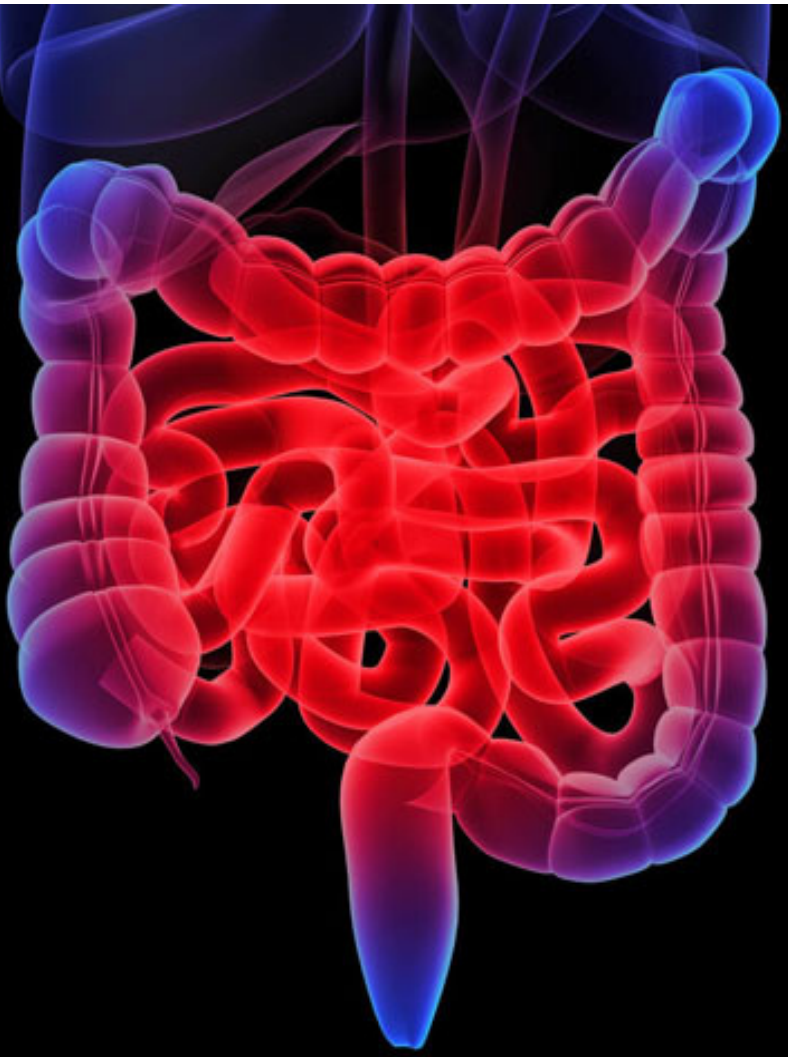

INFLAMMATORY BOWEL DISEASE

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The Role of Dietary Nutrients and Directed Interventions in the Management of Inflammatory Bowel Disease

Lindsey B Cundra, MD[1]; Steve M D'Souza, MD[1]; Byung S Yoo, MD[1]; Parth J Parekh, MD FACP[1]; David A Johnson, MD MACG FASGE MACP[2]*

[1]Department of Internal Medicine, Eastern Virginia Medical School, Norfolk VA, United States

[2]Professor of Medicine/Chief of Gastroenterology, Eastern VA Medical School, Norfolk VA, United States

Corresponding Author: David A Johnson, MD MACG FASGE MACP

Professor of Medicine/Chief of Gastroenterology, Eastern VA Medical School, Norfolk VA, United States

Email: dajevms@aol.com

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Abstract

Diet is known to play a profound role in the pathogenesis of inflammatory bowel disease (IBD) via mechanisms influencing the composition and function of the commensal microbiome. While difficult to isolate specific dietary components involved in the pathogenesis, etiology, or treatment of IBD, emerging data is consistent with the notion that a Western-style diet is associated with rising prevalence of IBD. Epidemiological studies have demonstrated an inverse association of IBD rates with the Mediterranean-style diet and clinical interventional studies have demonstrated efficacy in some dietary therapies, such as exclusive enteral nutrition, the specific carbohydrate diet, and the Mediterranean diet. Investigation of dietary patterns is inherently difficult when considering the complex interactions between dietary components, thus specific dietary targets presently remain a hypothesis. However, consumption of vegetables, fruits, and whole grains is advised, along with avoidance of red meat, high fructose corn syrup, trans- and saturated fatty acids. Quality and high-powered randomized controlled trials are needed for each dietary intervention as well as to provide insight into the benefits and harms of specific dietary components. We review the role of dietary nutrients and directed interventions in the etiology and management of IBD. Future prospects demonstrate the potential for an individualized approach to dietary therapy as the complex web of interactions between the gut microbiome, host dynamics, and dietary antigens are better understood.

Introduction

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease of the Gastrointestinal (GI) tract that includes Ulcerative Colitis (UC) and Crohn's Disease (CD). Both CD and UC undergo a relapsing-remitting course of transmural or mucosal inflammation, respectively. The etiology of IBD remains elusive yet is known to involve the gut microbiome and maladaptive inflammatory responses to environmental factors in susceptible hosts with genetic predispositions. Environmental factors such as dietary antigens can modify the composition and function of the host microbiome through sensing of intraluminal ligands, which result in changes in molecular traffic and a shift toward a pro-inflammatory state [1,2]. The related changes can affect epithelial barrier integrity, which predisposes the host to immune dysregulation, adverse health effects, and disease. Studies have linked refined sugar, animal protein, processed foods, and low-fiber foods to an increase in the prevalence of IBD [3-7]. These foods contain certain dietary components that may harm the GI system and have been explored in experimental studies: n-6

(omega-6) polyunsaturated fatty acids (PUFA), saturated fatty acids, trans unsaturated fatty acids, sugar substitutes, and food additives, such as carrageenan, maltodextrin, emulsifiers, and polysaccharides [8-17]. This dietary pattern is consistent with the typical Western Diet (WD), which is characterized by high intake of processed and pre-packaged food items, animal protein, dairy, and grains. Notably, the increasing incidence of IBD parallels urbanization and a shift toward a Western-style diet [18]. On the contrary, epidemiological studies have established an inverse association with rates of IBD and consumption of certain food products such as vegetables, fish, nuts, seeds, and extra-virgin olive oil, i.e. the Mediterranean Diet (MD) [19]. These foods contain nutritional elements that may confer distinctive health benefits and have been explored in experimental studies: Dietary fiber, short chain fatty acids (SCFAs), omega-3 fatty acids, plant polyphenols, phytochemicals, and certain amino acids [8,20-30].

It is difficult to isolate specific dietary components crucial in the pathogenesis, etiology, or treatment of IBD. Accordingly, it is important to investigate dietary patterns, such as the MD, low FODMAP diet, and exclusion diets, as well as symptom and plant-based diets. Exclusive Enteral Nutrition (EEN) has been extensively studied as a first-line therapy for pediatric patients with CD [31]. In adults, EEN has shown promising results however the utility of the diet is difficult to maintain in this population [32]. As such, dietary changes can be utilized in the treatment of IBD yet clinical trials investigating other dietary patterns are not as robust and have conflicting results [33-40]. The implementation and design of dietary clinical trials prove to be challenging. Patients with IBD however, frequently recognize how nutrition affects their health and may self-directly employ various dietary strategies in an effort to control their disease. Up to 50% of patients have reported that they felt diet could be the incendiary factor in their disease, citing food provocation of IBD symptoms (57%) and disease flares (60%) [41]. Dietary interventions, in the form of specific nutrients and broad dietary patterns, are known to modulate the microbiome and hold promise towards biomic balance and improved disease outcomes for IBD patients [2]. Nutrition is of paramount importance in the etiology, pathogenesis, and treatment of IBD. The summary of recommended and harmful nutrients is outlined in **Tables 1 and 2** [10,19,20,42-45].

