analysis showed curcumin significantly improved clinical and endoscopic remissions in patients with IBD [97]. These findings have not been replicated in those with CD. Further, although these studies demonstrate the ability of curcumin to induce remission in patients with active mild to moderate UC, demonstration of these findings in concordance with microbiome changes has not been studied.

3.3 Vitamin D

Vitamin D is a fat-soluble vitamin that is metabolized to form $25(OH)D_3$, and then hydroxylated to generate $1,25(OH)_2D_3$, one of the active metabolites. The active vitamin D hormone binds to the vitamin D receptor (VDR). The VDR is highly expressed in the intestinal tract. Vitamin D has been found to be deficient in up to 60% of patients with IBD [98, 99]. Vitamin D plays an important role in gut microbiota modulation [98, 100, 101]. Downregulation of the VDR has been associated with a decrease in *Lactobacillus*, and an increase in *Proteobacteria* [100]. Vitamin D mechanisms clearly modulate the gut microbiota, the significance of which will be discussed herein.

Vitamin D has been shown to correlate with disease activity in those with IBD. In a retrospective longitudinal study, serum vitamin D levels were inversely associated with inflammatory markers and clinical disease activity in patients with IBD [101]. Vitamin D protects the intestinal epithelial barrier and modulates the gut microbiota [100-102]. In addition, the VDR acts as a transcription regulator and is inversely correlated with markers of colonic inflammation [103]. VDR expression has been shown to affect the gut microbiome by promoting SCFA production and protecting intestinal barrier integrity. In murine models, vitamin D supplementation has demonstrated the ability to increase the microbiota species of *Clostridium, Bacteroides,* and *Proteobacteria ssp* [104]. In a large clinical study, there was a notable correlation between the active metabolite of vitamin D and butyrate producers [105]. Thus, it is possible that VDR, in combination with the active vitamin D metabolite, may inhibit the inflammatory response seen in IBD.

3.4 Vitamin D Supplementation in IBD

Vitamin D supplementation has been employed in several clinical trials with perceived potential to modulate the microbiota. In one study in patients with CD in remission, vitamin D supplementation resulted in significant shifts in gut microbiota composition [106]. In the study, an increase in the abundance of beneficial bacteria like *Alistipes, Parabacteroides, Roseburia,* and *Faecalibacterium* was observed. As previously mentioned, in patients with IBD, a reduced abundance of *Faecalibacterium* has been noted. It is an important commensal microbe that produces SCFAs. Moreover, in a prospective pilot study aimed to evaluate markers of intestinal inflammation and changes in the fecal microbiota, patients with active and inactive UC were supplemented with 40000 IU of vitamin D once weekly for 8 weeks [107]. The study showed an improvement in objective markers of inflammation following vitamin D replacement in patients with active UC. Across all participants, an increase in *Clostridium,* and *Enterobacteriacae spp.* was noted. However no overall change in fecal microbial diversity occurred following vitamin D supplementation. The authors suggested it is possible that vitamin D supplementation does not affect the gut microbiome, or that the difference between fecal and mucosal microbiotas was not observed in the small study. Optimization of vitamin D clearly may have effects on the immune system by improving the composition of the microbiome through a series of dynamic interactions, however larger clinical trials are warranted to draw this conclusion.

3.5 Polyphenols

Polyphenols are classified as organic chemicals and into five major classes (flavonoids, phenolic acids, tannins, lignans, and stilbenes). Their potential mechanism of ameliorating oxidative stress via anti-inflammatory properties makes them an attractive option for potential therapeutics. The link between IBD and dietary polyphenol has been variable in current literature. A large cohort study did not show an association of IBD and polyphenol intake, while other work has associated daily polyphenol intake (primarily in green tea) with decreased risk of IBD [108]. Resveratrol is a stilbene found in grapes and red wine associated with a lower risk for CD [109]. Epigallocatechin-3-gallate (EGCG), a flavonol found in teas, has been associated with a lower risk of both UC and CD [110-112].

It has been postulated that polyphenols exert antioxidant and anti-inflammatory effects mainly via mechanisms of regulating gut microbes [113]. EGCG has been associated with microbiome changes that may provide protection from IBD. One study evaluating efficacy of EGCG found an increase in abundance of *Akkermansia* and SCFAs, especially butyrate, in murine colitis models [112]. FMT from these treated mice into separate murine colitis models was demonstrated to reduce colitis and reproduce the microbiome compositional change and increase in SCFAs.

Resveratrol was found to increase microbial diversity, alter the F/B ratio, decrease the abundance of *Enterococcus faecalis*, and increase the abundance of *Lactobacillus* and *Bifidobacterium* [113]. In a study to explore the therapeutic efficacy of resveratrol on murine IBD models, resveratrol was found to significantly reduce disease activity indices and improve histologic alterations [114]. In another murine study, resveratrol treatment improved gut barrier integrity and ameliorated UC colitis models [115].

