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Oral Diets and Nutrition Support for Inflammatory Bowel Disease: What Is the Evidence?

Neha D. Shah, MPH, RD, CNSC[1,2]; Alyssa M. Parian, MD[3]; Gerard E. Mullin, MD, CNSP[3]; and Berkeley N. Limketkai, MD[1,2,3]

Abstract

Inflammatory bowel disease (IBD), which primarily includes Crohn's disease and ulcerative colitis, involves chronic inflammation of the gastrointestinal tract. The mechanisms of IBD pathogenesis are not well understood at this time, but likely involve an interaction between genetic, gut microbial, immune, and environmental factors. Emerging epidemiologic studies have suggested a relationship between specific dietary nutrients as an environmental factor and IBD risk. Clinical trials have also shown oral diets to have variable efficacy in affecting clinical outcomes for IBD. This review discusses the key studies that evaluated the use of various oral diets as well as nutrition support in the management of IBD. (*Nutr Clin Pract*. 2015;30:462-473)

Keywords

inflammatory bowel diseases; nutrition therapy; nutritional support; Crohn's disease; ulcerative colitis; diet fiber; gluten; lactose; enteral nutrition; parenteral nutrition

Introduction

Inflammatory bowel disease (IBD), primarily comprised of Crohn's disease (CD) and ulcerative colitis (UC), comprises a group of heterogeneous disorders of the gastrointestinal tract characterized by idiopathic chronic intestinal inflammation. Although the etiology of IBD is unclear, interactions between genetic and environmental factors are suspected to play a role in its pathogenesis. Genome-wide association studies have so far identified 163 IBD susceptibility loci, but these explain only a minority of disease incidence.[1] Some environmental influences may include geographic location, tobacco use, physical activity, sleep patterns, and especially alterations in diet.[2,3]

The development of IBD among immigrants to Western countries, particularly from locales with a traditionally low prevalence of IBD, has been partly attributed to the Westernization of their diet.[4] Immigrants to Western societies often assimilate dietary practices of their host countries, which may include a shift toward increased intake of fats and refined carbohydrates.[5] These dietary changes are thought to favor synthesis of proinflammatory cytokines, influence intestinal permeability, or alter the intestinal microbiota in ways that promote chronic inflammation.[6,7] Emerging epidemiologic studies have also shown a potential relationship between specific dietary nutrients as an environmental factor and IBD risk. In particular, high intake of total fats and omega 6 (ω-6) polyunsaturated fatty acids (PUFAs) in the diet appears to be associated with an increased risk for CD and UC,[8,9] while dietary fiber, especially from fruits and vegetables, may have a protective effect from CD or UC.[10-12]

Patients often seek dietary advice in the hope that optimizing their diet would treat or help manage their IBD. They may change their diets based on self-perceptions that specific foods will aggravate or resolve their symptoms.[13-15] While up to 90% of IBD patients consider dietary guidance an important facet of their medical care, only 20% of them feel they receive adequate information about diet changes, risk of nutrition deficiencies, and foods that offer nutritional value.[16] In this review, we present and discuss key studies that evaluated the use of oral diets and nutrition support in the management of IBD. It is hoped that this information will aid both clinicians and patients to have informed discussions about the role of diet and nutrition for IBD.

Oral Diets

Fat

Among the diverse structural and functional roles of fatty acids in human physiology, fatty acids are mediators in the inflammatory cascade.[17] In particular, the omega-3 (ω-3) PUFAs that

From [1]Digestive Health Center, Stanford Health Care, Palo Alto, California; [2]Division of Gastroenterology & Hepatology, Stanford University School of Medicine, Stanford, California; and [3]Division of Gastroenterology & Hepatology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

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Corresponding Author:
Neha D. Shah, MPH, RD, CNSC, Digestive Health Center, Stanford Health Care, 900 Blake Wilbur Drive, Garden Level, Palo Alto, CA 94304, USA.
Email: neshah@stanfordhealthcare.org

include α-linolenic acid, docosahexaenoic acid (DHA), and eicosapentaenoic acid are believed to have immunomodulatory properties. By contrast, the omega-6 (ω-6) PUFAs that include linoleic acid (LA) and arachidonic acid have proinflammatory properties. Both ω-3 and ω-6 PUFAs are metabolized by cyclooxygenase and lipoxygenase to eicosanoid signaling molecules (ie, prostacyclins, thromboxanes and leukotrienes). Although both ω-3 and ω-6 PUFA-derived eicosanoids possess proinflammatory properties, the former has a significantly diminished effect. A higher ω-3:ω-6 PUFA ratio would lead to competitive inhibition in favor of the weaker proinflammatory eicosanoids. Some additional putative mechanisms for ω-3 PUFA's immunomodulatory effects include inhibition of T-lymphocyte proliferation, regulation of chemokine receptor and cytokine gene expression, modulation of antigen presentation, and alteration of the gastrointestinal flora.[17]