Table 1: Summary of recommended dietary nutrients

Recommend high intake of dietary fiber from whole food sources
Recommend omega-3 fatty acids in form of extra-virgin olive oil, fish, and dairy
Recommend Vitamin D supplementation

Table 2: Summary of harmful dietary nutrients and additives.

Avoid consumption of animal proteins, especially red meat and processed food
Avoid consumption of refined carbohydrates, sugar substitutes and high-fructose corn syrup
Avoid consumption of n-6 polyunsaturated fatty acids and trans unsaturated fatty acids
Avoid consumption of pre-packaged food items, especially those containing carrageenan, maltodextrin and emulsifiers

The impact of diet in the etiology of IBD

The epidemiology of IBD shows a higher prevalence in northern Europe and North America compared to the Asia-Pacific region [6,46]. The prevalence of IBD in North America ranged from 0.3% to 0.5% since 2000 with a similar prevalence observed in Northern Europe, Western Europe, and Oceania [18,47-54]. The prevalence of IBD in Asia, specifically in Japan, South Korea, and Hong Kong, are 0.076%, 0.042%, 0.043%, respectively, in 2014 [55-57]. The incidence of IBD in the traditionally low prevalent areas including Eastern Europe, East and South Asia, South Africa, and South America are rapidly increasing [58-63]. These observations provide insight into that impact of industrialization and the resultant change in eating habits towards a more WD on the incidence of IBD [46]. The incidence of IBD in developing nations, where IBD was once rare, have increased as these nations have become more industrialized [46].

The geographic prevalence differences may also reflect regional and socioeconomic related dietary patterns. The geographical variation and diet pattern are evident in a study which compared the diet of northern France to that of southern France [4]. The diet of the northern half reflected the WD, which includes butter, eggs, potatoes, cheese, and added fat and sweets, and the southern half reflected the diet consisting of fruit, vegetables, fish, and olive oil. The study also showed that there are socioeconomic factors in choosing diet as evidenced by low to medium socioeconomic population favoring the WD. In addition, the study also demonstrated that the higher education and income-tax level influenced the choice and adherence to prudent diet [4].

Among many environmental factors which increase the risk of IBD, diet has been shown to be a key component of pathogenesis [6]. The WD consists mainly of refined sugar, omega-6 polyunsaturated fats, and processed meats, notably deficient of fruits, vegetables, and fiber [58]. This diet, majorly seen in North America and Western Europe, plays a major role in the pathogenesis of IBD [5,6]. The WD, consisting of meats, fatty foods and refined sugar, increases the risk for CD in females while a prudent diet with vegetables, fruits, olive oil, fish, grains, and nuts decreases this risk [3]. The pathophysiology behind the increasing risk of IBD with WD is thought to be due to production of proinflammatory cytokines, increased intestinal permeability, and alteration of intestinal microbiome.[7]

How diet affects the pathogenesis of IBD

The WD has been associated with an alteration of gut microbial diversity, intestinal colonization with pathobionts and disruption of intestinal barrier integrity/permeability [64]. These changes promote an innate response which in turns leads to chronic inflammation [47]. The gut microbiome and host show a symbiotic relationship, and the intestinal colonization of microbiome begins soon after birth [21,65]. Subsequently, the effect of diet on the gut microbiome is observed even with a formulary or breastfeeding diet [66]. The gut microbiome of African children showed an abundance of *Bacteroidetes* and relative paucity of *Firmicutes* and *Enterobacteriaceae* compared to the gut microbiome of Italian children, suggesting a difference in dietary patterns [67]. How diet influences the composition of the gut microbiome is well observed in the effect of WD. The consumption of the WD leads to an increase of certain microbiomes such as *Bacteroides* and *Ruminococcus* [68]. Specifically, the components of the WD have a unique influence in changes of the microbiome. It is suggested that high consumption of

animal protein and saturated fat are associated with prevalence of *Bacteroides* while high consumption of carbohydrates is associated with an abundance of *Prevotella* [69]. High fat/high sugar diets also increase susceptibility to colonization of Adherent-Invasive E. Coli (AIEC) or pathobionts [12]. Additionally, a high fat diet promotes proliferation of *Bilophilawadsworthia*, a sulphite-reducing pathobiont, and leads to local inflammation and elevated levels of lipopolysaccharides (LPS) [70].

The WD has a high level of dietary fat, and LPS has been shown to be the bridge between the diet and gut pathology [71]. LPS is a large polymolecule consisting of an O-antigen, core polysaccharides, and lipid A. Specifically, lipid A triggers a proinflammatory response through Toll-like receptor 4 (TLR-4-)-CD-14 of intestinal epithelial cells and immune cells [71]. The LPS, derived from gram-negative bacteria, directly promotes intestinal tight junction permeability through an upregulation of TLR-4-CD14, leading to further proinflammatory responses through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)pathway [71,72]. The upregulation of these receptors and its downstream effectors modulate the intestinal gut barrier ultimately promoting intestinal permeability.

The role of specific dietary nutrients in IBD: Macromolecules

Amino acids

Protein and amino acids serve as a source of energy for metabolism as well as regulators of homeostatic pathways [73]. High protein intake, mainly animal protein, is associated with an increased risk of UC and CD [9,19]. Animal protein typically contains a higher content of essential dietary amino acids, especially leucine, methionine, cysteine, and lysine. Additionally, plant-based protein is less digestible than animal protein due to structural differences as well as presence of other compounds that reduce amino acid bioavailability [74]. This suggests that higher amino acid availability from animal protein sources may increase their individual effects on IBD pathogenesis.

Dietary consumption of glutamine and arginine serve as immunomodulators that mediate inflammatory response in colitis [24-26,75]. Diets rich in glutamine and arginine improve clinical and biochemical markers in chemical-induced colitis [24,25,75,76]. Histidine, a precursor for histamine, has been shown to reduce symptoms of immune-mediated colitis [77]. Tryptophan is associated with T-regulatory cells and immune tolerance. Supplementation of tryptophan has been demonstrated to reduce the inflammatory response in experimental colitis [78]. Threonine increases intestinal mucus production, which promotes integrity of the epithelial barrier [79,80].

Consumption of some amino acids may have a proinflammatory effect as well. High concentrations of branded-chain amino acids (BCAAs) such as leucine, isoleucine, and valine have been associated with oxidative stress (through the formation of reactive oxygen species (ROS)) as well as NF-κB expression and subsequent cytokine upregulation in mononuclear cells [81]. The majority of amino acids, including BCAAs, have a cumulative anti-inflammatory effect in low concentrations [82]. However, some amino acids, including non-essential amino acids (e.g. glutamine, cysteine....) activate the mTOR pathway to upregulate expression of inflammatory cytokines and inhibit autophagy [83]. Dysbiosis may contribute to this effect, as altered metabolism by local flora through urease expression can increase microbial amino acid production and contribute to worsening of colitis [84].

