



Published in final edited form as:

Gastroenterology. 2015 May ; 148(6): 1087–1106. doi:10.1053/j.gastro.2015.01.007.

Diet in the Pathogenesis and Treatment of Inflammatory Bowel Diseases

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Abstract

Some of the most common symptoms of the inflammatory bowel diseases (IBD, which include ulcerative colitis and Crohn's disease) are abdominal pain, diarrhea, and weight loss. It is therefore not surprising that clinicians and patients have wondered whether dietary patterns influence the onset or course of IBD. The question of what to eat is among the most commonly asked by patients and among the most difficult to answer by clinicians. There are therefore substantial variations in dietary behaviors of patients and recommendations for them, although clinicians do not routinely endorse specific diets for patients with IBD. Dietary clinical trials have been limited by their inability to include a placebo control, contamination of study groups, and inclusion of patients receiving medical therapies. Further challenges include accuracy of information on dietary intake, complex interactions between foods consumed, and differences in food metabolism among individuals. We review the roles of diet in the etiology and management of IBD, based on plausible mechanisms and clinical evidence. Researchers have learned much about the effects of diet on the mucosal immune system, epithelial function, and the intestinal microbiome; these findings could have significant practical implications. Controlled studies of patients receiving enteral nutrition and observations made from patients on exclusion diets have shown that components of whole foods can have deleterious effects for patients with IBD. Additionally, studies in animal models suggested that certain nutrients can reduce intestinal inflammation. In the future, engineered diets that restrict deleterious components but supplement beneficial nutrients could be used to modify the luminal intestinal environment of patients with IBD—these might be used alone or in combination with immunosuppressive agents, or as salvage therapy for patients who do not respond or lose responsiveness to medical therapies. Stricter diets might be required to induce remission, whereas more sustainable exclusion diets could be used to maintain long-term remission.

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Keywords

IBD; diet; pathogenesis; therapy

The inflammatory bowel diseases (IBD) comprise chronic immune-mediated inflammatory diseases of the intestinal tract, typified by Crohn's disease (CD) and ulcerative colitis (UC). Their pathogenesis is complex and involves genetic and environmental factors. Advances in DNA sequencing technology led to the association of 163 genetic polymorphisms with risk for IBD¹, and efforts are underway to identify additional risk loci. However, in total, these loci only account for about 13% of CD and 7% of UC disease variance. Furthermore, studies of the level of concordance of CD or UC between identical twins estimated the maximum contribution of genetic factors to IBD to be approximately 10% for UC and 30%–40% for CD. Therefore, it appears that environmental factors make largest contributions to IBD risk.

IBD is believed to arise in individuals with a genetic predisposition to immune dysregulation upon exposure to specific environmental factors (reviewed in²). Among the environmental factors associated with IBD, diet and the intestinal microbiota are the most likely to be modifiable, making them targets for prevention and treatment of IBD. However, the diet can modify the composition of the gut microbiota and their production of absorbable metabolites, so studying the effects of these factors on IBD pathogenesis is complicated. We review the relationship between diet and IBD with a focus on current and future strategies for prevention and treatment of patients with IBD (Figure 1).

Epidemiology

IBD is most prevalent in northern Europe and North America,³ and less common in the Asia-Pacific region, with the exception of Australia.⁴ The incidence of IBD has been rapidly increasing in many parts of the world, including Asia, typically occurring first in more-industrialized countries.⁵ This contributed to the hypothesis that Westernization of our lifestyle is linked to the rising incidence of IBD, as well as other immune-mediated diseases.^{6–9} Diet is one of the more obvious environmental factors linked to industrialization.

Immigrants often change their diet and have been studied to assess environmental risk factors. Several studies found that immigrants to Israel had a higher prevalence of IBD than Israeli born populations.^{10–12} However, later studies found the incidence and prevalence of CD to be comparable among Jews in southern Israel, but a lower incidence in Arab Israelis; this difference could be attributed to genetic and/or environmental factors.¹³

Early-life exposures are important determinants of risk for IBD, and could affect results of immigrant studies. In Sweden, a region of high IBD incidence, second-generation but not first-generation immigrants developed IBD at rates comparable to the native Swedish population, suggesting the importance of early-life exposures.¹⁴ However, later environmental changes can also be important. For example, Acosta et al. observed that people newly diagnosed with IBD in the Galicia region of Spain were more likely than those without IBD to have immigrated to an industrialized European country and then returned.¹⁵

Humans' first dietary exposure is invariably breast milk or formula, which is typically derived from cow's milk. Breastfeeding was associated with lower incidence rates of IBD in a recent meta-analysis (pooled odds ratio, 0.69).¹⁶ This is likely to result from the protective effects of breast milk,¹⁷ rather than a harmful effect of cow's milk-based formula, since IBD is rare before weaning.¹⁸ Researchers have shown that breast milk alters the composition of the gut microbiota in neonates¹⁹. However, there are dramatic changes in the gut microbiota after weaning regardless of whether the initial diet is breast milk or formula.²⁰ So, early-life solid food exposures might also be important in determinants of risk for IBD.

Numerous observational studies have attempted to identify dietary patterns that contribute to the risk for IBD. These studies point to an increased risk of IBD among people who consume greater amounts of meat and fats—particularly polyunsaturated fatty acids and omega-6 fatty acids—and lower risk among people with diets high in fiber, fruits, and vegetables.²¹ Findings from the European Investigation into Cancer and Nutrition (EPIC) Study and the Nurses' Health Study are particularly noteworthy because of their prospective design.^{22–24} The EPIC study associated greater consumption of linoleic acid (an n-6 polyunsaturated fatty acids [PUFA] present in high concentrations in red meat, cooking oils, and margarine) with a higher incidence of UC.²² In contrast, people who consumed higher levels of n-3 PUFA docosahexanoic acid were less likely to be diagnosed with UC.

In the Nurses' Health Study, greater consumption of long-chain n-3 PUFAs and a higher ratio of n-3:n-6 PUFAs again appeared to protect against development of UC.²³ The Nurses' Health Study has also examined the association between fiber intake and incident IBD. Nurses consuming large amounts of fiber, particularly fruits, were approximately 40% less likely to be subsequently diagnosed with CD, although no association was observed for UC.²⁵ Of course diet alone is inadequate to cause IBD. There is evidence for a gene–diet interaction, in which variants in genes for fatty acid metabolism affect the relationship between IBD risk and PUFA consumption.²⁶ Together, these findings support the hypothesis that consumption of fruits and possibly vegetables, rather than meats and fats, can lower the risk of IBD.

Nutrient-Dependent Regulation of Intestinal Inflammation in Animal Models

Many dietary nutrients have been shown to help regulate mucosal immune function, such as vitamins, amino acids, and short-chain fatty acids—many of which are influenced by the gut microbiota (reviewed in²⁷) (Figure 1). We focus on studies describing the effects of diet on animal models of intestinal inflammation (Table 1). Given the epidemiologic associations between diet and IBD pathogenesis, various nutrients have been studied in rodent models of IBD. The nutrients studied include macronutrients, which can be roughly classified into fats, proteins, carbohydrates, and minerals or vitamins.

High-fat diets have been found to increase the severity of colitis that develops in mice^{28, 29}. The essential fatty acids have been studied extensively in animal models of IBD. Addition of PUFAs to the diets of mice had variable effects in preventing or treating colitis^{30–34}. Specific amino acids are thought to be immunomodulatory, such as glutamine and arginine, and might be involved in mediating responses to metabolic stress, such as when the intestine

in inflamed³⁵. Glutamine and arginine have been shown to improve clinical and biochemical parameters of chemical-induced colitis when added to diets of mice^{36–39}. Biogenic amines such as histamine, an important regulator of physiological functions of the gut, might also affect the immune response in patients with IBD. Histamine is derived from the amino acid histidine, and dietary histidine can reduce symptoms of immune-mediated colitis in mice⁴⁰. Tryptophan is a precursor to immunoregulatory biogenic amines, such as kynurenine, via indoleamine 2,3-dioxygenase activity, promotes development of T-regulatory cells and immune tolerance⁴¹. Additionally, threonine could enhance barrier function by augmenting intestinal mucus production. Dietary supplementation with tryptophan and threonine has been shown to reduce features of colitis in piglets and mice^{42, 43}.