Earlier studies that linked dietary fat intake with IBD pathogenesis were performed in Japan. Between 1966 and 1985, a large survey of 16,500 to 68,000 individuals was conducted that included annual dietary interviews over 5 consecutive days.[8] An analysis of 242 newly diagnosed CD patients revealed that increased dietary total fat, animal fat, ω-6 PUFA, and ω-6:ω-3 PUFA intake ratio correlated with incident CD. A later hospital-based, case-control study that looked at dietary risk of UC found that consumption of Western food (eg, bread, butter, margarine, cheese, meats, ham, and sausage), and margarine in particular, was associated with a risk of UC.[9] The European Prospective Investigation into Cancer (EPIC) studied 203,193 men and women (aged 30–74 years at enrollment) who completed country-specific food frequency questionnaires.[18] During the median 4 years of follow-up, there were 126 incident cases of UC. In an age-, gender-, and center-matched case-control design, the highest quartile of LA consumption was associated with an increased risk of UC after adjusting for tobacco use and total energy intake. Higher DHA consumption was inversely associated with UC risk, after adjusting for tobacco use, total energy intake, and other listed fatty acids.

There are no randomized trials that have specifically investigated overall dietary fat intake and induction or maintenance of remission in IBD; studies that evaluated the role of fat for induction of remission have primarily been performed in the context of enteral nutrition (EN; see the EN section). Nonetheless, there are limited studies that have investigated the use of an oral diet rich in ω-*3* PUFA as induction therapy in UC and maintenance therapy in CD and UC. Food sources rich in ω-3 PUFA include flax, fish, nuts, and seeds.

The use of ω-3 PUFA supplementation is of great interest, mainly in the form of fish oil capsules for the treatment of IBD. A detailed discussion of its use extends beyond the scope of this review of oral diets. In brief, there are no randomized controlled trials evaluating the use of ω-3 PUFA in active CD. For maintenance of remission in CD, a Cochrane Collaboration meta-analysis showed marginal benefit of ω-3 PUFA, but a subgroup analysis of the larger and more robust studies revealed similar relapse rates between the ω-3 PUFA and placebo groups.[19-24] In active UC, the studies at this time have inconsistently shown improvement or no benefit in clinical, endoscopic, and histologic scores with the use of ω-3 PUFA. For maintenance of remission in UC, three randomized trials involving 138 participants found no difference in relapse rates between the fish oil and placebo groups.[25-31]

Fiber

There are varying definitions of dietary fiber used in the literature and clinical setting. In general, dietary fiber is considered to be an intact, plant-based carbohydrate that is nondigestible by humans. It is, however, digestible by intestinal microbes through the process of fermentation. The role that dietary fiber plays in gastrointestinal health depends on the type, amount, and characteristics (fermentability, viscosity, solubility) of the fiber consumed.[32] The soluble, fermentable fibers include guar gum, inulin, fructo-oligosaccharides (fructans), galacto-oligosaccharides (galactans), and pectin; they are found in foods such as barley, legumes, nuts, seeds, oats, onions, garlic, and rye. The insoluble, slightly fermentable/nonfermentable fibers include cellulose and lignin and are found in foods such as fruit and vegetable skins, flax seed, quinoa, and wheat bran. Benefits of dietary fiber for gastrointestinal health include increasing water and bulk in stools to facilitate passage of stool through the intestinal tract and promoting bacterial fermentation of fiber into short-chain fatty acids (SCFAs) in the colon.[33] SCFAs, such as acetate, butyrate, and propionate, serve as fuel for colonocytes and are thought to modulate intestinal inflammation by enhancing the biodiversity of the intestinal microbiota toward nonpathogenic strains that may serve as a colonic mucosal barrier to pathogenic strains.[34] Therefore, it is hypothesized that a low-fiber diet along with diminished production of SCFAs would alter the intestinal microbiota in ways that up-regulate production of proinflammatory cytokines, while a high-fiber diet would increase production of SCFAs to aid in the treatment of IBD.[34]

The low-fiber diet. The term *low-residue diet* is often used interchangeably with *low-fiber diet*, but there are subtle differences. The historical origins of the low-residue diet stem from the belief that reducing food "residue" entering the intestinal tract would reduce gastrointestinal distress.[35] The term *residue* informally refers to any food that is nondigestible (dietary fiber) or any food that contributes to an increased stool output.[36] This is in contrast to the prior description of dietary fiber. In the low-residue diet, restrictions are placed on some dairy and meat products in addition to nondigestible fiber to reduce residue.

Although there are limited studies to support the practice, patients have traditionally been instructed to restrict their dietary fiber intake in the setting of active IBD, with the intent of reducing passage of stool antigens into the inflamed areas as

well as reducing the frequency of stools. The diet has also been used to theoretically minimize the risk of obstruction in the setting of known CD strictures. In a randomized Italian trial of 71 adult active CD patients already following the low-residue diet (described as avoidance of legumes, whole grains, nuts, fruits, and vegetables), there was no difference in outcomes (ie, surgery, hospitalization, prolonged bed rest, partial obstruction, or new inflammatory mass) between those who remained on the low-residue diet or those who transitioned to a normal diet (described as a gradual reintroduction of fiber).[37] Some patients reported symptoms with consumption of other foods, such as dairy and spicy foods, suggesting that food intolerances may not necessarily have been due to fiber. The study authors concluded that restrictions on dietary fiber intake may not be necessary.