3.6 Polyphenol Supplementation in IBD

Polyphenol supplementation has been employed in two studies with potential to regulate disease activity [116]. In a pilot study, oral EGCG supplementation was associated with decreased UC activity index in comparison to controls [112]. In a randomized, double-blinded, placebo-controlled study, 50 patients with active UC supplemented their diets with 500 mg resveratrol or placebo for 6 weeks [116]. Serum inflammatory markers were assessed at baseline, and at the end of the study. Resveratrol supplementation led to a significant reduction in inflammatory markers. The authors concluded that supplementation with 500 mg resveratrol can modify disease activity in patients with UC. However, demonstration of these findings in concordance with microbiota changes has not been studied. Future studies and clinical trials are clearly needed to confirm the perceived potential of resveratrol, and its likely effect on the gut microbiome in humans. It has been noted that oral polyphenols have low bioavailability, when undergoing metabolism in the intestine the bioavailability of resveratrol is less than 1% [117-119]. It has also been suggested that rectal administration may provide benefit due to high direct mucosal exposure, although further study is needed to explore the clinical applications.

4. Diets and the Gut Microbiota

4.1 Notable Diets in IBD

Emerging data, through large epidemiolocal studies, demonstrate a typical Western diet (WD) is associated with the rising prevalence of IBD and systemic low-grade inflammation [120]. The WD is characterized by a high intake of processed and pre-packaged food items, as well as animal protein, dairy, grains, refined sugar, and low fiber foods. Such food items contain high amounts of n-6 PUFAs, saturated fatty acids, sugar, and sugar substitutes. Importantly, these food items also lack fiber, n-3 fatty acids, and plant polyphenols. As discussed previously, these dietary components are important for gut barrier integrity, intestinal microecology, and immune function. On the contrary, there is a negative association of IBD rates with the consumption of food items characteristic of the Mediterranean diet (MD) [121]. Although there are strong epidemiological associations, few interventional trials and clinical studies have been pursued given the inherent difficulty in studying dietary patterns. However, few are underway and will greatly add to our understanding, which will be discussed herein.

Historically, exclusive enteral nutrition (EEN) has proven efficacy in IBD [38, 122-126]. EEN is a first line therapy in pediatric CD but is not routinely used as first-line therapy in adults as its application varies around the world [123, 126-129]. EEN may induce remission via modulation of the gut microbiota, however the mechanisms by which are still not well understood. In adult patients with mild to moderate biologic naive CD, a dietary modification of EEN, titled the Crohn's disease exclusion diet (CDED) with or without partial enteral nutrition, was effective for induction and maintenance of remission [130]. The diet is highly restrictive and is designed to exclude food items that adversely affect the microbiome [130-132]. The specific carbohydrate diet (SCD) is a dietary intervention focused on consumption of specific carbohydrates, like monosaccharides, and excludes disaccharides, and most polysaccharides [133]. The SCD has been demonstrated to induce and maintain remission in pediatric patients with IBD albeit the majority of evidence is based on small case studies and adherence can be challenging [133-138].

In review of the ESPEN guidelines, there is no diet that is generally recommended for adult patients with IBD [139]. However, several diets may prove to be an effective and a viable option for adults. The low fermentable, oligo-, di-, monosaccharides, and polyols (FODMAPs) diets have shown promise in improving functional symptoms [140, 141]. The low FODMAP diet is associated with improvement in IBD disease symptom severity according to a recent Cochrane review. However, the research does not support the diet affecting disease activity or inflammatory markers [140-143]. Large clinical studies have been completed and are also underway for the MD, which will be discussed herein [144-147].

The MD is characterized by vegetables, fish, nuts, seeds, extra-virgin olive oil, fruits, whole grains, dairy, as well as low amounts of red meat [148]. These food items are abundant in fiber, n-3 fatty acids, and plant polyphenols. These dietary components and high-level adherence to the MD influence the composition and function of the gut microbiome with a beneficial impact on inflammation and the metabolome [149, 150]. Studies have found an interconnection between the MD and microbial metabolites, such as an increase in SCFAs and butyrate-producing bacteria [149, 150]. The studies demonstrated an increase in *Firmicutes, Bacteroidetes, Clostridium,* and a decrease in the abundance of *Proteobacteria* and *Bacillaceae*. A recent controlled interventional study investigated dietary intake and gut microbiota in patients with CD in remission [151]. Fifteen patients with quiescent CD consuming a low plant-based, and high meat-based, diet received a 12-week structured diversified dietary intervention based on the MD. The study noted an increase in *Faecalibacterium*, and *Bifidobacterium*, and a decrease in *Proteobacteria*. These findings suggest the MD can induce positive changes in the gut microbiota, implying a mechanism by which diet induces remission in IBD.

4.2 Conclusion

While the exact etiology of IBD is unknown, there exists an imbalance of pro-inflammatory and anti-inflammatory mediators which modulate immune responses to environmental factors in a genetically susceptible host. The wide-ranging effect of the microbiome is imperative in this illustration as diet influences the evolution of host-specific changes in the microbial community. Interestingly, the specific dietary factors responsible are not yet well defined. However, certain dietary patterns such as the MD have been shown to direct toward immunologic optimization, intestinal integrity, and a balanced microbiome. Further, several noteworthy dietary supplements also appear to hold significant therapeutic potential for IBD management approaches.

Author Contributions

Dr. Johnson DA contributed to the construction of the project; all authors wrote and edited the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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