Plant polysaccharides and poorly digestible fibrous plant components have, overall, been shown to reduce features of colitis in mice (reviewed in⁴⁴). This is believed to occur via increased production of short-chain fatty acids (SCFAs), which might increase barrier function by serving as a source of energy for colonocytes⁴⁵. SCFAs also promote immune tolerance by increasing development of T-regulatory cells, via G-protein coupled receptor-dependent and epigenetic effects through histone acetylation (recently reviewed in⁴⁶). The anti-colitic effects of plant-based compounds have also been studied, including curcumin⁴⁷, green tea,⁴⁸ and other polyphenols such as resveratrol⁴⁹, and fermented grains⁵⁰.

There are several dietary vitamins and minerals that are thought to be involved in the pathogenesis of IBD, based on studies of rodents and observational studies of humans. Dietary calcium and vitamin D are important for patients with IBD, not only for bone health, but also because vitamin D is involved in anti-inflammatory pathways⁵¹. Studies of animal models of IBD have supported the importance of calcium and vitamins. In HLA-B27 transgenic rats, a highcalcium diet inhibited diarrhea and intestinal permeability⁵². Mice with dextran sulfate sodium-induced colitis had firmer stools, less blood loss, and weight recovery following administration of the active form of vitamin D⁵³. Vitamin D was shown to promote epithelial cell resistance to injury and suppress the inflammatory response to luminal antigens.

Iron also appears to have a complex role in development of intestinal inflammation^{54, 55}. Iron catalyzes the formation of oxygen radicals, which can cause cellular injury and increase activation of the transcription factor NF κ B, which perpetuates inflammation^{56–58}. Excess iron can increase the ratio of CD8+ T cells to CD4+ T cells. Iron is also used by bacteria and has been linked with invasive strains that promote inflammation⁵⁴. Ingested iron, particularly iron sulfate, has been directly implicated in intestinal inflammation and alteration of gut microbiota in mice^{59, 60}. For example, TNF^{ARE/WT} mice develop ileitis with when fed an iron sulfate containing diet, but are protected from ileitis when placed on iron sulfate-free diets, even with parenteral iron replacement⁵⁹. In this model, iron induces endoplasmic reticulum stress in intestinal epithelial cells and sensitizes the epithelium to apoptosis, induced by cytotoxic T-cells⁵⁹. Whether heme iron, the predominant form in meat, has the same effects is unknown. However, dietary heme has been shown to increase the severity of colitis in rodents^{61, 62}.

The purpose of animal studies is to identify mechanisms of pathogenesis that can be translated to human disease. For example, defined-formula diets are powerful tools for treatment of IBD and have been evaluated in rodent models of IBD⁶³. Devkota et al demonstrated how diet can alter the intestinal microbiota to contribute to the development of colitis in mice; a diet high in milk fat promoted the expansion of the low-abundance sulphitereducing bacteria *Bilophila wadsworthia* and the increased incidence of colitis⁶⁴. These bacteria caused induction of an inflammatory immune response, and also promoted development of colitis in interleukin-10 knockout, but not wild-type, mice. These findings reveal a possible mechanism by which the Western diet alters the composition of the gut microbiota to promote inflammation and other immune disorders.

Dietary Interventions in Humans with IBD

Findings from epidemiology studies, animal studies, and analyses of clinical anecdotes have provided the basis for prospective trials that modified diets and evaluated disease progression in patients with IBD. Enteral nutritional therapy can induce disease remission; this observation and results of epidemiology studies provide compelling evidence for the role of food in IBD pathogenesis and treatment. Human studies of food and IBD can generally be categorized into groups of elimination diets, exclusion of specific inflammatory mediators, inclusion of anti-inflammatory mediators, and inclusion of prebiotics (Table 2).

Epidemiologic studies associated red meat and n-6 PUFA intake with incidence of IBD^{22, 24}. Chiba et al prospectively studied the role of a semi-vegetarian diet in 22 subjects in Japan over the course of 2 years⁶⁵. The semi-vegetarian diet (allowed milk and eggs; fish once per week; other meat once every 2 weeks) was associated with a high rate of maintenance of disease remission. Fiber has an important role in intestinal transit, and the soluble form is fermented to SCFAs—an important source of nutrients for colonocytes⁶⁶. Although increased stool output and greater stool bacterial content have been associated with increases in fiber intake, high fiber intake has not been associated with clinical endpoints^{67–69}. Omega-3-PUFAs have anti-inflammatory properties, but 2 randomized controlled trials found no effect on relapse, at 1 year, in patients with quiescent CD⁷⁰.

Vitamin D can be obtained from food, supplements, or sun exposure. Vitamin D deficiency is common in the United States and among patients with IBD. Researchers have tested whether vitamin D can be used to treat IBD. In an observational study, patients with documented correction of vitamin D deficiency were less likely to require surgery for IBD, during a specific follow-up period, than those who remained vitamin-D deficient⁷¹. A small randomized trial of patients with CD in clinical remission demonstrated numerically and nearly statistically significant lower rates of clinical relapse among patients given 1200 IU daily of vitamin D3, compared with placebo⁷².

The specific-carbohydrate diet, which involves strict restriction of grains, most dairy, and refined sugars is gaining interest in the medical community, but has not been extensively studied. Aside from 1 randomized study, clinical studies of elimination diets have been limited by their non-randomized design. Researchers have performed a variety of smaller hypothesisgenerating studies on prebiotics, but 2 large, randomized, controlled studies of the

effects of fructo-oligosaccharides and inulin showed no clear benefit for subjects with active CD^{73, 74}. Studies of the effects of food on IBD are limited by the difficulty in accurately capturing dietary intake as well as the potential for complex interactions between foods. Further, proportions of food intake, compared with other dietary components, are a challenge to determine⁷⁵.

Bowel Rest, Parenteral Nutrition, and Fecal Diversion

Parenteral nutrition (PN) has been shown to benefit malnourished, ill patients with CD, but little is known about the exact effects of eliminating oral intake of food, which promotes bowel rest^{76, 77}. Observational studies have demonstrated short-term avoidance of surgery with PN and bowel rest, but little effect on eventual need for surgery^{76, 78, 79}. The benefit of complete bowel rest was not demonstrated in a study that compared the effects of a combination of PN and bowel rest with those of PN and an oral diet—disease activity was similar between groups⁸⁰.

Whereas bowel rest does not improve long-term outcomes of patients with CD, fecal diversion does⁸¹; this might provide insight into the pathogenesis of IBD. In subjects with active luminal CD who underwent ileocolonic resection and placement of a diverting ileostomy, the neo-terminal ileum had a normal appearance, based on endoscopy and histology evaluation, 3–6 months after surgery^{82, 83}. In these patients, infusion of proximal ileum effluent into the distal ileum for 7 days resulted in histological changes consistent with infiltration of inflammatory cells⁸². Some component of the fecal stream therefore appears to contribute to recurrence of inflammation following surgery.

Fecal diversion is not always successful in inducing remission. However, response has been associated with serologic detection of an antigen from *Pseudomonas fluorescens*^{84, 85}. Additionally, early use of antibiotics has been shown to delay recurrence of disease after surgery for CD^{86, 87}. These findings suggest an interaction between diet and the gut microbiota that promote inflammation in patients with CD. Dietary components could alter the gut microbiota, directly stimulate the immune system, or be metabolized into compounds that induce inflammation. Further studies are needed to determine whether some or all of these are involved^{82, 88}.