The high-fiber diet. Early evidence of the potential benefits of dietary fiber in established CD was suggested by the Bristol Royal Infirmary (United Kingdom), where 32 adult active CD patients treated with a fiber-rich, unrefined carbohydrate diet were compared with 32 adult active CD patients who received no dietary instructions.[38] The patients in the fiber-rich group had fewer and shorter hospitalizations. Moreover, although many had known strictures, none developed intestinal obstruction. One diet-treated patient and 5 controls underwent intestinal resection, although the numbers were small and not statistically significant. However, subsequent studies failed to demonstrate a clear benefit of fiber on clinical outcomes. A larger multicenter randomized controlled trial based on the same Bristol high-fiber diet found no difference in intestinal resections, hospital admissions, or change in symptom scores (Harvey-Bradshaw Index) among 352 adult patients with inactive or mildly active CD.[39,40]

The data for dietary fiber in UC are similarly weak but more promising. In the first trial to compare 20 g of fiber (*Plantago ovata* seeds as a soluble, fermentable fiber) with drug therapy (mesalamine) for the maintenance of remission in 105 adult UC patients, there was no difference in relapse rates among the 3 groups with fiber only, mesalamine only, or fiber and mesalamine.[41] The 2 groups that consumed fiber were nonetheless found to have increased fecal butyrate levels. These findings led the investigators to conclude that dietary fiber may be equivalent to mesalamine in efficacy. However, caution is needed when interpreting these findings. The study investigators admit they recruited fewer than the required sample size of 434 participants; their results may therefore be due to type II error rather than true equivalence between fiber and mesalamine.

The vegetarian diet. The vegetarian diet focuses on the inclusion of fiber-rich plant-based foods while reducing intake of foods of animal origin. At this time, there are very limited studies exploring the effects of the vegetarian diet on IBD. A small prospective study in Japan had 22 adult patients with quiescent CD follow a semivegetarian diet for 2 years. The patients were instructed to include fruits, vegetables, legumes, potatoes, and yogurt in the diet daily while reducing intake of fish to once a week and meat to every 2 weeks. The only medications used as maintenance therapy were mesalamine or sulfasalazine. Clinical remission was defined as the absence of gastrointestinal symptoms that would prompt treatment. For the 16 patients who remained on the diet throughout the study, the 2-year remission rate was 92% at 2 years; by contrast, for the 6 patients who switched to an omnivorous diet, the 2-year remission rate was significantly lower at 25%.[42] Notable limitations of the study included a small sample size and a lack of endoscopic or histologic endpoints.

Carbohydrates

In contrast to dietary fiber, which is defined as a nondigestible carbohydrate, the carbohydrates described here are digestible by intestinal and pancreatic enzymes.[43] The monosaccharides (eg, glucose, galactose, and fructose) do not require enzymes for digestion. The disaccharides (eg, lactose, maltose, and sucrose) consist of 2 linked monosaccharides and require intestinal enzymes for digestion prior to absorption. Dietary starch is a polysaccharide, and once digested by the pancreatic enzyme amylase, it will yield disaccharides and oligosaccharides (short chain of monosaccharides). Any undigested carbohydrates that enter the colon may undergo bacterial fermentation.

The influence of carbohydrates on IBD pathogenesis is largely theoretical at the moment. Some hypothesize that excessive intake and/or impaired digestion of carbohydrates may adversely alter the intestinal microbiota and lead to aggravation of symptoms and disease activity. By extension, the application of carbohydrate-restrictive diets is also postulated to help treat IBD. However, the evidence for a role in IBD pathogenesis or treatment is either inconsistent or weak.[44,45]

The lactose-free diet. Lactose is a disaccharide derived from glucose and galactose and is hydrolyzed by the intestinal brush border enzyme lactase (β-D-galactosidase).[46] The primary source of lactose in the diet is found in dairy products. Lactase expression can decline over time, variably manifested in different ethnic populations, such as most Thai children as early as 2 years of age[47] or just 15% of Finnish adults.[48] The development of lactase deficiency results in an inability to digest lactose, thus serving as an osmotic agent and separately as a substrate for colonic bacterial fermentation and growth (and overgrowth).[46] Both mechanisms can independently lead to gastrointestinal symptoms of abdominal bloating, flatulence, and diarrhea due to lactose malabsorption. The tolerance to lactose is dose dependent, as lactose content varies from one dairy product to another.[49] The treatment of lactose malabsorption therefore does not require a completely lactose-free diet but a graduated reduction of lactose intake.