Carbohydrates

Carbohydrates serve as a key source of nutrition for host cells as well as gut microbes. These can be categorized as digestible and non-digestible [85]. Digestible carbohydrates include mono- and di-saccharides as well as starches. Non-digestible carbohydrates are mainly found as components of dietary fiber. Variations in intake of carbohydrates may contribute to IBD pathogenesis or mitigation.

High sugar and soft drink consumption are associated with increased UC risk when combined with low vegetable intake [10]. Overall dietary sugar and sweetener consumption increases risk of CD, whereas, sweetened confectionery consumption, but not overall sugar consumption is associated with increased risk of UC [11]. Cohort data does not suggest however, that higher overall carbohydrate, sugar, or starch consumption is found in patients with CD or UC [86]. This suggests that other environmental factors such as sugar/fiber ratio or genetic predisposition may modify the effect of digestible carbohydrates on IBD pathogenesis. Additionally, high sugar and fat consumption (such as that seen in the WD) has been demonstrated to decrease mucus layer thickness, increase epithelial permeability, and promote cytokine production in murine models [12].

Decreased consumption of oligo-, di-, and monosaccharides such as seen in a low-FODMAP diet is associated with improvement in IBD disease symptom severity [87]. High consumption of digestible carbohydrates is believed to saturate intestinal absorptive capacity, and the increased luminal presence leads to bacterial fermentation and dysbiosis [12,88,89]. This is further evidenced by poor fructose absorption in CD, and poor lactose tolerance seen in CD and UC [90]. High luminal sugars can also increase luminal water retention due to osmotic effect.

Dietary fiber can be divided into soluble and insoluble fiber, and most sources contain both types in varying ratios [91]. Soluble fiber can be fermented into SCFAs by colonic flora, mainly *Firmicutes*. SCFAs have a variety of anti-inflammatory local effects, including inhibition of cytokine production, immunoglobulin secretion, and mucus production, which enhances the epithelial barrier [23]. Insoluble fiber acts as an osmotic agent that promotes retention of luminal water and contributes to stool bulking [92]. Overall dietary fiber consumption, decreases the risk of CD and UC, mainly from high fruit and vegetable intake respectively [8,20].

Fatty acids

Dietary fat has varied effects on the immune system and inflammatory cascade [93]. Composition of this fat can be classified into saturated and unsaturated, of which the latter can further be classified into monounsaturated, omega-6, and omega-3 fatty acids [93]. Fat intake can be described as a percentage of overall calorie and fat consumption. High fat consumption is associated with a proinflammatory state [13]. This effect is mainly seen through proliferative changes in the colonic microbiome that promote epithelium-microbe interactions and lead to cytokine production and is demonstrated in high-fat diets such as the WD [12].

Saturated fats are the densest form of nutrition storage in the body. Intake of saturated fat as a percentage of overall fat intake is associated with higher likelihood of hyperlipidemia and weight gain [94]. Within the gut, saturated fats contribute to persistent changes in microbial composition that induce insulin resistance and obesity [94]. It is likely that the mecha-

nism for this occurs through epithelial barrier dysfunction and increased immune-microbe interaction [71]. This is believed to be through an increase in the prevalence of hydrogen sulfide producing bacteria, which inhibit epithelial metabolism of butyrate, a SCFA.

Unsaturated fats such as monounsaturated fatty acids (MUFAs), omega-6 polyunsaturated fatty acids (N-6 PUFAs) and omega-3 polyunsaturated fatty acids (N-3 PUFAs), each play a different role in IBD pathogenesis [93]. Metabolism of all fatty acids can occur for energy production, however, omega-6 and omega-3 fatty acids can also be metabolized into inflammatory mediators through the arachidonic acid pathway [95]. The association of MUFAs with IBD is unclear as there is conflicting evidence on benefit vs harm [93]. The N-6 PUFAs are converted into inflammatory mediators (eicosanoids) through the arachidonic acid pathway [96]. In patients with IBD, the metabolism of N-6 PUFAs is increased through enzymatic upregulation of phospholipase A2, an enzyme early in the pathway [14]. The N-3 PUFAs are metabolized to anti-inflammatory mediators that inhibit the immune response, as well as decrease microbe-associated TLR-dependent reaction [28,29].

The role of specific dietary nutrients in IBD: Micronutrients

Vitamins

Patients with IBD are at increased risk of micronutrient deficiencies due to poor absorption. Water soluble vitamins, especially B vitamins, including B6 (pyridoxine), B7 (biotin), B9 (folic acid), and B12 (cobalamin), as well as fat-soluble vitamins A, D, and K have been demonstrated to be variably deficient.

Vitamin B6

Vitamin B6 (pyridoxine) includes several compounds that can be metabolized to pyridoxal phosphate, the metabolically active form [97]. It can be obtained from both dietary sources as well as through production by commensal colonic flora. It is absorbed primarily through passive diffusion [98]. Pyridoxal phosphate is a critical cofactor in cellular metabolism of amino acids and fats, and also plays a role in salvage of ROS [99]. Vitamin B6 is reduced in inflammatory conditions including UC and CD [100]. Dietary restriction of Vitamin B6, however, reduces colonic inflammation [101]. The disruption in methionine metabolism and elevated homocysteine due to low B6 cofactor availability may contribute to this effect, although the mechanism is still unclear.

Vitamin B7

Biotin is an important cofactor in macronutrient metabolism and other metabolic processes, and may also serve as a regulator of gene expression [98]. It is principally derived from protein-bound dietary sources and colonic microbial production/absorption [98]. It is absorbed through a sodium-dependent multivitamin transporter protein located on the brush-border epithelium [98]. Biotin deficiency is seen in a greater proportion of IBD patients when compared to controls [102]. This deficiency is associated with a proinflammatory response through tumor necrosis factor (TNF) and NF-κB upregulation [102,103].

Vitamin B9

Folate is a cofactor for amino acid metabolism and deficiency is associated with macrocytic anemia [98]. It is primarily absorbed from dietary sources through uptake in the small bowel as well as from commensal microbial sources in the colon [98]. Patients with IBD have a higher risk of folate deficiency due to malabsorption [104]. While there has not been a clear protective linkage between folate and IBD, it has been demonstrated to function as a methyl group donor for DNA methylation of key inflammatory cytokine genes including IL-1 and TNF and inhibiting macrophage response to LPS [105]. Folate deficiency has also been associated with an increased risk for IBD-related colorectal cancer [106].

Vitamin B12

Vitamin B12 (cobalamin) is a water-soluble cofactor that is responsible for many metabolic processes and deficiency is associated with a wide spectrum of pathologies including macrocytic anemia and neurological changes [107]. Cobalamin is initially bound to salivary haptocorrin for gastric acid protection and subsequently transferred to gastric produced intrinsic factor (IF) to form a B12-IF complex [108]. This complex is absorbed through interaction with cubulin, a membrane bound protein located in the distal ileum. B12 deficiency is more common in CD than UC [102]. However, while CD patients with ileal resection are at high risk of B12 deficiency, presence of ileal disease does not appear to significantly increase the likelihood of B12 deficiency [109].