Exclusive Enteral Nutrition (EEN)

EEN therapy is the only dietary intervention that has been rigorously tested and shown to induce remission of CD^{89–91}. EEN therapy with elemental, semi-elemental, or polymeric formula diets has been widely studied and shown to induce remission of CD; it is therefore the first-line therapy in many parts of the world^{92, 93}. The most common protocol involves the administration of a defined formula at 100% of caloric needs for 4–12 weeks⁹⁰. Although partial enteral nutritional therapy might also provide clinical benefit⁹⁴, EEN appears superior for the induction of remission⁹⁵. A smaller percentage of calories and nutrients, provided by the defined formula, may be required to maintain remission, allowing flexibility in the diet⁹⁴.

In addition to reducing symptoms of CD, EEN has been associated with mucosal healing, which may be a superior predictor of long-term outcome^{89, 96–98}. Perhaps the most promising findings came from a prospective trial of children with CD, randomized to groups given oral corticosteroids or EEN with a polymeric formula for 10 weeks⁸⁹. In the short term, EEN was as effective as corticosteroids in producing clinical remission. However, EEN was significantly more effective than corticosteroids in healing the mucosa, based on endoscopic and histologic analyses. Overall, EEN has the ability to spare the use of steroids and other immunosuppressive therapies. In children, EEN can increase linear growth, bone health, and lean mass accrual^{99–102}.

As for other therapies for IBD, patient selection appears to be important. EEN is most commonly prescribed for patients who have CD, rather than UC. Early studies demonstrated less satisfactory outcomes in patients with UC¹⁰³ or CD that primarily involved the colon¹⁰⁴. A prospective study that compared clinical and endoscopic remission by ileal, ileocolonic, or colonic disease location found that the rates of remission were the lowest among patients with only colonic disease¹⁰⁴. However, 2 systematic reviews were unable to form a conclusion regarding disease phenotype and response to EEN^{105, 106}.

A recent review of EEN in adults with CD demonstrated general poor compliance; the poor palatability of formula and low patient motivation were likely to be contributing factors¹⁰⁷. Two studies of EEN in treatment-naïve adults demonstrated clinical remission, based on intention to treat analysis, in 80% and 82% of subjects, respectively^{108, 109}. This suggests that prior exposure to immunosuppressive therapy is associated with poorer outcomes with EEN. However there are no data, as yet, that one factor causes the other. There might be a relationship between disease duration and reversibility of tissue damage.

Interestingly, it is widely recognized that the efficacy of EEN does not change with the composition of formula. A Cochrane review of EEN for induction of remission in CD evaluated the effects of formula composition and found no difference in efficacy¹⁰⁵. A meta-analysis of adult study subjects demonstrated no significant differences in outcomes with protein content (elemental, semi-elemental, or polymeric). An analysis comparing low fat (<20 g fat/1000 kcal) vs high fat (>20 g fat/1000 kcal) formulas found no difference in outcomes, nor did a further analysis of very low-fat formula (<3 g fat/1000 kcal). Furthermore, an evaluation of long-chain triglyceride content at the thresholds 5%, 10%, and 15% of total energy similarly found no difference in outcomes¹⁰⁵.

Digestion and Absorption of Whole Foods vs Defined-formula Diets

Although nutritional therapy, via EEN, is effective for patients with CD, little is known about its mechanisms. These could involve reductions in luminal antigens and food exclusion, direct anti-inflammatory effects of the formula, improved nutrition, or changes to the gut microbiota^{110–113}. Several interesting clinical observations have been made. For example, the composition of the formula does not affect outcome, but increases in proportion of total caloric intake from formula are associated with greater effectiveness. Also, EEN is more effective in patients with ileocolonic, compared with colonic, disease

alone or patients with UC. These observations will lead to better dietary recommendations for patients with IBD, but what insights do they provide into the mechanisms of EEN?

Mechanisms involving the physical properties of food

The mechanisms of digestion and absorption of food are well described (for a review, see^{114, 115}), but affected by the food's physical form. A diet of diverse, colorful, whole-foods may activate digestion differently than repetitive or bland diets such as EEN. The mechanoreceptor responses induced by the volume of ingested food at a meal might be reduced if formula is sipped slowly or infused at a slow rate.

Elemental formulas are prescribed for EEN in certain parts of the world. These formulas comprise L-amino acids or protein hydrolysates, simple carbohydrates (no fiber), fatty acids, vitamins, minerals, and trace elements. Elemental formulas are readily absorbed in the proximal small bowel, with minimal residue reaching the distal small bowel and colon.¹¹⁶ In fact, the proximal small bowel develops increased villous height but the distal small bowel and colon develop atrophy, similar to that observed in animals fed intravenously. Elemental formulas slow gastric emptying and acid secretion and release of pancreatic enzymes, and are thought to reduce overall bacterial mass.¹¹⁷ It may be that EEN is effective by completely eliminating the residue that reaches the distal small intestine and colon; diets that include table foods are unlikely to be able to reproduce this. Ultimately, if specific residues promote inflammation, restriction diets could be used in management of IBD.

Mechanisms involving the delivery of essential nutrients

Another reason that the EEN is effective could involve improved delivery of essential nutrients. Patients with active IBD have lower levels of several amino acids, such as tryptophan and histidine¹¹⁸, and other micronutrients. Some of these, such as tryptophan, can modulate immune function and affect the composition of the gut microbiota^{41, 119}. Others, such as threonine, help maintain barrier function and an adequate mucous layer¹²⁰. Patients with acute inflammation are likely to have higher nutrient demands in the restitution process, so there would be different nutritional requirements during disease exacerbation and remission. This would support the concept of EEN for induction of remission and PEN for maintenance.

Formulas enter the intestine in an emulsified liquid solution that readily exposes the nutrients to digestive enzymes. Formulas containing whole proteins have similar nitrogen and fat absorption to that of whole foods, but fecal wet weight, dry weight and transit time are somewhat reduced.¹²¹ The absorption of energy and lipids from pureed whole foods is similar to that from an elemental formula, but protein absorption is greater with the whole foods, likely due to increased pancreatic enzyme secretion.¹²² The lipid components of formula include a mixture of FA, with up to 60% medium chain triglycerides that are rapidly absorbed without emulsification and longer chain FA, all in an emulsified liquid form. The total fat content, however, is rarely greater than 30% of energy and thus unlikely to overwhelm bile acid emulsification capacity. By contrast, the fat content of whole foods meals varies considerably, and may be quite high. Studies that have compared high vs. low fat formula for EEN have not consistently demonstrated different efficacy,¹⁰⁵ indicating that

fat content of the formula is less important, although differing types of fats may be important. Maltodextrin usually provides the carbohydrate of non-elemental EEN formulas; it is readily digested and absorbed. Carbohydrates from whole foods may be presented as long-chain polysaccharides embedded inside a grain or vegetable matrix or simple sugars.

EEN also provides Dietary Reference Intake levels of 24 micronutrients (vitamins, minerals, trace elements) in a volume of 1200–1500 mL/day. By contrast, the micronutrient content of whole foods will vary considerably based on the specific foods ingested, whether they are raw or cooked, the micronutrient content of the soil where plants were grown, whether fish were exposed to sunlight, the diet of cattle, and many more variables. Bioavailability will also be affected, by the presence of other micronutrients from the meal that can increase it or compete for absorption. Phytic acid, oxalate, and polyphenols, typically found in the bran portion of grains,^{123, 124} are considered anti-nutrients because they interfere with mineral absorption. For example, phytates bind iron and zinc, polyphenols bind iron and oxalates bind calcium,¹²⁵ thus reducing their absorption. Formulas do not contain phytates or oxalates. However, they provide only 24 micronutrients, whereas whole foods, especially those from plant origins, are a complex matrix of up to thousands of phytochemicals¹²⁶ of variable physiological significance.

Mechanisms involving the composition and function of the gut microbiota

IBD is associated with alterations in the composition of the intestinal microbiota characterized by decreased diversity, reduced proportions of Firmicutes, and increased proportions of Proteobacteria and Actinobacteria¹²⁷. EEN might benefit patients via its effects on the composition of the gut microbiota. Although modest dietary changes have a relatively limited effect on the composition of the gut microbiota¹²⁸, extreme interventions, such as use of EEN, are likely to have more substantial effects¹²⁹, in part due to altered carbohydrate composition.