Patients with IBD were often instructed in the past to implement a lactose-free diet and avoid all dairy products because of perceived dairy sensitivity or lactose intolerance.[50] To our knowledge, there are no studies that specifically evaluate lactose as a mediator in IBD pathogenesis or whether lactose restriction alters the natural history of the disease. Lactose intolerance is reported in 40% to 70% of CD patients.[51-53] However, the prevalence of true lactose malabsorption is unclear in IBD, as gastrointestinal manifestations of IBD can often mimic symptoms of lactose malabsorption. In a German study of 49 active CD patients and 24 controls, the prevalence of self-reported milk intolerance was 46.9% and 16.6%, respectively.[52] Milk intolerance was also significantly greater among CD patients with active disease and longer disease duration. Pathologic H_2 breath testing and decreased lactase activity, as measured through intestinal mucosal biopsies, were similarly greater among those with active disease compared with those in clinical remission but not when compared with healthy controls. There was nonetheless poor sensitivity (44.4%) and specificity (63.2%) of lactase activity and milk intolerance. These findings suggest that milk intolerance in CD may occur via a mechanism independent of lactose malabsorption. Similarly, a study of 165 of both active and quiescent CD patients in New Zealand found that perceived intolerance to dairy products was more likely attributable to fat content rather than the presence of lactose.[54] Even in non-IBD populations, symptoms of lactose intolerance are not necessarily due to lactose malabsorption. A randomized controlled trial of milk or lactose-hydrolyzed milk administered to non-IBD participants with self-reported severe lactose intolerance did not find a difference in symptom manifestations between treatment arms.[55]

In summary, restriction of lactose intake may subjectively lead to symptomatic improvement in some IBD patients, although the underlying mechanism may be less frequently due to lactase deficiency than an effect of IBD itself.

The specific carbohydrate diet. The specific carbohydrate diet (SCD) was originally proposed by Dr Sidney Hass in the 1920s to treat celiac disease. In the late 1950s, Canadian biochemist Elaine Gottschall had her ill 8-year-old daughter, who was diagnosed with UC, follow the diet under the guidance of Dr Haas. Her daughter was reported to have experienced a resolution of symptoms within 2 years and remained symptom free after returning to a regular diet years later. Gottschall later popularized the diet in her book *Breaking the Vicious Cycle* in the late 1980s.[56]

The SCD advocates the elimination of all disaccharides, oligosaccharides, and polysaccharides from the diet. Some prohibited foods include high-lactose dairy, all starchy vegetables, all grains, and foods with added sugar. The theory purports that bacterial fermentation of poorly digested carbohydrates results in the production of metabolic by-products that may contribute to intestinal inflammation and disruption of gut integrity and injury. As monosaccharides do not require digestion, the diet thus recommends consumption of monosaccharides as the sole source of carbohydrates in the diet, such as lactose-free yogurt and fresh fruits as a source of fructose. The consumption of fresh meats, poultry, fish, and eggs is acceptable. The SCD program recommends maintaining the diet for a year while with active disease and for at least another year after symptoms disappear.[56] After this elimination phase, 1 food item can be gradually reintroduced per week, while monitoring for a recurrence of symptoms. If symptoms return, the SCD calls for a return to the original carbohydrate restrictions. Long-term adherence to the diet is challenged by its restrictive nature, particularly when eating at restaurants or traveling.

Many patients report interest in exploring the SCD based on anecdotal success stories from others, although there are currently very limited studies that have formally evaluated its effectiveness for the treatment of IBD. A small retrospective case series described outcomes in 7 pediatric patients with active CD who had received SCD (without immunosuppressive medications) as treatment for an average of 15 months (range, 5–30 months). Patients experienced complete resolution of symptoms within 3 months after initiating the diet. Laboratory markers (ie, C-reactive protein, hematocrit, albumin, and stool calprotectin levels) also showed overall improvement but were inconsistently collected and could not be statistically evaluated.[57] A subsequent prospective case series described the effect of SCD in 9 pediatric active CD patients (3 medication naïve, 1 on mesalamine, 1 on budesonide, and 4 on immunomodulators), showing improvements in symptom scores at weeks 12 and 52.[58] Capsule endoscopy findings, as measured by the Lewis score, improved at week 12 but not at week 52. Erythrocyte sedimentation rate (ESR) and albumin otherwise remained unchanged throughout the study. There are so far no published controlled trials evaluating the efficacy of SCD for IBD. Moreover, there are no studies examining possible mechanisms for an effect of SCD on IBD.

The low-FODMAP diet. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) refer to a cluster of short-chain fermentable carbohydrates that exist in varying concentrations in foods.[59] Not all carbohydrates are considered FODMAPs; foods high in FODMAPs include those high in fructose, lactose, fructans/galactans, and polyols (sugar alcohols). Entry of undigested FODMAPs into the intestinal tract may result in luminal distension via 2 principal mechanisms.[59] First, FODMAPs exert osmotic pressure, thus drawing fluid into the intestinal lumen. Second, FODMAPs eventually undergo fermentation by colonic bacteria, promoting excess colonic gas formation and, over time, bacterial overgrowth. These pathophysiologic changes lead to functional symptoms of abdominal pain, gas, bloating, cramping, and diarrhea.

Most FODMAP studies conducted so far have assessed the impact of the low-FODMAP diet on IBS, where institution of the diet for a 6- to 8-week trial period was linked to a reduction of gastrointestinal symptoms.[59] During the trial period, which serves as the elimination phase, high FODMAPs are completely removed from the diet. After the trial period, high-FODMAP foods are slowly reintroduced into the diet to identify triggers based on tolerance. In contrast to the SCD, we anticipate that the low-FODMAP diet may be easier to follow for the short term because of the greater variety of low-FODMAP grains, dairy, fruits, and vegetables allowed in the diet.