Vitamin A

Vitamin A is a group of fat-soluble compounds including retinol, retinoic acid, and several carotenoids [110]. Similar to other fat-soluble compounds, these molecules are emulsified in the stomach and duodenum, incorporated into mixed micelles and subsequently absorbed into enterocytes through a saturable transmembrane protein transporter [110]. Disruption of digestion and emulsification may contribute to deficiency, which can cause several ocular pathologies, immune compromise, and epithelial dysfunction [111]. Retinoic acid, one of the vitamin A compounds, mediates mucosal inflammatory response through promotion of T-reg lymphocytes and also induces class switching of IgA-producing B cells [112]. Deficiency of vitamin A can contribute to loss of this regulatory function as well as decreased integrity of the gut epithelial barrier [113,114]. There are a high percentage of CD and UC patients with vitamin A deficiency, although it is unclear if this precedes local inflammation or is a result of disease progression [115].

Vitamin D

Vitamin D is a fat-soluble vitamin that plays an important role in bone metabolism by regulating bone density and serum calcium. Patients with IBD, are at risk for vitamin D deficiency due to avoidance of sun exposure due to symptoms as well as due to malabsorption [116]. Treatment of vitamin D deficiency is associated with disease improvement [43]. More work is needed to evaluate the effect on bone health in IBD patients [117]. In addition to regulating bone density, vitamin D also appears a play a key role in immune regulation [118]. Vitamin D Receptor (VDR) acts as a transcription regulator and VDR expression is inversely associated with markers of colonic inflammation without change in serum vitamin D levels [118]. It is possible that vitamin D-VDR binding may inhibit the inflammatory response seen in IBD. It is presumed that long term vitamin D supplementation is associated with improved outcomes, however due to a proposed interaction with inflammatory mediators, vitamin D3 supplementation during active flare may prevent the beneficial effect on bone density.

Vitamin K

Vitamin K compounds are utilized by proteins in the coagulation cascade as well as in bone metabolism [119]. Similar to other fat soluble vitamins, vitamin K absorption occurs through digestion and emulsification into mixed micelles and subsequent absorption by brush border enterocytes [119]. Deficiency of vitamin K is common in IBD due to malabsorption is more prevalent in CD [120]. Patients with vitamin K deficiency are at increased risk for osteoporosis [121]. A proposed mechanism for this association is through altered microbiome in IBD patients leading to decreased conversion of vitamin K1 to K2 (menaquinones), which are involved in maintenance of bone mineral density. This is supported by decreased efficacy of vitamin K supplementation in these patients [122].

Minerals

Iron

Chronic inflammatory states may contribute to poor mineral absorption. Iron is an essential component of heme and is vital for oxygen delivery [123]. It is well recognized that iron deficiency can lead to a microcytic anemia [123]. Patients with IBD are at high risk for iron deficiency due to a combination of poor absorption due to mucosal inflammation, as well as poor utilization associated with chronic disease [97]. Oral supplementation of iron in patients with active IBD may be difficult, due the symptoms of GI upset, as well as poor absorption [124]. Additionally, oxidation of luminal iron may contribute to epithelial damage, as increased intracellular iron accumulation may be associated with upregulation of ROS that contributes to ferroptotic cell death as seen in UC [125].

Zinc

Zinc deficiency is frequently seen in patients with IBD and is associated with poor outcomes in both CD and UC [126]. Zinc is associated with increased cell proliferation as well as inhibition of ROS production that cumulatively can contribute to progression of the inflammatory cascade [127]. This deficiency is associated with increased interleukin production as well as oxidative stress that may contribute to IBD progression [128]. Treatment of CD patients with zinc supplementation has been demonstrated to improve epithelial barrier function and decrease risk of clinical relapse [129].

Selenium

Elemental selenium becomes incorporated into cysteine-containing proteins, including ROS-inhibiting glutathione peroxidases. These selenoproteins are also involved in anti-inflammatory switching of macrophages from M1 to M2 subtypes [130]. Selenium deficiency is commonly seen in IBD, though it is unclear if supplementation is effective in the setting of mucosal inflammation [131].

Phytochemicals

Phytochemical consumption is proposed to have varying effects depending on presence of specific compounds, though the main proposed mechanism is maintenance of the intestinal epithelial barrier [30]. Of these, phenols have been demonstrated to inhibit production of proinflammatory cytokines such as TNF-a and upregulate anti-inflammatory cytokine IL-10 production. Phenols also have poor bioavailability and may regulate microbial proliferation by affecting colonization and adhesion [30]. Flavonoids have also been demonstrated to inhibit ROS-NF-kB pathway and decrease oxidative stress. This is attributed to increased presence of hydroxyl groups that can act as electron donors to directly inhibit ROS. Resveratrol and curcumin have both been studied for possible therapeutic effect in IBD [21,22].

Curcumin

Curcumin is a bright yellow substance found in turmeric, a member of the ginger family, Zingiberaceae. As a dietary supplement, it has been purported to be an anti-inflammatory and antioxidant agent due to it a potent inhibition of NF-κB activation and inhibition of TNF-mediated actions [131-134]. In animal studies, curcumin has been inhibit NF-κB activation and CD4+ T cell infiltration in murine models of trinitrobenzene sulfonic acid (TNBS)-induced colitis [135].

Curcumin has been investigated as a dietary supplement in several small studies. One pilot study of 10 patients with IBD examined the impact of a dietary curcumin supplement for a period of 3 months [136]. Clinical indices improved in all subjects, with reductions in concomitant medications in 4/5 UC patients [136]. Efficacy for this supplement was also evaluated in a trial assessing 6 month relapse of IBD rates, whereby patients were randomized to receive 2 g/day of curcumin in combination with Sulfasalazine (SZ), mesalamine, or placebo plus SZ or mesalamine [137]. Notably only 2/43 patients treated with curcumin in combination with SZ or mesalamine relapsed during the 6 months of therapy, whereas 8/39 patients who received placebo with SZ or mesalamine relapsed during the same period (4.65% versus 20.51%; P=.040). Clinical and endoscopic evaluation scores were also significantly improved by during this time (Clinical activity index (CAI) and endoscopic index (EI); CAI (P = .038) and EI (P = .0001).

In those with mild-to-moderate UC, patients were randomly assigned to groups given curcumin capsules (3 g/day, n = 26) or an identical placebo (n = 24) for 1 month [138]. Improved clinical remission rates were evident with curcumin (53.8% versus 0%; P = .01), clinical response (65.3% versus 12.5%; P < .001) and endoscopic remission (38% versus 0%; P = .043) [138]. These findings have not been replicated in CD patients. A recent study reported that curcumin was no more effective than placebo in preventing CD recurrence in a randomized controlled trial of patients who underwent surgery for CD and received thiopurine treatment [139]. The sum of the evidence indicates curcumin may be a safe alternative for patients with UC however more data is needed before recommending this supplement in patients with CD.

Food Additives

Many food additives may contribute to the inflammatory cycle of IBD [140]. Sugar substitute consumption is associated with dysbiosis and upregulation of proinflammatory markers [141]. Maltodextrin is a polysaccharide frequently used as a filler in processed food [142]. Dietary consumption of maltodextrin is associated with poor epithelial function through endoplasmic reticulum stress and subsequent decreased mucus production [15]. This likely manifests through decreased mucus increasing immune-microbe interactions and activation of the LPS-TLR-4 inflammatory cascade.