Prebiotic oligosaccharides, such as inulin and its fructo-oligosaccharide derivatives or galactooligosaccharide (GOS), have been proposed to improve gut microbial health^{130–132}. Prebiotics are resistant to digestion in the stomach and small bowel, but ferment in the colon. Breast milk contains substantial quantities of GOS, which promotes growth of bifidobacteria in the infant colon, and vegetables are a source of inulin. Although ingestion of excess prebiotics can produce flatulence or diarrhea, due to gas produced by fermentation, the SCFAs produced aid in the absorption of sodium and hepatic control of lipid and carbohydrate metabolism, and supply energy to colon, heart, brain, and muscle cells¹³¹. In addition, SCFAs are important for T-regulatory cell development and maintenance of mucosal immune homeostasis^{133, 134}. Resistant starch, a component of potatoes, bananas, pasta, and bread, is similar to prebiotics in that it is not digested in the upper gastrointestinal tract, but fermented in the colon to SCFAs¹³².

There is controversy over whether IBD can be effectively treated by altering the composition of the gut microbiota. We are only beginning to identify the specific bacteria involved in these processes. *Faecalibacterium prauznitzii* have anti-inflammatory properties,¹³⁵ and inulin supplementation increases concentrations of *F prauznitzii*¹³⁶. However, patients treated with EEN were reported to have reduced concentration of *F*

prauznitzii and butyrate¹³⁷. Furthermore, 2 large randomized controlled studies of fructooligosaccharides and inulin showed no clear benefit for patients with CD^{73, 74}. It is possible that the effectiveness of EEN does not result from alterations in the composition of the gut microbiota, but rather alterations in the beneficial or harmful metabolites produced the gut microbiota. Examples of such associations are beginning to emerge in other fields¹³⁸ and this is an important area of research of IBD.

Mechanisms involving alteration in bile acids

Diet can affect production of bile acids, which act on the gut microbiome. In a reciprocal manner, the gut microbiota regulates bile acid metabolism and synthesis^{139, 140}. There are multiple potential mechanisms by which the effects of diet on bile acids could also affect development of IBD. One pathway could involve the farnesoid X receptor, a bile salt receptor proposed to preserve epithelial barrier function and downregulate inflammatory cytokines. Alternatively, diet-induced changes in bile acids that alter the composition of the gut microbiota, could affect IBD onset and progression by affecting production of potentially toxic compounds by sulfite-reducing bacteria, or by promoting T-helper 1 cell-mediated immune responses^{64, 141}.

Mechanisms involving reduced exposure to deleterious compounds

EEN helps patients avoid many additives and other potentially detrimental ingredients found in prepared foods. In addition to the lack of phytates and oxalates, which might reduce absorption, formulas do not contain the chemical additives or preservatives found in many processed foods. Furthermore, formulas do not contain gluten, a normal component of wheat, barley, and rye that can reduce absorption in subjects with gluten sensitivity, celiac disease, or wheat allergy.¹⁴² The formulas prescribed for EEN are generally not immunogenic, although whey or casein can induce allergic reactions in individuals with a true milk allergy (rare).¹⁴³ However, soy protein may be tolerated by these patients. Other potential protein-based allergens that have been identified in whole-food diets are generally not included in EEN formulas.

Other Approaches to Restriction Diets

Several diets popularized in recent years have focused on elimination of potential harmful substances¹⁴⁴. The specific carbohydrate and Paleolithic diets aim to eliminate putative harmful food components. The specific carbohydrate diet excludes all sugars other than monosaccharides: glucose, fructose, and galactose. Processed meats are also avoided because they may contain other sugars. The Paleolithic diet emphasizes intake of lean meats from non-domesticated animals as well as fruits and vegetables. The diet aims to achieve a low ratio of n-6:n-3 PUFAs. However, there is little evidence of the efficacy of these diets from wellcontrolled studies. These restriction diets have been largely popularized through anecdotal evidence, shared without guidance from the medical community. Because they have little scientific basis, these diets require critical appraisal. Sigall-Boneh et al reported that the combination of a partial enteral nutritional and a restriction diet induced remission and mucosal healing in approximately 70% of patients with CD, thereby making partial

enteral nutritional a more attractive option¹⁴⁵. Unfortunately, the restriction diet used in the study may be difficult to maintain.

The superiority of EEN to partial enteral nutritional, and the rapid recurrence of inflammation following restoration of intestinal continuity, support the hypothesis that the exclusion of specific types of foods has therapeutic benefit. Ritchie et al found no difference in outcomes of CD between patients who consumed refined vs natural sugars⁶⁹. Given the epidemiologic associations between red meat, n-6 PUFA, and incidence of IBD, researchers performed a prospective trial of a semi-vegetarian diet^{22, 24, 65}. They showed that the diet was effective in maintaining remission over 2 years.⁶⁵

Most studies of diet and IBD generally involved broad food avoidance or supplementation. However, individualized food avoidance, based on detection of IgG4 to specific food antigens, have been shown to reduce clinical symptoms but not C-reactive protein.¹⁴⁶. Whereas formulas chosen for EEN are nutritionally complete, extreme exclusion diets may put patients at risk for caloric or specific-nutrient deficiencies.

Future Directions

Dietary interventions might be used to treat patients with active IBD, maintain their remission, or even prevent this disease. Dietary interventions for the treatment of UC are limited and generally have not been effective. In contrast, EEN has been consistently demonstrated to be effective for CD, although it is not effective for all patients. Based on these experiences, interest has turned to exclusion diets, which would allow patients to eat a limited diet of whole foods without exacerbating the disease. Patients' own experimentation often leads them to identify a number of foods that they believe worsen their symptoms, in essence creating their own personal exclusion diet. For most, this approach is not sufficient to control inflammation. Given the evidence that EEN can reduce symptoms and mucosal inflammation, there is reason to believe that diets and/or dietary supplements could be derived that would provide therapeutic benefit. Improving our understanding of the mechanism of EEN could help to inform the creation of such diets.

An important first step in the development of therapeutic diets for IBD is to improve our methods of studying diet. Clinical studies on food and IBD are limited by the difficulty in accurately capturing dietary intake as well as the potential for complex interactions between foods. Further, proportions of food intake, relative to other dietary components, is challenging to capture⁷⁵. Differences in food metabolism can vary among individuals. The same food products can even differ, based on preservation, processing, packaging, and preparation. Food science is an area open to further study.

Although data from animal models and in vitro experiments can help guide the development of dietary interventions, clinical trials are also needed. Dietary intervention trials face several challenges that traditional drug trials do not. Most obvious is the inability to use placebo as a control. The need for open-label designs could bias participants and investigators, so alternative strategies are needed. These could include having a separate blinded evaluator for subjective outcomes such as clinical remission or reduced mucosal ulcerations, or relying on objective measures such as biomarkers to assess efficacy. The gut

microbiome might also be used as a biomarker of dietary intake in the context of subjects' genotypes, disease phenotypes, and dietary intake exposures. Results from open-label studies can also be distorted if participants become aware of the study hypothesis; these studies may need to withhold information from participants on the study's main question or the diets the participants are placed on.

It is extremely difficult to recruit newly diagnosed patients to clinical trials. As such, trials of dietary therapy will generally be conducted in subjects receiving other medical therapies. With availability of increasingly effective therapies, the ability to detect a difference in outcomes with dietary interventions may be limited. One approach to overcome this challenge could be studies of different diets in patients undergoing withdrawal from specific treatments.

Given that IBD encompasses likely far more than 2 diseases (CD and UC), it is unlikely that all patients with IBD can be managed with dietary interventions alone. However, the development of effective dietary interventions that could be used as sole therapy for subsets of patients and adjunctive therapy for other patients would be a major step forward. Adjunctive dietary therapy could reduce the frequency of disease relapse and/or the degree of immunosuppression necessary to control the disease—both of which are important and valued by patients.