There are limited studies investigating the association between FODMAPs and IBD at this time. A pilot cohort study of 52 active CD patients and 20 active UC patients recently evaluated the role of the low-FODMAP diet in improving functional symptoms. The patients received individualized nutrition counseling for the low-FODMAP diet by registered dietitians for 3 months.[60] About 70% of the patients were compliant with the diet, and dietary compliance was associated with an improvement in abdominal pain, bloating, and diarrhea but not in constipation. The study findings suggest that the low-FODMAP diet may improve functional symptoms. However, data regarding the diet's effect on intestinal inflammation or disease natural history are lacking at this time.

The Paleolithic diet. The principle behind the Paleolithic diet proposes that modern humans are similar in their genome from those within Paleolithic-era hunter-gatherer societies and the introduction of new foods through agricultural advancements has contributed to poor genetic adaptation to these evolutionary changes in diet. The changes in diet are also theorized to predispose genetically susceptible individuals to developing modern chronic diseases (eg, diabetes, cardiovascular disease, and obesity) that were uncommon in the hunter-gatherer societies.[61] Advocates for the diet favor consumption of foods similar to what were eaten by hunter-gatherers; these include meats from wild game, which is considered to be high in protein, high in PUFAs, and low in saturated fat. The diet is also devoid of grains, refined sugar, and dairy; uncultivated fruits and vegetables are the only prescribed sources of carbohydrates and dietary fiber.[62]

There is interest to use the Paleolithic diet for weight, cardiovascular disease, and type II diabetes management, with few small studies suggesting possible efficacy. Several websites and blogs also promote the diet as a treatment for IBD; however, there are currently no published studies that have evaluated its efficacy in IBD.

Gluten

Gluten is a grain protein found in wheat, barley, and rye. A gluten-free diet entails complete elimination of food sources of wheat, barley, and rye, as well as foods that may have hidden gluten. Substitutions to help comply with a gluten-free diet include foods that are naturally gluten free as well as foods made from gluten-free grains, such as beans, potato, and rice. Traditionally, the gluten-free diet had been used solely as a medical treatment for celiac disease. Recently, there has been a growing trend toward the use of the gluten-free diet for other digestive disorders because of non–celiac disease patients self-reporting a reduction or disappearance in symptoms (eg, abdominal pain, bloating, and diarrhea) after implementing a gluten-free diet.[63] Patients often pose the question whether the gluten-free diet may benefit those with nonceliac IBD.

The gluten-free diet. There are currently very limited data on the use and benefit of a gluten-free diet in IBD. In a recent cross-sectional study, a gluten-free diet questionnaire was distributed to 1647 IBD patients enrolled in the Crohn's & Colitis Foundation of America Partners cohort.[64] Patients were asked whether they had ever been on a gluten-free diet, still remained on it, been diagnosed with celiac disease or gluten sensitivity, experienced a reduction in symptoms while on the diet, and felt that being on the gluten-free diet had resulted in fewer IBD flares. The study showed that 65% of all patients who had tried the gluten-free diet reported a reduction in symptoms, especially fatigue, and 38% of all patients reported a reduction in severity of flares. The study suggests that the implementation of the gluten-free diet could possibly assist with the management of symptoms in patients with IBD. There is a clearly a need for additional well-designed, prospective studies at this time.

Nutrition Support

Among patients who are unable to maintain adequate nutrition intake orally, EN and parenteral nutrition (PN) are mechanisms to provide nutrition support. EN is the preferred route of nutrition delivery, particularly when patients retain a functional gastrointestinal tract.[65] EN physiologically delivers nutrients into the gastrointestinal tract, is more cost-efficient, and is associated with fewer overall complications than PN. PN is indicated in those at risk for undernutrition with a nonfunctional gastrointestinal tract, with a lack of enteral access to place a feeding tube, or who cannot tolerate the EN regimen well.

The European Society for Parenteral and Enteral Nutrition established guidelines in 2006 for the use of EN and PN in IBD.[65] The guidelines recommend that EN should be used to promote growth and be the first line of therapy for pediatric patients with active CD, whereas in adults, EN should be used to address undernutrition and as sole therapy when corticosteroids are not feasible. EN in the treatment and maintenance of remission in UC has not been proven, so it is not recommended. PN is not indicated for primary or maintenance therapy of CD and UC, although it can be used to address undernutrition or high-output fistulas if EN is not feasible. The use of PN during a period of bowel rest has not proven to be effective in both CD and UC.