Emulsifying agents are implicated in IBD [140]. Carrageenan is a polysaccharide food additive that is derived from seaweed and is commonly used as a thickening agent. Carrageenan consumption is associated with LPS-TLR-4 related inflammatory

changes and aggravation of colitis [16]. Consumption of carboxy methyl cellulose (CMC) and polysorbate-80 (P80) is associated with increased incidence of colitis and predisposition to metabolic syndrome in murine models [17].

Dietary interventions in IBD

It is difficult to isolate one dietary component in the pathogenesis, etiology, or treatment of IBD. Hence, the investigation of dietary patterns provides a broader view of associations. The dietary pattern, however, is complicated to deconstruct due to validation of specific intakes, patterns, additives, contaminants, and external factors (e.g. weight, sleep, exercise, alcohol/tobacco). Although the epidemiological associations discussed previously are strengthened by clinical studies, there are several limitations, and few are interventional [18,19]. The only dietary intervention with proven efficacy in IBD is EEN. Recognizably, dietary treatment for UC has generally been limited and ineffective as compared to CD [6,33].

Despite the promise of dietary interventions as a treatment for IBD, few studies have been performed to give credence to the ideal diet [33]. To date, studied diets include EEN, Partial Exclusion Nutrition (PEN), exclusion diets, the specific carbohydrate diet (SCD), low FODMAP diets, low residue diets (LRD), low microparticle diets, symptom-guided or IgG-4 diets, the Semi-Vegetarian Diet (SVD) and the MD [33-40,143,144]. The summary of findings isoutlined in **Table 3**. Notably, PEN has not shown to be as effective as EEN, although a modified version of PEN (a CD exclusion diet where in PEN was combined with a highly restricted diet) may prove effective and a viable option for adults [145]. The SCD has demonstrated improvement in functional GI symptoms improvements and there are several trials currently underway [146-148]. Likewise, low FODMAP diets have shown promise in improving functional GI symptoms [149,150]. On the contrary, due to its low fiber content, LRD may potentially harm patients and should be avoided in IBD [37,161]. Similarly, the low microparticle diet has not proven to be effective [38]. Other diets that show promising promising, albeit limited results, include: The IgG-4 guided elimination diets, the SVD, and the MD [39,40,152]. Several large clinical studies are underway for the MD and SCD, which will add greatly to our current understanding of the role of diet in IBD [153,154].

Table 3: Summary of dietary interventions.

Exclusive Enteral Nutrition (EEN)	Recommended in pediatric CD; has been shown to alter the microbiome and decrease intestinal inflammation.
Partial Enteral Nutrition (PEN)	Not as effective as EEN; Combined with exclusion diet shown to be effective, further study warranted.
Exclusion Diets	Highly variable, may improve symptoms depending on group excluded.
Specific Carbohydrate Diet (SCD)	Avoids foods that are thought to lead to intestinal injury caused by an overgrowth and imbalance toward pro-inflammatory gut microbes; further study warranted.
Low FODMAP	May improve functional symptoms.
Low Residue Diet (LRD)	Not advised.
Low Microparticle Diet	Not advised.
IgG-4 Guided Diet	Not currently clinically feasible.
Semi-Vegetarian Diet (SVD)	Avoids meat and high-fat foods that may promote inflammation.
Mediterranean Diet (MD)	Promotes diet high in omega-3's and low in omega-6's, which may reduce inflammation; further study warranted.

Exclusive enteral nutrition (EEN)

This diet involves substituting 100% of daily nutritional requirements as an artificial nutritional supplement in powder or liquid form, administered orally or through a feeding tube for up to 8 weeks [155]. There has been no observable difference in formulations when considering remission rates or side effects between elemental, semi-elemental, and polymeric formulas [32]. After the 6-8 weeks, an oral diet with solids is reintroduced. Few side effects have been reported emphasizing the great utility of the treatment modality. [156]. There is demonstrated efficacy in active CD and is a first line therapy for pediatric CD [143]. This has been used successfully as the initial treatment in children with CD for induction of remission with rates approaching approximately 80 to 83% [31,32,155]. Early publications demonstrated inadequate outcomes in patients with UC; perhaps due to the greater role of the gut microbiome in CD [157,158]. Early studies also demonstrated less satisfactory outcomes in CD that primarily involved the colon due to differential healing rates between ileal and colonic mucosa [159,160]. The authors postulated it could be due to differing effects on the bowel flora [159]. However a recent meta-analysis showed that, there was inadequate data to determine if disease location affected EEN efficacy [161]. Nevertheless, many other studies support EEN regardless of the site of inflammation [32,155,161].

A meta-analysis of pediatric studies indicated that EEN had equivalent response to corticosteroids in children with active CD [162]. A recent Cochrane review of 27 studies (1,011 participants) concluded that very low quality evidence suggests that EEN may be more effective than corticosteroids in children [32]. In children, 83% (24/29) of EEN patients achieved remission compared to 61% (17/28) of steroid patients (RR 1.35, 95% CI 0.92 to 1.97). This low risk and noninvasive therapy is well established as widely recommended for pediatric patients (by the European Crohn's and Colitis Organisation (ECCO), European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). Interestingly, EEN is used less commonly in Western countries with Europe, Australia, and Canada showing significantly more routine use than other parts of North America [163]. Notably, EEN is not routinely used as first-line therapy in adults, attributable to the unpalatable formulations which lead to poor adherence [164]. There is, however, evidence to support the use of EEN with select adult populations, specifically those with a new diagnosis of

CD with ileal involvement. Clearly this requires offering to those who are motivated to adhere to the EEN regimen [32,165].

The mechanism underlying EEN's efficacy remains undefined. It has been postulated that the effect is due to elimination of dietary antigens, enhancement of barrier function via modifications in tight junction proteins, reduction of proinflammatory mediators as well as nutritional repletion of micronutrients [155,156,166-168]. This has shown to positively impact inflammatory markers and cytokine signaling pathways, and improve endoscopic, histologic, and biological indices [156,160,168,169]. Furthermore, it improves mucosal healing and enhances growth and overall nutritional status in children [170]. Of particular significance, EEN influences gut microbial diversity and offers a pathogenic mechanism for reduction of the mucosal inflammation in CD [171]. Microbial diversity is reduced in CD patients as compared with controls and an increase in the abundance of *Bacteroidetes* and *Proteobacteria* and a decrease in that of *Firmicutes* have been observed [172]. EEN can lead to a decrease in bacterial diversity and the *Bacteroides* group and reduced disease activity [173,174]. Significant modification of the fecal microbiota has been observed in CD patients undergoing EEN therapy [175]. It has been proposed that mutations in pattern-recognition receptors is a key driver of CD, which suggests that defective sensing and killing of bacteria may drive the onset of disease [172].