Development of diets that prevent the onset of disease is a much greater challenge. It would require identification of people who are at high risk for disease, presumably based on genetic testing and/or use of other biomarkers. Diets aimed at preventing onset of disease would need to be highly palatable, since adherence to such a diet would need to be life long. Adherence to therapeutic diets is a major challenge even for patients with established diagnoses. However, if science is able to direct more specific and evidence-based dietary recommendations, it is likely that a market for palatable foods could be developed for patients with IBD.

Incorporating the advances in our understanding of diet and its effect on the gut microbiome and the mucosal immune system (Figure 1), we provide a vision for how dietary engineering might be used to modify the intestinal lumen and its microbes to treat IBD as either primary or adjunctive therapy (Figure 2). Several strategies are being developed to modify the gut microbiota, such as next-generation probiotics, whereas EEN has already been shown to be effective in inducing remission in patients with active CD. Although the magnitude of efficacy of defined formula diets to treat active CD appears to correlate with the extent of exclusion of whole foods, the specific foods that perpetuate active disease have not been identified. As further research identifies components of whole foods with deleterious effects, or nutrients in defined formula diets that benefit patients with IBD (Figure 1), it may be possible to develop sustainable long-term diets, composed of selected whole foods and a dietary supplement, for treatment of gastrointestinal diseases. The proportions of these would need to be determined empirically, based on the responses of individual patients. Upon relapse of disease, intensive environmental therapy could be reinitiated to induce remission—an approach currently used with defined formula diets in selected populations. Modifications to the intestinal environment might be effective as individual therapy, in

combination with immunosuppressive agents to increase response and/or reduce drug dose, or as salvage therapy for patients who do not respond or lose responsiveness to immunosuppressive agents.

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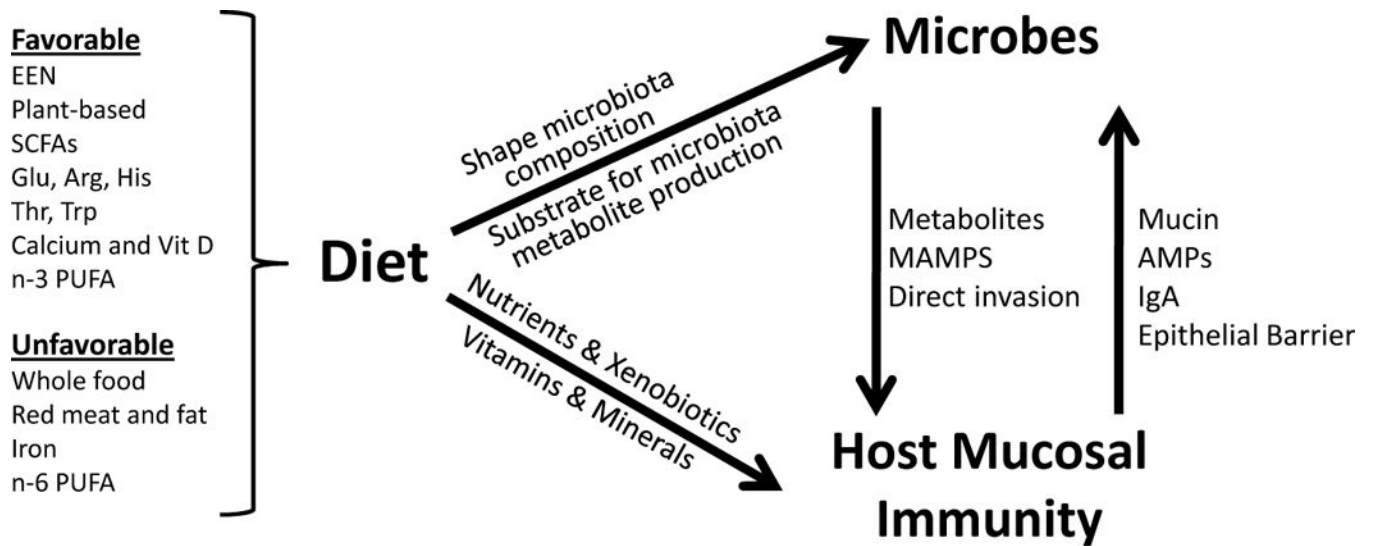


Figure 1. Effects of Diet on the Intestinal Microbiota and Immune System During Development of IBD

There is evidence from epidemiologic, animal, and clinical studies that certain components of diet can promote or prevent against intestinal inflammation. Diet not only affects the composition of the gut microbiota but also serves as substrate for microbial synthesis of metabolites, which affect the mucosal immune system. Microbes also act the immune system of the intestinal mucosa, through the engagement of innate immune receptors with specific microbial products (mucosally-associated molecular patterns, MAMPS). In turn, the host mucosal immune system fortifies mucosal barrier function and interacts with the gut microbiota through the production of mucin, anti-microbial peptides (AMPs), and IgA.

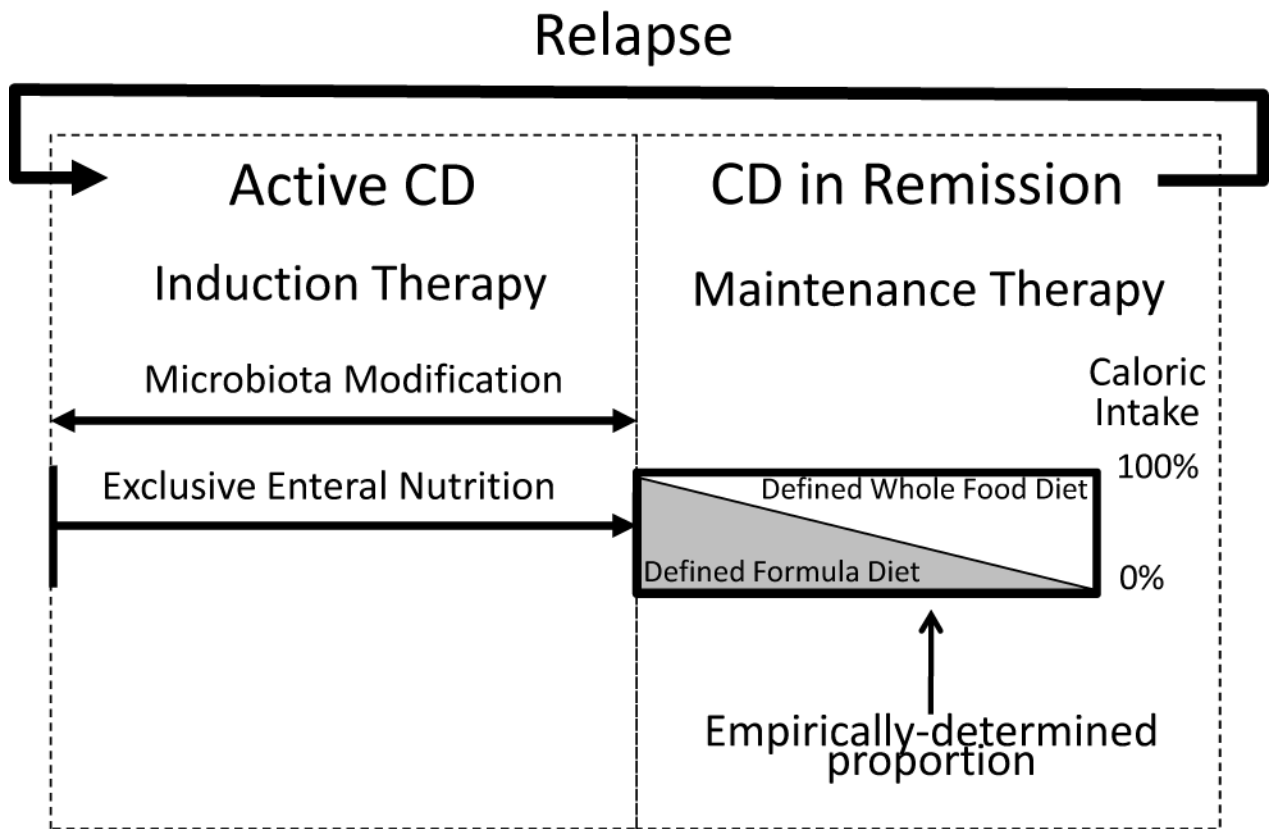


Figure 2. Altering the Luminal Environment of the Intestine as an Adjunct Therapy for IBD
 The luminal environment of the gut might be modified by alteration of the microbiome and/or diet to induce and/or maintain remission in patients with IBD. Such an approach might have value as an adjunct to currently used immunosuppressive agents, to increase response and/or reduce drug dose, or as salvage therapy for patients who do not respond or lose responsiveness to immunosuppressive agents.