Enteral Nutrition

EN, as an exclusive or supplemental form of nutrition, has generated interest as a treatment modality for IBD, while possibly reducing reliance on pharmacologic immunosuppressants. Although the exact mechanisms are unclear, the use of EN in IBD is hypothesized to promote mucosal healing in the gastrointestinal tract by favorably altering the intestinal microbiota, reducing intestinal permeability, enhancing barrier defense and adaptation, and promoting a reduction of proinflammatory cytokines.[66] Several prospective studies have shown that both pediatric and adult patients with active CD achieved remission, had endoscopic and histologic healing, and exhibited lower proinflammatory cytokine levels in mucosal biopsies after receiving short-term EN.[67,68] The study participants were not on immunosuppressive medications, suggesting that mucosal healing occurred through a dietary influence on inflammation. Because of strong concerns for corticosteroid use in children, EN is often first-line therapy for pediatric patients with active CD. Japan is one of the very few countries where EN is routinely used for both pediatric and adult CD patients, but it is not the first-line therapy for adult patients.[69]

Types of primary enteral formulas include polymeric and elemental enteral formulas. The term *polymeric* refers to the presence of intact proteins in the enteral formula that require digestion by gastric, intestinal, and pancreatic enzymes. The term *elemental* refers to the inclusion of free amino acids in the formula, and its nutrients require minimal or no digestion.[70] In a study of pediatric patients with active CD, there were no significant differences between the use of polymeric and elemental formulas for inducing remission, although the polymeric formula promoted favorable weight gain.[71,72] A Cochrane review comparing 10 studies with 334 CD patients similarly found no difference between the use of elemental, semielemental, and polymeric formulas at inducing remission in CD.[73]

Exclusive enteral nutrition (EEN) refers to the use of 100% EN as the sole source of nutrition. However, since EEN requires avoidance of all foods, adherence can be challenging to the patient because of its possible impact on social behavior. EN may have poor palatability and tolerability as well. The use of partial EN to supplement an oral diet is therefore of great interest to patients and clinicians. However, a randomized trial of 50 pediatric patients with active CD found EEN to be significantly more effective than partial EN (50% EN, 50% diet) at 6 weeks in reducing diarrhea, platelets, and ESR.[74] Moreover, only EEN led to a rise in hemoglobin and albumin levels. On the other hand, there may still be a role for supplemental EN for the maintenance of remission in CD. A randomized trial of 51 adult patients with quiescent CD showed that the half-EN group had a lower relapse rate than the no-EN group.[75] Both groups were permitted an unrestricted diet and were on mesalamine or azathioprine, if already on it at enrollment.

The long-term use of EN has also been investigated for its impact on maintaining remission. In one prospective study, 40 adult patients with quiescent CD were assigned to either (1) nocturnal elemental EN via self-inserted nasogastric tube, while consuming a low-fat diet of 20 to 30 g during the day, or (2) no EN or diet therapy.[76] The patients were not on corticosteroids or other immunosuppressive medications at the time of enrollment. The investigators discovered that the 1-year rate of relapse, endoscopic inflammation scores, and proinflammatory cytokines levels were significantly higher in the non-EN therapy group. The study suggests that long-term use of EN in patients in remission from CD may have a role in maintenance of remission.

Several studies compared the efficacy of EN as treatment in CD to various medical therapies. A meta-analysis compared EN therapy with corticosteroids in pediatric patients with active CD and found no significant differences in the remission rates between the 2 forms of therapies.[77] However, a Cochrane review of 6 studies with 192 active CD patients treated with EN and 160 active CD patients treated with corticosteroids showed a pooled odds ratio of 0.33 (95% confidence interval, 0.21–0.53) favoring corticosteroids, suggesting that corticosteroids are more effective than EN at inducing remission.[73] A 2-year randomized trial compared the use of supplemental elemental EN, 6-mercaptopurine (6-MP), and no additional therapy for maintaining remission in 95 adults with CD.[78] Most patients were permitted to continue use of 5-aminosalicylates and/or sulfasalazine at the time of enrollment. Remission rates for elemental EN and 6-MP were similar, while rates were greater than for controls. When assessing the benefit of EN among patients already on immunosuppression, 1 study evaluated 56 adult CD patients stably maintained on infliximab (5 mg/kg every 8 weeks); 32 were supplemented with nocturnal EN and a low-fat diet, and the remaining 25 received no additional EN or dietary restrictions.[79] The rates of clinical remission were the same in both arms, suggesting that EN may not provide added benefit for those in remission while on biologic therapy.

Given the theoretical proinflammatory properties of some lipids, the effect of fat composition in enteral formulas has been investigated. Varying amounts of medium-chain triglyceride content in EN have not been shown to differ in remission rates in 36 adult patients with active CD.[80] Similarly, in a Cochrane subgroup analysis of EEN therapy for the induction of remission in CD, there was no significant difference in EN formulations with low fat (<20 g/1000 kilocalories [kcal]) and high fat (> 20 g/1000 kcal) after 4 to 6 weeks; the subgroup included 209 active CD patients from 7 studies.[73] Additional analysis did not reveal a significant difference in induction of remission when comparing very low fat (<3 g fat/1000 kcal) versus low-to-high fat, or low (<10%) versus high (> 10%) long-chain triglycerides. On the other hand, some data suggest that the type of fat may instead be the more important consideration. The European Group on Enteral Nutrition in Crohn's

Disease randomized 62 adult patients with active CD to 1 of three 3 arms: (1) polymeric EN rich in oleic acid (an ω-9 monounsaturated fatty acid; 79%) and low in linoleic acid (an ω-6 PUFA; 6.5%), (2) polymeric EN rich in linoleic acid (45%) and low in oleic acid (28%), and (3) corticosteroids.[81] Treatment failure was lack of remission after 4 weeks of therapy. Corticosteroids were found to be superior to EN. In the intention-to-treat analyses, both EN formulations had similar response rates, although in the per-protocol analyses, which excluded noncompliant participants, LA-rich EN had a greater response rate than the oleic acid–rich formulation. These findings may conflict with the concept of ω-6 PUFAs having proinflammatory effects. On the other hand, the study suspects that an excess of oleic acid may negate the benefit of EN, rather than ω-6 PUFAs being a therapeutic component of EN. The sample size was too small, and no placebo-controlled arm was present to make firm conclusions from the findings.