Although EEN research is robust in pediatric CD, variation exists in the adoption with adult patients. It may be an effective therapy for select patients, especially those with a new diagnosis of CD, ileal involvement, intolerant of steroid side effects, and those motivated to adhere to the EEN regimen [32,165]. The difficulty in adoption of the therapy in adults has been attributed to perceived intolerance and noncompliance in adults, frequently due to poor acceptance of a nasogastric/nasoenteric tube and unpalatable formulations [176]. Two studies of EEN in treatment-naïve adults demonstrated clinical remission in 80% and 82% of patients, respectively [177,178]. The adults were treatment-naïve which suggests that prior exposure to other treatment modalities leads to poorer outcomes. When analyzing the efficacy of EEN in adults compared to corticosteroids, a Cochrane meta-analysis found corticosteroids demonstrated superiority over EEN in remission rates wherein 45% (87/194) of EN patients achieved remission compared to 73% (116/158) of steroid patients (RR 0.65, 95% CI 0.52 to 0.82) [32]. However, patients receiving EEN were more likely to withdraw from treatment due to inability to tolerate the nasogastric tube or poor palatability of the formulation. In fact, in an analysis accounting for the withdrawals, there was no statistically significant difference in overall remission rates seen between patients treated with enteral nutrition or steroids [32]. This suggests improved efficacy in highly motivated patients. Furthermore, the evidence is defined as very low-quality data reflective of the difficult nature of designing and implementing dietary clinical trials. The authors concluded corticosteroid therapy may be more effective than EEN for induction of clinical remission in adults with active CD however further research is required to establish this due to the low-quality data. Future endeavors should focus on more high quality RCTs in adult populations and more palatable formulations [32].

Partial enteral nutrition (PEN)

The use of PEN has been studied clinically as an attractive alternative to EEN given that PEN allows continued consumption of whole foods products [144]. Research has illustrated that exclusivity is an important determinant of efficacy in EEN [179,180]. In one study, 50 children with CD were randomly assigned to receive 50% of oral nutrition via elemental formula (PEN) with an unrestricted diet or 100% of oral nutrition via elemental formula (TEN) for six weeks [179]. Remission rate with PEN was nearly one-third lower than with TEN (15% versus 42%; P = 0.035). Further, pediatric Crohn's disease activity index scores did improve with both treatments, but the reduction was greater with TEN (P = 0.005). More recently, 23 children with CD were randomly assigned to receive a novel PEN regimen of 90% of nutrition via an elemental formula with the remaining 10% as an unrestricted diet [180]. The study found that 65% of the children entered remission. This is a decrease from the 83% remission rates as reported with EEN [32]. These studies demonstrate that the total exclusion of specific types of food has a better therapeutic benefit then partial exclusion, albeit PEN is a more attractive option.

A recent study sought to develop an alternative diet wherein PEN was combined with a highly restricted diet, called the CD Exclusion Diet (CDED), designed to avoid foods that would promote inflammation or negatively affect the microbiome [145]. Specifically, gluten, dairy products, gluten-free baked goods and breads, animal fat, processed meats, products containing emulsifiers, canned goods, and all packaged products were excluded. This intention-to-treat analysis was conducted on 47 patients, 34 being children, over a period of 6 weeks and response and remission were obtained in 37 (78.7%) and 33 (70.2%) patients, respectively. This modified diet showed significant remission rates in adults (69%) and normalization of CRP levels occurred in 70% of patients in remission. More recently, these results were corroborated in a 12-week prospective trial of children with mild to moderate CD [181]. At week 12, 28 (75.6%) of 37 children given CDED plus PEN were in corticosteroid-free remission compared with 14 (45.1%) of 31 children given EEN and then PEN (P = .01). Although this was a marked improvement compared to previous studies, the diet is extremely restricted and hard to follow. Unfortunately, any of the restriction diets used in the studies can be difficult to maintain. Notwithstanding, PEN is ineffective in inducing remission compared to EEN, although a combined strategy may prove effective and a viable option for adults.

Exclusion diets

In recent years there has been increased popularity and focus on dietary strategies that focus on elimination of potentially harmful substances. These diets are known as exclusion or elimination diets and are administered by excluding food groups that are thought to influence symptomology. Alternatively, these diets can be administered with the intent to reintroduce foods groups later, after symptoms resolve [58]. On an individual basis, one can eliminate foods that the patient deems to be a specific trigger for their disease. The theory behind the exclusion or elimination diet is to induce remission by avoiding dietary triggers, or by avoiding components of the diet that confer proinflammatory properties. It has been suspected that there may be individualized food sensitivities underlying the disease pathogenesis in IBD and that avoidance of these dietary antigens may improve disease mechanisms for these patients [39].

The research surrounding exclusion diets has been controversial. The evidence is very limited due to the initial clinical design, specific interventions, and choice of populations [182]. In particular, several studies do not describe detailed dietary ma-

nipulations, making replication of the study impossible [182]. Moreover, the exclusion of whole food groups can aggravate nutritional deficiency or caloric deficits. These diets may be difficult for patients to follow and the restrictive nature can negatively impact their quality of life [183]. Several studies in recent years have been popularized as an elimination or exclusion diet: the SCD, a low FODMAP diet, the LRD, the low microparticle diet, or the IgG-4 guided exclusion diet [184]. Given the difficult nature of conducting dietary intervention RCTs, there is little evidence of the efficacy of these diets. In a recent Cochrane review of 18 randomized controlled trials (1878 randomized participants) that assessed dietary interventions for the induction and maintenance of remission in IBD, there is insufficient evidence to determine whether certain exclusion diets improve clinical remission rates in active CD or maintenance of remission in inactive CD [182]. Further, exclusion diets are not recommended to achieve remission in active CD, even if the patient suffers from individual intolerances [185]. It is important to note, however, that the quality of evidence was assessed to be very low [182].

Specific carbohydrate diet (SCD)

The SCD is a dietary intervention that has been proposed to induce and maintain remission in patients with IBD [34]. It was initially developed by the gastroenterologist Sydney Haas as a therapy for celiac disease and became very popular in subsequent years by Gottschall [34,186]. The diet is considered well balanced in most food groups such as fruit, vegetables, nuts, meat, eggs, and butters. It is very restrictive in the types of sugars that are allowed, as the diet is comprised of exclusively monosaccharides such as glucose, fructose, and galactose and excludes disaccharides and most polysaccharides thought to be proinflammatory [187]. Additionally, processed meats are avoided because they can contain excluded sugars. The diet specifically excludes sugar, fructose corn syrup, artificial sweeteners, all grains, corn, canned vegetables or fruit, most legumes, starchy tubers, dairy products high in lactose, commercial oils and mayonnaise, and most food additives and preservatives [187].

The diet postulates that carbohydrate intolerance is central to its efficacy [188]. The underlying concept being that undigested complex carbohydrates are malabsorbed and then fermented in the colon. These malabsorbed carbohydrates can produce proinflammatory byproducts and acid [146,188]. This can lead to worsening of symptomology such as diarrhea, bloating, flatulence, and bacterial overgrowth [187]. It is hypothesized that avoidance of these carbohydrates will mitigate small bowel mucosal injury thereby preventing symptoms [187]. However, this area of research is ongoing.