Table 1

Dietary Interventions in Animal Models of IBD.

Food Category	Study, Year	Methods/animal model	Results
<i>Immunologically-mediated colitis:</i>			
Dietary milk fat	Devkota et al, 2012 ¹	Wild type and Il10 ^{-/-} animals were fed one of 3 diets – low fat, high fat with 37% PUFA, high fat with 37% milk fat.	Bloom of <i>Bilophila wadsworthia</i> in the stool from animals fed the milk fat (MF) diet. The MF Il10 ^{-/-} group had an increase in colitis incidence and severity. There was also an increase in proinflammatory cytokines in this group.
High cholesterol	Gao et al, 2010 ²	2-glutathione peroxidase-deficient mice were fed one of two atherogenic diets (high cholesterol or high cholic acid)	The high cholesterol diet aggravated colitis by weakening the colon unfolded protein response.
High Fat	Gruber et al, 2013 ³	TNF-producing CD8 T cell-dependent ileitis; High fat diet versus control.	High fat diet aggravated ileal inflammation, reduced tight junction proteins, increased translocation of endotoxin, tissue pathology more severe.
Green tea polyphenols	Oz et al, 2013 ⁴	DSS and Il10 ^{-/-} ; Once colitis developed, animals treated with sulfasalazine or 1 of 2 green tea polyphenols.	Green tea polyphenols improved antioxidant levels and attenuated severity of colitis analogous to sulfasalazine.
Semi-synthetic diet	Wagner et al, 2013 ⁵	TNF delta ARE/WT mice; Normal chow or semisynthetic diet with and without added gluten.	Transfer to semisynthetic diet at 7 weeks of age protected against ileitis. Glutenfortified semisynthetic diet induced ileal inflammation.
Omega-3	Bosco et al, 2013 ⁶	Rag-2	Increased dietary intake of fish oil did not prevent experimental colitis.
Omega-3	Whiting et al, 2005 ⁷	SCID; ω -3-enriched or control diet for 3 weeks before colitis induction by transplantation of CD45RB T cells.	Transplanted ω -3-fed animals had significantly reduced pathology scores, colonic tumor necrosis factor-alpha, interleukin-12, and interleukin-1beta compared with animals fed standard diet.
Curcumin	Nones et al, 2009 ⁸	mdr1a ^{-/-} mice; Control (AIN-76A), control +0.2% curcumin or control +0.1% rutin	Curcumin, but not rutin, significantly reduced histological signs of colonic inflammation in mdr1a ^{-/-} mice.
Curcumin	Larmonier et al, 2008 ⁹	Investigated the effects of dietary curcumin (0.1–1%) on the development of colitis, immune activation, and in vivo NF-kappaB activity in germ-free IL-10 ^{-/-} or IL-10 ^{-/-} ;NF-kappaB(EGFP) mice colonized with specific pathogen-free microflora.	Limited effectiveness on Th-1 mediated colitis in IL-10 ^{-/-} mice, with moderately improved colonic morphology, but with no significant effect on pathogenic T cell responses and in situ NF-kappaB activity.
Curcumin	Ung et al, 2010 ¹⁰	IL-10 gene deficient mice gavaged daily for 2 weeks with 200 mg/kg per day curcumin emulsified in carboxymethyl cellulose	Both oral curcumin and carboxymethyl cellulose, appeared to have modifying effects on colitis. However, curcumin had additional anti-inflammatory effects mediated through a reduced production of pro-inflammatory mucosal cytokines.
Calcium	Schepens et al, 2009 ¹¹	HLA-B27 transgenic rats were fed a purified high-fat diet containing either a low or high calcium concentration (30 and 120 mmol CaHPO4/kg diet, respectively) for 7 wk.	The calcium diet significantly inhibited the increase in intestinal permeability and diarrhea with time in HLA-B27 rats developing colitis compared with the control transgenic rats.
Germinated barley (GBF; prebiotic)	Kanauchi et al, 2008 ¹²	CD45RB(high) T cell chronic colitis model	Body-weight loss and occult blood were reduced in the mice that had been fed with GBF. In these mice,

Food Category	Study, Year	Methods/animal model	Results
			there were also reductions in IFN-gamma mRNA expressions and IL-6 in the colonic mucosa, as compared with the control group. GBF also attenuated mucosal damage and mucin positive goblet cell depletion. Conversely, TGF-beta expression significantly increased in the GBF group, compared with the control group.
Elemental diet	Kajiura et al, 2009 ¹³	IL-10 $-/-$	Elemental diet suppressed inflammation in IL-10 $-/-$ mice. There were changes in the microbiome associated with the elemental diet by T-RLFP.
Elemental diet	Andou et al, 2009 ¹⁴	IL-10 $-/-$; Single amino acid diet versus mixture.	In the IL-10 $-/-$ -transfer model, dietary histidine, but not alanine, reduced histologic damage and colon weight and TNF-alpha mRNA expression. Histidine inhibited LPS-induced TNF-alpha and IL-6 production by mouse macrophages in a concentration-dependent manner, whereas alanine or histidine-related metabolites had no such effect. Histidine inhibited LPS-induced NF-KB in macrophages.
TGF-beta	Schiffirin et al, 2005 ¹⁵	HLA B-27 rats; Casein-based rat-adapted diet containing TGF-beta or a control casein-based diet without TGF-beta.	The test diet improved diarrhea and the colonic inflammation as shown by a lower inflammatory score (2.43 \pm 1.13 vs 4.42 \pm 0.53, $p < .05$), lower mucosal thickness (431.25 \pm 72.29 vs 508.57 \pm 81.32 microm, $p = .08$) and decreased IFN-gamma mRNA expression.
TGF-beta	Oz et al, 2004 ¹⁶	Five-week-old IL-10 $-/-$ mice (in BALB/c background) were fed either an enteral diet (Diet-A) containing TGF-beta 2 or a control enteral diet (Diet-B) not rich in TGF-beta 2.	IL-10 $-/-$ mice fed a TGF-beta 2 containing diet gained more weight, did not develop diarrhea or prolapse, had lower pathological scores.
Fiber	Koleva et al, 2012 ¹⁷	4-week-old HLA B-27 transgenic rats were fed 8 g/kg body weight inulin or fructooligosaccharides (FOS) for 12 weeks, or not.	Colitis was significantly reduced in all FOS-fed rats compared to the control diet, whereas inulin decreased chronic intestinal inflammation in only half the number of animals.
<u>Chemical colitis:</u>			
Monotonous diet	Nagy-Szakal et al, 2013 ¹⁸	DSS colitis- mice; Monotonous diet versus cycling 2 different diets	Monotonous diet improved colitis.
Olive oil	Takashima et al, 2014 ¹⁹	DSS colitis – rats; 5% extra virgin olive oil added to AIN diet	Olive oil improved disease activity score, body weight, histological score, gene expression, cell proliferation and apoptosis.
Olive oil	Camuesco et al, 2005 ²⁰	DSS colitis – rats; Olive oil based diet with or without fish oil	Colitic rats fed the olive oil-based diet had a lower colonic inflammatory response than those fed the soybean oil diet, and this effect was increased by the dietary incorporation of (ω -3) PUFA.
MCT-rich formula	Papada et al, 2014 ²¹	TNBS colitis – rats; 5 groups – control, TNBS-colitis, TNBS colitis + LCT rich diet, TNBS colitis + MCT rich diet, TNBS colitis + infliximab	The MCT-rich diet decreased IL-6, IL-8 and intercellular adhesion molecule-1 (ICAM-1) levels and glutathione S-transferase (GST) activity, while the LCT-rich diet reduced only ICAM-1 levels and GST activity. Neither elemental formula