Parenteral Nutrition

PN has historically been administered to permit continued nutrition in CD or UC patients placed on bowel rest. The rationale of bowel rest is to limit intestinal exposure to proinflammatory antigens while allowing mucosal healing and reducing risk of surgical interventions.[82] Controlled trials of PN use in IBD are sparse but have so far found no conclusive role for PN or bowel rest. In an early randomized study of 47 adult patients with severe acute colitis (CD and UC) receiving intravenous prednisolone, PN and bowel rest resulted in a greater reduction of daily bowel movement frequency and stool weight.[83] There were otherwise no significant differences in clinical parameters, need for urgent surgery, or mortality in the overall cohort. In subgroup analyses, according to IBD type, bowel rest led to significantly less surgery (0/16 vs 14/27) in the CD patients; there was no difference among the UC patients. A subsequent trial of 51 adult patients with active CD compared the effects of PN and bowel rest, EN, or supplementary PN with unrestricted food. There was no difference in 1-year remission rates among the 3 arms.[84]

Future Directions

Nutrition research is a particularly challenging endeavor because of notable limitations in blinding, control of dietary intake, dietary recall, and unclear interactions among multiple conutrients in food. The study of diet and IBD is further complicated by the heterogeneity of disease presentation and medical treatment approaches. Short-term research priorities should include randomized controlled trials to evaluate the efficacy of different diets (eg, high fiber, vegetarian, SCD, FODMAP) that were shown in smaller studies to have potential benefit in IBD. Omega-3 supplementation may help maintain remission in CD, but the current results have been inconsistent. It is notable that different formulations and doses of fish oil were provided in the studies. Head-to-head comparisons at different doses may therefore help suggest optimal dosing of fish oil for the treatment of IBD, which can then be studied in a larger randomized trial setting.

A common nutrient in many of the oral diets discussed here is carbohydrates, either in their role as fiber to promote production of SCFAs or for their restriction to reduce malabsorption. Anecdotal evidence suggests that varying levels of carbohydrate restriction (ie, FODMAP, SCD) may contribute to a reduction of symptoms. The possible mechanisms of effect may include a reduction in proinflammatory components, malabsorbed nutrients that manifest as diarrhea, or bacterial fermentation of carbohydrates. Further clinical investigation is needed to delineate whether dietary effects stem from mere avoidance of symptomatic triggers (ie, reduced intake of less-tolerated foods during active inflammatory disease) or actual immunomodulatory properties.

Beyond clinical trials, basic and translational research is also important to help clarify the mechanisms of nutrient effect on inflammation. Nutrition is known to influence the gut microbiome; it is conceivable that pro- or anti-inflammatory effects of nutrition are largely mediated by the microbiota. Thus, molecular characterization of both nutrient-microbiome and microbiome-IBD relationships may provide clues about mechanisms. These endeavors, as a whole, will guide future studies that clarify the pathogenesis and/or identify future therapies for IBD.

Conclusion

There is strong interest among patients to explore dietary strategies to prevent or manage IBD, particularly related to modification of fiber, carbohydrates, fats, and gluten as nutrients of interest. However, data on the use of oral diets to treat or alter the natural history of IBD largely remain inconclusive (see Table 1 for a summary of oral diets for IBD). We cannot recommend a specific oral diet to treat IBD, other than to limit foods that are felt to aggravate symptoms. Patients would benefit from individualized nutrition counseling to obtain guidance on diet. EN appears to have potential for use in the induction and maintenance of remission for CD, but it is also limited by its potential to affect social behavior and tolerability. The historical practice of bowel rest and PN is not clearly supported by research evidence, although PN may have a role to address undernutrition, where EN is not feasible. Although the current evidence does not yet support specific dietary strategies as primary therapies for IBD, this does not indicate a lack of benefit. There is yet a dearth of data, and more studies are needed clarify a role of oral diets and nutrition support for IBD.

Table 1. Summary of Oral Diets for Inflammatory Bowel Disease.