The changes in dietary carbohydrates can alter the microbiome or barrier function [151]. The microbiota of patients with CD is characterized by a decrease in commensal bacteria *Firmicutes* and *Bacteroides* as well as a relative increase in *Enterobacteriaceaea*, a proinflammatory microbe [189,190]. Whereas EEN has demonstrated a decrease in microbial diversity, SCD has been associated with an increase in microbial diversity [151]. This composition change was observed in a study that compared the effects of the SCD versus a LRD on the composition complexity of microbiome and whether these changes correlated with resolution of symptoms in patients with IBD [151]. Prior to the initiation of treatment, IBD patients had more *Bacteroides fragilis* and a decreased abundance in *Clostridium lactatifermentans***.** After the intervention, SCD increased microbiome diversity whereas the LRD decreased microbiome diversity. These changes were associated with clinical improvement. SCD also increased *F. prausnitzii* [151]. A part of the decreased abundance of phylum *Firmicutes* is associated with a reduced abundance of *Faecalibacterium prausnitzii* (*F. prausnitzii*), a member of the *Clostridium leptum* group [191]. The increased abundance of *F. prausnitzii*, a butyrate-producing bacteria, may translate into a beneficial and anti-inflammatory role in the mucosa [189]. More recently, similar findings were demonstrated in 12 pediatric patients with UC and CD [192]. Mean Pediatric Crohn's Disease Activity Index (PCDAI) and Mean Pediatric Ulcerative Colitis Activity Index (PUCAI) decreased at 12 weeks, from 28.1±8.8 to 4.6±10.3 and from 28.3±23.1 to 6.7±11.6, respectively. Microbiome analysis showed *Bacteroides* and *Firmicutes* inverted in abundance from 67% and 31% at baseline to 30 and 70% at 2 weeks on SCD [192].

Although there have been few studies exploring SCD in the pediatric population, it has been shown to be effective for inducing and maintaining remission in pediatric CD [147,148,193]. In a small case series of seven children with CD on the SCD without immunosuppressive medication, all patients experienced remission of symptoms on SCD (average 14.6 ± 10.8 months) [147]. Pediatric CD activity indices, serum albumin, CRP, hematocrit and stool calprotectin all improved [147]. These findings were similar to a retrospective chart review of 11 patients; children with CD were initiated on the SCD simple (diet alone, antibiotics or 5-ASA) or SCD with immunomodulators (corticosteroids and/or stable thiopurine dosing) protocol and were followed for one year [148]. In both groups, hematocrit, albumin and ESR values improved while on strict SCD and appeared stable after liberalization (P = 0.006, 0.002, 0.002 respectively). The difference in study design and self-reporting is not ideal. In addition, these were small case studies. In a larger series of patients, a survey-based study, 50 patients with IBD were following the SCD. The study demonstrated that 66% of patients reported complete resolution of IBD symptoms on the SCD (average 9.9 months) [146]. The majority of these patients were adults (41/50).

Notwithstanding the preceding discussion, 8/10 pediatric patients with active CD on the SCD demonstrated significantly improved clinical and mucosal improvements at 12 weeks (PCDAI improved from 21.1 ± 5.9 to 7.8 ± 7.1; P = 0.011; Lewis Score (LS) declined significantly from 2153 ± 732 to 960 ± 433; P = 0.012), but not at 52 weeks, although improvements in disease index scores did persist at 52 weeks [193]. Overall, it appears SCD may be beneficial for the pediatric population, although the majority of evidence herein is based on small case studies. Further, adherence can be challenging. As has been demonstrated in other dietary interventions, rigorously designed RCTs and large clinical trials are lacking concerning SCD and are critically needed to affirm results. Fortunately, a large clinical trial is ongoing for SCD. The Trial of Specific Carbohydrate and Mediterranean Diets to Induce Remission of Crohn's Disease (DINE-CD study) is a multicenter randomized, open-label trial slated to be complete by 2020 [153].

Low FODMAP diet

The low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol diet (FODMAPs) consists of eliminating foods high in short-chained carbohydrates, termed FODMAPs, due to their fermentability and poor absorption [194]. Because FODMAPs are poorly absorbed in the intestine, they will distend the intestinal lumen with liquid and gas [194]. Thus avoidance of these compounds can improve Functional Gut Symptoms

(FGS), like bloating, nausea, and distention, found in functional bowel disorders and irritable bowel syndrome (IBS) [195,196]. To this point, research supports the use of a low-FODMAP diet for the symptom management of IBS [35]. In a RCT of 73 patients, half were randomized to a low FODMAP versus SCD diet. IBS symptoms such as bloating and distention were shown to improve in the low FODMAP diet group whereas the group with SCD had a low but not significant improvement [35]. Additionally, according to a recent Cochrane review, the low FODMAP diet may also improve CD symptoms [182]. Several plausible mechanisms have been posited and are similar in efficacy to the underlying concept of SCD. By reducing the gaseous by products of undigested complex carbohydrates, there would be a notable improvement in symptomology such as diarrhea, loading, flatulence, and bacterial overgrowth. Further, avoidance of these carbohydrates can mitigate gaseous distention, osmotic diarrhea, and shifts in the gut microbiome [149,150,197].

Because a significant proportion of patients with IBD experience FGS, a low FODMAP diet should be considered as a therapeutic modality. In two recent reports, a low FODMAP diet improved FGS in patients with IBD [149,150]. Following dietary intervention with low FODMAPs, there was a significant decrease in severity for most symptoms as well as the composite score; in addition to a large increase in satisfactory relief of symptoms between baseline (14/88,16%) and the low FODMAP diet (69/88, 78%; P = 0.001) [149]. In the second study, 52 patients with CD and 20 with UC received low FODMAP dietary advice for at least 3 months [150]. At the end of the study, it was reported that up to 70% of patients were adherent to the diet, and overall symptoms, including abdominal pain, bloating, and diarrhea, improved in both CD and UC (P <0.02 for all). For CD, the efficacy was associated with dietary adherence (P = 0.033) and inefficacy with non adherence (P =0.013). These studies illustrate that utilization of a low FODMAP diet in patients with IBD and FGS is a viable and effective treatment modality [149,150,194,195,197]. The research, however, does not support the diet affecting disease activity or inflammatory markers. Nevertheless, more controlled dietary interventions are indicated to elucidate whether low FODMAP affects disease mechanisms.

Low residue diet (LRD)

The rational for use of a LRD in patients with IBD, is to limit 'residue' or indigestible material that primarily constitute the bulk of stool, such as fiber [37]. The perception being that fiber can irritate the bowel [40]. The goal of the diet is to reduce the frequency and volume of stools as a therapeutic management option for bowel prep or as part of the treatment of acute relapses in different bowel diseases [37]. Specifically, the diet requires elimination of whole grains, dairy, legumes, fruit, vegetables, and certain meats. The avoidance of fiber, however, is worrisome and not recommended in patients with IBD [198]. Clinical studies investigating this diet are sparse with the first mention of the diet in 1975, wherein a prospective study of 70 Italian patients with active CD were randomized to a LRD or to continue their normal diet [199] The study concluded no significant outcomes between the groups. More recently, a small pilot study in CD investigated the microbiome changes with the LRD [198]. It was demonstrated that the LRD diet was associated with a decreased diversity of the microbiome, a worrisome outcome. A diet low in fiber may accelerate the dysbiosis in IBD [198]. Although the research is sparse, it demonstrates LRD may potentially harm patients and should be avoided in IBD. Moreover, LRD was recently removed from the American Academy of Nutrition and Dietetics' Nutrition Care Manual due to limited scientific evidence and lack of a unified definition of "residue" [37].