Food Category	Study, Year	Methods/animal model	Results
			affected IL-10 levels. Diet did not affect colitis score.
Red meat	Le Leu et al, 2013 ²²	DSS colitis – mice; 4 groups – control diet, high amylose maize starch diet, cooked red meat diet, amylose maize starch + cooked red meat diet	Intake of red meat aggravated DSS-induced colitis whereas co-consumption of resistant starch reduced the severity of colitis.
Red meat	Schepens et al, 2011 ²³	TNBS colitis – rats; High-fat control diet vs. similar diet supplemented with heme	Heme rats: Higher fecal wet weight, increased luminal cytotoxicity by fecal water cytotoxicity assay, decreased food intake. No change in histologic score.
High fat	Vieira de Barros et al, 2011 ²⁴	DSS colitis – rats; Five groups: control normal fat non-colic or control colitis, high soybean fat group colitis, high fish fat group colitis, or high-fat soybean plus fish oil colitis.	High-fat diets did not exacerbate colitis.
High fat	Van der Logt et al, 2013 ²⁵	DSS colitis – mice; Normal chow versus high-fat diet with or without heme	High fat diet mice lost more weight. Heme supplementation further aggravated weight loss. No difference in histological score.
Green tea and other polyphenols	Bruckner et al, 2012 ²⁶	DSS colitis – mice; green tea polyphenol	Improved body weight, less histological damage, increased antioxidant activity with green tea polyphenol supplementation.
Green tea and other polyphenols	Oz et al, 2005 ²⁷	DSS colitis – mice; Treatment with 3 antioxidants including green tea polyphenols	All 3 antioxidants provided protection against DSS-induced colitis.
Green tea and other polyphenols	Mazzon et al, 2005 ²⁸	DNBS colitis – rats; Green tea extract vs. no green tea extract	Treatment with green tea extract attenuated diarrhea and weight loss. There was also improvement in histological score in green tea group.
Green tea and other polyphenols	Youn et al, 2009 ²⁹	DSS colitis – mice; Oral administration of resveratrol or piceatannol	Oral administration of resveratrol or piceatannol for 7 days attenuated DSS-induced inflammatory injury.
Omega-3	Mbodji et al, 2013 ³⁰	TNBS colitis – rats; 5-ASA or 5-ASA plus PUFA	Decreased inflammatory score and reduced NF-kB activation in PUFA group.
Omega-3	Ibrahim et al, 2012 ³¹	TNBS colitis – rats; ALA-rich formula vs. isocaloric corn oil formula.	Decreased expression of adhesion molecules in ALA group.
Omega-3	Tyagi et al, 2012 ³²	DSS colitis – rats; Varying rations of dietary LA to ALA	Substitution of 1/3 LA with ALA mitigated experimental colitis by clinical, biochemical, and histological parameters.
Omega-3	Matsunaga et al, 2008 ³³	DSS colitis – mice; Mice were fed a control diet, omega-3 fat-rich diet, omega-6 fat-rich diet, or saturated fat-rich diet.	The omega-3 fat diet group, but not the other fat diet groups, showed exacerbated colitis with a further decrease of adiponectin expression.
Omega-3	Nieto et al, 2002 ³⁴	TNBS colitis – rats; Rats were treated with TNBS and fed diets enriched in olive oil (OO), fish oil (FO), or purified pig brain phospholipids (BPL), as sources of monounsaturated and PUFA of the (ω -3) and (ω -3) + (ω -6) series.	Rats with colitis fed FO at 1 wk showed significantly less macroscopic and microscopic colonic damage.
Curcumin	Sugimoto et al, 2002 ³⁵	TNBS colitis – mice; 0.5%, 2.0%, or 5.0% curcumin was added to chow	Treatment prevented and improved wasting and histologic scores.
Curcumin	Jian et al, 2005 ³⁶	TNBS colitis – rats; 2.0% curcumin in the diet after colitis induced.	Treatment prevented and treated wasting and histopathologic signs of colitis.

Food Category	Study, Year	Methods/animal model	Results
Curcumin	Zeng et al, 2013 ³⁷	TNBS colitis – rats; Intragastric administration of curcumin or sulfasalazine daily for one week.	Disease activity index decreased more rapidly in the curcumin-treated group than in the sulfasalazine-treated group ($p < 0.05$).
Resistant starch	Moreau et al, 2003 ³⁸	DSS colitis – rats; DSS or no DSS. The rats were fed a basal diet (BD), or a FOS or resistant starch (RS) diet creating six groups: BD-control, BD-DSS, FOS-control, FOS-DSS, RS-control and RS-DSS.	At days 7 and 14, caecal and distal macroscopic and histological observations were improved in RS-DSS compared with BD-DSS and also with FOS-DSS rats. Caeco-colonic SCFA were reduced in FOSDSS and RS-DSS groups compared with controls.
Amino acids	Xue et al, 2011 ³⁹	DSS colitis – rats; glutamine (0.75 g/kg/d) or sham was administered to rats by oral gavage during 7-day DSS treatment.	Decreased bleeding and diarrhea in glutamine group.
Amino acids	Liu et al, 2013 ⁴⁰	DSS colitis – rats; Mixture of threonine (0.50 g/d), methionine (0.31 g/d), and monosodium glutamate (0.57 g/d) or an isonitrogenous amount of alanine (control group).	Increased regeneration/ reepithelialization after 10-day supplementation. The spontaneous resolution of inflammation was not affected by the supplementation.
Amino acids	Coburn et al, 2012 ⁴¹	DSS colitis – mice; L-Arg supplementation	L-Arg supplementation improved the clinical parameters of survival, body weight loss, and colon weight.
Amino acids	Ren et al, 2014 ⁴²	DSS colitis – mice; Effects of graded dose of arginine (0.4%, 0.8%, and 1.5%) or glutamine (0.5%, 1.0% and 2.0%) supplementation	Dietary arginine or glutamine supplementation had significant ($P < 0.05$) influence on the clinical and biochemical parameters (T-SOD, IL-17 and TNF- α).
Amino acids	Giris et al, 2007 ⁴³	TNBS colitis – rats; The rats were divided into four groups. Group 1 had TNBS colitis alone, group 2 had TNBS-induced colitis and glutamine 1 g/kg/day intragastric gavage for 3 days before TNBS solution administration and 15 days following TNBS solution administration, group 3 had glutamine alone 1 g/kg/day intragastric gavage for 18 days before being euthanized, and group 4 had gavage for 18 days before being euthanized	Glutamine reduced colonic damage (histology) in TNBS-induced colitis.
Fermented brown rice	Kataoka et al, 2008 ⁴⁴	DSS colitis – rats; The inhibitory effects of brown rice fermented by <i>Aspergillus oryzae</i> (FBRA), a fiber-rich food, on the induction of acute colitis by dextran sulfate sodium (DSS) were examined.	Feeding a 5% and 10% FBRA-containing diet significantly decreased the ulcer and erosion area in the rat colon stained with Alcian blue. In another experiment, 10% FBRA feeding decreased the ulcer index (percentage of the total length of ulcers in the full length of the colon) and colitis score, which were determined by macroscopic observation.
Combination	Joo et al, 2013 ⁴⁵	DSS colitis – mice; C57BL/6 mice received 2.5% DSS in drinking water for 5 d to induce colitis. Then, they were given 0.25 mL of glutamine, fiber, and oligosaccharide (GFO) mixture or a 20% glucose solution twice daily for 10 d. Another set of mice receiving unaltered drinking water was used as the control group.	The body weight loss and disease activity index were significantly lower in the GFO-treated mice compared with the glucosetreated mice ($P < 0.05$). The decrease in colon length induced by DSS was significantly alleviated in GFO-treated mice compared with glucose-treated mice ($P < 0.01$). In addition, the histologic findings showed that intestinal inflammation was significantly attenuated in mice treated with GFO. Furthermore, treatment with GFO significantly

Food Category	Study, Year	Methods/animal model	Results
			inhibited the DSS-induced increase in the mRNA expression of IL-1 β .