Diet	Claim in IBD	Foods (Partial List)	What Does the Current Evidence Say?	
			CD	UC
Low-fiber diet	A reduction in dietary fiber intake would reduce passage of stool antigens to inflamed bowel as well as reduce the bulk and frequency of stools. Patients have traditionally been instructed to reduce fiber while in an active flare or with intestinal strictures.	*Food restrictions* Bran, beans, berries, lentils, quinoa, all fruit/vegetable skins, nuts, seeds, prunes, raw/cooked vegetables (eg, artichokes, asparagus, corn), whole grains *Food allowances* Banana, cream of wheat, white bread, white rice, peeled fruits, cooked vegetables (eg, beets, carrots, potatoes)	Limited studies do not clarify current practice of fiber restriction during active flares or in the presence of CD stenosis.	There are no published trials that have evaluated its use in UC.
High-fiber diet	The inclusion of high-fiber foods in the diet would promote production of short-chain fatty acids to modulate intestinal inflammation.	*Food restrictions* None *Food allowances* Bran, beans, lentils, nuts, seeds, oats, quinoa, all fruits and vegetables, whole grains	The studies failed to demonstrate a benefit in clinical outcomes in active CD. To our knowledge, there are no studies of the use of the diet in quiescent CD.	Although the studies showed more promising results than with CD, the overall evidence is weak.
Vegetarian diet	An increase in fiber-rich plant-based foods would promote production of short-chain fatty acids to modulate intestinal inflammation.	*Food restrictions* Meat, poultry, fish (*a complete vegetarian diet would eliminate these foods) *Food allowances* Dairy, eggs, beans, fruits, vegetables, lentils, nuts, whole grains	One study found possible efficacy as maintenance therapy, but the study was limited by its small sample size and lack of endoscopic or histologic endpoints. There are very few studies at this time to support its use.	There are no published trials that have evaluated its use in UC.
Lactose-free diet	An elimination of all lactose from the diet would address lactose malabsorption and intolerance.	*Food restrictions* All dairy with lactose *Food allowances* Lactose-free dairy	In lactose malabsorption, there is no need to completely restrict lactose; instead, reduce lactose intake as tolerated. IBD patients may report lactose intolerance, but this may not necessarily be due to lactose malabsorption. There are so far no studies that have evaluated the effect of lactose on IBD activity.	There are minimal studies at this time investigating lactose sensitivity in UC.
Specific carbohydrate diet	The bacterial fermentation of poorly digested carbohydrates would result in intestinal inflammation.	*Food restrictions* Beans, most canned foods (eg, meats, vegetables), high-lactose dairy (eg, cow's milk), grains (eg, cereals, breads, pastas),	Few small uncontrolled studies showed some improvement in symptoms but with inconsistent changes in inflammatory markers.	There are no published trials at this time that have evaluated its use in UC.

(continued)

Table 1. (continued)

Diet	Claim in IBD	Foods (Partial List)	What Does the Current Evidence Say? CD	What Does the Current Evidence Say? UC
		lentils, starchy vegetables (eg, corn, potatoes, yams), table sugar *Food allowances* Lactose-free dairy (eg, homemade yogurt, hard cheeses such as cheddar), fresh/cooked fruits and nonstarchy vegetables (eg, spinach), nut flour, honey		
Low-FODMAP diet	A reduced intake of fermentable carbohydrates (excess fructose, lactose, fructans, galactans, and polyols) in the diet would help reduce symptoms, similar to its effects on irritable bowel syndrome.	*Food restrictions* Beans, lentils, high-lactose dairy, wheat, barley- and rye-based grains (eg, cereals, breads, pastas), high-FODMAP fruits and vegetables (eg, apples, pear, prunes, stone fruits, watermelon, artichokes, cauliflower), honey, garlic, onion, inulin *Food allowances* Low-lactose/lactose-free dairy, gluten-free–based grains (eg, corn, potato, quinoa, rice), low-FODMAP fruits and vegetables (eg, banana, orange cantaloupe, strawberries, carrots, potatoes, spinach), table sugar	There is evidence to suggest that the diet may help reduce functional symptoms. Studies are needed to assess its effect on intestinal inflammation.	There are no published trials at this time that have evaluated its use in UC.
Paleolithic diet	The diet practiced by hunter-gatherer societies of the Paleolithic era may reduce the risk of chronic diseases that were uncommon in primitive societies. There are websites and blogs now promoting the diet for the treatment of IBD.	*Food restrictions* All grains, dairy, sugar, starchy vegetables (eg, potatoes) *Food allowances* Meat, fruits, vegetables	There are no studies at this time that have evaluated its use in CD.	There are no studies at this time that have evaluated its use in UC.
Gluten-free diet	Elimination of all gluten-containing foods would help reduce intestinal inflammation and symptoms in nonceliac IBD, as seen in celiac disease.	*Food restrictions* wheat, barley- and rye-based grains, hidden gluten (eg, soy sauce, soups and sauces made with wheat flour) *Food allowances* Gluten-free–based grains, dairy, fresh/cooked fruits and vegetables	There are currently very limited data on its use and benefit in CD.	There are currently very limited data on its use and benefit in UC.

CD, Crohn's disease; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Statement of Authorship

N. D. Shah and B. N. Limketkai, contributed to the conception and design of the review; N. D. Shah and B. N. Limketkai contributed to the acquisition, analysis, and interpretation of the data; N. D. Shah and B. N. Limketkai drafted the manuscript; N. D. Shah, A. M. Parian, G. E. Mullin, and B. N. Limketkai critically revised the manuscript; N. D. Shah, A. M. Parian, G. E. Mullin, and B. N. Limketkai agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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