Low microparticle Diet

A 'microparticle' in terms of a dietary strategy refers to man-made, submicron-sized, particles derived from food additives and excipients [200,201]. It has been postulated that the typical WD exposes the GI tract to an incredibly large amount of microparticles each day. Microparticles are adjuvants in antigen-mediated immune responses, and have been found to accumulate in the phagocytes of intestinal lymphoid aggregates and induce a cytokine response in the presence of LPS [200]. Microparticles have been implicated in both the etiology and pathogenesis of IBD [200,201]. Considering these findings, a clinical investigation exploring how a microparticle diet could affect IBD outcomes was designed [38]. Over a period of 16 weeks, 83 subjects with active CD enrolled in the 2×2 design wherein patients were randomized to a diet low or normal in microparticles. The study found no differences between groups in clinical disease activity or inflammatory markers. As such, a low microparticle diet lacks efficacy and is not recommended for IBD.

IgG-4 guided exclusion diet

In an effort to tailor a more personalized approach to dietary interventions, IgG-4 guided elimination or exclusion diets work by evaluating common food items for the targeted effect on IgG-4 titers, an antibody produced in response to an antigenic stimulus [39,202]. Avoidance of food antigens correlated with IgG antibodies have been shown to reduce clinical symptoms but document a lack of correlation with inflammatory biomarkers and clinical disease indices [39,202]. Although clinical symptoms are not a reliable measure of underlying inflammation [203].

In a recent double-blinded randomized sham-controlled setting study, 16 common food items were evaluated for IgG-4 food antigen response [39]. 4 food groups were eliminated in the intervention group associated with the highest IgG-4 titer (the true diet group) [39]. This was compared to a group wherein the 4 food groups eliminated were associated with the *lowest* IgG-4 titers. The patients were followed for a period of four weeks. The researchers found significant improvements in quality of life (QOL) as measured by the Short Inflammatory Bowel Disease Quality of Life Questionnaire (SIBDQ) (3.05; P = 0.05) and clinical disease activity indices, as measured by the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw Index (HBI), (41; P =0.009). Milk, beef, pork, and eggs were the most commonly excluded food types in the true diet group. As with other studies, the findings did not detect a correlation between inflammatory markers and disease activity or symptoms, but these findings corroborate that IgG-4 guided exclusion diets have the potential to improve disease activity. Interestingly, in a small pilot study, IgG-4 guided exclusion diets did result in a significant symptomatic improvement in 90% of patients with an objective fall in ESR from 23 to 17 mm/h (P = 0.021) [204]. This approach may be useful in clinical practice where a more personal approach can be utilized.

Other popular diets

Semi-Vegetarian diet (SVD)

In an effort to avoid excessive restriction and given the epidemiological associations with potentially harmful meat and/or dietary fat intake, the SVD was designed as an appropriate alternative with periodic elimination of proinflammatory dietary nutrients, such as omega-6 series of polyunsaturated fatty acids (n-6 PUFA), red meat, and saturated and trans-fat [40]. The PUFA are defined as "essential" fatty acids since they are not synthesized in the human body and are mostly obtained from the diet. Existing data based on epidemiological and observational studies has led to the hypothesis that red meat consumption may be associated with relapse of CD. Hence the SVD is a lacto-ovo-vegetarian diet that attempts to exclude meat products but allows them in a limited capacity [40]. For instance, the diet allows dairy and eggs, but limits meat to once every two weeks and fish to once per week. Recently, a prospective RCT (n = 22) compared SVD to an omnivorous diet in patients and found a significant prevention of relapse in the SVD group compared to that of individuals following an omnivorous diet (P = 0.003) [40]. For the SVD group, the remission rate was 100% (16/16) at 1 year and 92% at 2 years whereas the omnivorous group remission rate was 67% (4/6) at 1 year and 25% at 2 years. SVD compliance was 73%. Although the number of subjects was limited, the SVD demonstrates it may be a more effective means of maintaining remission in CD compared to an omnivorous diet. However, this is the only clinical study to date on the SVD. Interestingly, a recent RCT comparing high-meat consumption (consumed a minimum of 2 servings/week of red or processed meat (high meat, n = 118) versus not more than 1 serving per month (low meat, n = 96) for 49 weeks found that no significant difference in time to any (P = .61) or moderate/severe (P= .50) relapse [205]. The diet compliance rate averaged 57% throughout the study. The authors noted that adherence to a diet completely absent of red and processed meat would be required to reduce the rate of CD flares [205]. Comparing the adherence rates of the studies brings into question how compliance affects meaningful clinical outcomes. Clearly, further study is warranted to better understand how reducing or eliminating meat consumption can affect outcomes in IBD.

Mediterranean diet (MD)

The MD is characterized by a high intake of vegetables, fruits, whole grains, olive oil, fish and nuts as well as low amounts of red meat and dairy [36]. The dietary components of the MD (high in fiber, polyunsaturated fatty acids, antioxidants, vitamins and plant polyphenols; low in omega-6 and saturated fat) suppress inflammation via microbiota induced mechanisms and are found in high quantities in vegetables, fruit, nuts, seeds, and extra-virgin olive oil. We previously discussed the CDED diet, which has a lot of overlapping nutritional components with the MD [181]. The Dietary Guidelines for Americans recommends the MD to improve health and to prevent disease based on evidence of modest benefits on CVD risk factors in primary prevention [206].

Many components of the MD pattern have been shown to be beneficial in IBD. Recently, it has been published that adherence to a MD is also associated with a lower risk of later-onset CD [158]. Over the course of 20 years, in a large Swedish population of 83,147 individuals, 164 cases of CD and 395 cases of UC cases were diagnosed. This equated to an incidence rate of 12 cases/100,000 person-years and 28 cases/100,000 person-years. The average follow-up time of participants was 17 years. Non-adherence to the MD conferred an adjusted population attributable risk of 12%. Adherence to the MD has also been correlated to a decrease in inflammatory markers and found to beneficially impact the gut microbiota and associated metabolome [207,208]. Studies have found significant associations between adherence to the MD and increased levels of fecal SCFAs and *Firmicutes* [208]. Low adherence was associated with elevated urinary trimethylamine oxide, which is associated with increased cardiovascular risk [208]. In a 6 week study, adherence to a Mediterranean-inspired anti-inflammatory diet decreased established biomarkers of inflammation and, using a transcriptomic approach, significant changes in gene expression [207]. These studies highlight the interrelatedness between the MD and the microbiome.

Further trials for dietary interventions involving the MD are ongoing. The DINE-CD study is a multicenter randomized, open-label trial slated to be complete by 2020 [153]. Another ongoing study titled, 'Mediterranean diet as an add-on therapy for induction of remission in patients with active Crohn's disease', is a randomized parallel assignment double blinded controlled trial of eight weeks of the MD versus 8 weeks of the LRD [154]. Completion of these studies will add much needed insight into the current framework of dietary interventions.

Conclusion

Dietary therapy is a readily identifiable adjunctive treatment for IBD. At present, there is scientific evidence that promotion of the Mediterranean diet should be a standard recommendation for CD, with recognizably less evidence-based support for UC. Recognizably, we lack large RCTs to recommend patients the ideal diet. Although EEN is not a reasonable option in adults, it has been recognized as the strongest link between diet, the microbiome and IBD, and suggests that minimizing potentially harmful food ingredients may improve disease outcomes in IBD. The SCD and CDED also prove to be promising avenues for dietary therapies. Understanding by healthcare providers and patients that dietary treatments are adjunctive and in parallel to treatment with pharmacotherapy.

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