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Table 2

Human studies on diet and IBD

Food category	Study, year	Methods	Results
Elimination			
Crohn's disease exclusion diet	Sigall-Boneh et al, 2014 ¹	Retrospective review: 47 subjects treated with a "Crohn's disease exclusion diet" and up to 50% calories from polymeric formula over 6 weeks.	Clinical remission achieved in 70% subjects.
Specific carbohydrate diet (SCD)	Cohen et al, 2014 ²	Prospective design: 10 subjects with CD on SCD followed over 12 weeks.	Improvement in PCDAI and intestinal appearance as assessed by capsule endoscopy.
Specific carbohydrate diet	Suskind et al, 2014 ³	Case series: 7 subjects with CD on SCD.	Duration on SCD: 5–30 months (mean 14.6 months). Improvements in PCDAI and CRP.
Anti-inflammatory diet	Olendzki et al, 2014 ⁴	Case series: 11 subjects (8 CD, 3 ulcerative colitis) followed diet, which targeted dysbiosis, for at least 4 weeks.	Improvement in clinical symptoms and ability to reduce medications.
Allergen Elimination Diet (IgG)	Rajendran et al, 2011 ⁵	Prospective study: 40 Pts with symptomatic CD tested for IgG4 antibodies to 14 specific food antigens. Top 4 foods removed for 4 week period.	29/40 completed study. 26/29 had significant decrease in modified CDAI, ESR, and IgG4 titers for excluded foods.
Semi-Vegetarian	Chiba et al, 2010 ⁶	Prospective 2 year study evaluating efficacy of semi-vegetarian diet (SVD) on maintaining clinical remission.	16/22 subjects maintained diet. 15/16 on SVD maintained remission.
FODMAP	Croagh et al, 2007 ⁷	Combined retrospective and prospective study assessing 13 subjects with ileal pouch, and 2 subjects with ileal rectal anastomosis on FODMAP exclusion diet	No improvement in pouchitis.
Low residue	Levenstein et al, 1985 ⁸	Randomized diet trial of 70 subjects with CD on low residue vs. normal Italian for mean 29 months.	Diet history showed normal diet had 3 times greater fiber intake. No differences in steroids, surgeries, or clinical disease activity.
Pro-inflammatory mediators			
Low Microparticle diet	Butler et al, 2007 ^{9*}	Macrophages (from CD and healthy controls) incubated with microparticles (aluminosilicates and titanium dioxide) before assay for cytokine production and phagocytic activity	Microparticles along did not stimulate activity. In presence of lipopolysaccharide, microparticles could induce more profound cytokine response (IL-8, TNFa, IL-10).
	Lomer et al, 2005 ¹⁰	RCT over 16 weeks with 83 subjects enrolled in 2x2 design: low or normal micro-particles and/or calcium.	No differences between groups in clinical disease activity or inflammatory markers.
Emulsifiers	Roberts et al, 2013 ¹¹	Evaluation of data on emulsifier consumption by country and the correlation with CD incidence.	Positive correlation between emulsifier exposure and CD incidence.
	Roberts et al, 2010 ^{12*}	plant fibers vs. emulsifiers on translocation of mucosa-associated e.coli using M-cell monolayers and human Peyer's patches.	reduced E coli translocation across M-cells; apple and leek fiber had no significant effect. Polysorbate-80 increased E coli translocation 59 fold.
Anti-inflammatory			
Omega 3	Cabre et al, 2012 ¹³	Systematic review: included 19 RCTs	No clear benefit of omega-3 fatty acids.

Food category	Study, year	Methods	Results
	Feagan et al, 2008 ¹⁴	Two randomized, placebo-controlled multi-center studies (EPIC-1 and EPIC-2). Subjects with quiescent Crohn's disease were randomly assigned to receive either 4 grams/day of omega-3 free fatty acids or placebo for up to 58 weeks.	No difference in rates of clinical relapse at 1 year in either trial.
Curcumin	Holt et al, 2005 ¹⁵	Pilot study of 5 subjects with ulcerative proctitis and 5 with CD treated with curcumin for 3 months	All 5 subjects with ulcerative proctitis had improvement in global score. CDAI improved in all CD subjects.
Vitamin D	Ananthakrishnan et al, 2013 ¹⁶	Retrospective cohort study: 3217 subjects; evaluating 25-OH vitamin D status and clinical outcomes.	Low 25-OH vitamin D levels associated with increased risk for surgery and hospitalization. Correction of 25-OH vitamin D associated with decreased risk for surgery
	Jorgensen et al, 2010 ¹⁷	RCT with 94 subjects with CD in remission randomized to 1200 IU vitamin D3 daily vs. placebo for one year.	Rate of disease relapse lower in subjects treated with D3 (13%) vs. placebo (29%), p=0.06
Prebiotic			
Inulin	Joossens et al, 2012 ¹⁸	RCT with 67 subjects randomized to oligofructose-enriched inulin (OF-IN) or placebo over 4 weeks.	In placebo group, no significant changes in fecal microbiota. In OFIN group, decrease in <i>Ruminococcus gnavus</i> and increase in <i>B longum</i> after 4 weeks.
Fructose oligosaccharides (FOS)	Benjamin et al, 2011 ¹⁹	Placebo-controlled RCT with 103 subjects randomized to 15 grams/day of FOS or placebo for 4 weeks	No difference in clinical response. No difference in fecal concentration of bifidobacteria or <i>F prausnitzii</i> at week 0 or 4.
Fiber	Ritchie et al, 1987 ²⁰	Multicenter prospective randomized trial over 2 years assessing a diet with unrestricted sugar intake and low in fiber vs. a diet with little sugar intake and high in unrefined carbohydrates; 352 subjects enrolled.	Difference in sugar and fiber intake between groups as expected, but no differences in clinical endpoints.
	Berghouse et al, 1984 ²¹	Case-crossover study with 5 CD and 5 ulcerative colitis subjects with ileostomies. Evaluated on 2 weeks of a Western diet, then 2 weeks on a diet rich in unrefined cereals.	Unrefined cereal group had greater weight of ostomy output as well as higher bacterial flora per gram.
	Heaton et al, 1979 ²²	Retrospective comparison between 32 subjects with CD instructed on fiber-rich, unrefined carbohydrate diet vs. 32 subjects with no dietary instruction.	Mean follow-up of 52 months. Diet-instructed group had less refined sugar, greater fiber intake, as well as fewer admissions and less surgery.
Wheat grass	Ben-Arye et al, 2002 ²³	Placebo-controlled RCT of 23 subjects with active UC randomized to 100 mL/day wheat grass juice vs. placebo for 1 month.	Wheat grass group with greater improvement in disease activity and physician global assessment.
Germinated barley	Kanauchi et al, 2002 ²⁴	RCT with 18 subjects with mild/moderately active ulcerative colitis randomized to germinated barley 20–30 gram/day for 4 weeks vs. baseline anti-inflammatory therapy.	Germinated barley group with lower disease activity at 4 weeks.
Dietary yeast	Barclay et al, 1992 ²⁵	Study of 19 subjects with dietary yeast inclusion for 1 month and yeast exclusion for 1 month.	Clinical disease activity higher during time of yeast exposure.

* Denotes study was conducted ex vivo

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