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Diet as a Trigger or Therapy for Inflammatory Bowel Diseases

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The most common question asked by patients with inflammatory bowel disease (IBD) is, "Doctor, what should I eat?" Findings from epidemiology studies have indicated that diets high in animal fat and low in fruits and vegetables are the most common pattern associated with an increased risk of IBD. Low levels of vitamin D also appear to be a risk factor for IBD. In murine models, diets high in fat, especially saturated animal fats, also increase inflammation, whereas supplementation with omega 3 long-chain fatty acids protect against intestinal inflammation. Unfortunately, omega 3 supplements have not been shown to decrease the risk of relapse in patients with Crohn's disease. Dietary intervention studies have shown that enteral therapy, with defined formula diets, helps children with Crohn's disease and reduces inflammation and dysbiosis. Although fiber supplements have not been shown definitively to benefit patients with IBD, soluble fiber is the best way to generate short-chain fatty acids such as butyrate, which has anti-inflammatory effects. Addition of vitamin D and curcumin has been shown to increase the efficacy of IBD therapy. There is compelling evidence from animal models that emulsifiers in processed foods increase risk for IBD. We discuss current knowledge about popular diets, including the specific carbohydrate diet and diet low in fermentable oligo-, di-, and monosaccharides and polyols. We present findings from clinical and basic science studies to help gastroenterologists navigate diet as it relates to the management of IBD.

Keywords: Inflammatory Bowel Disease; Diet; Short-Chain Fatty Acids; Microbiome.

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are broadly assumed to result from exposure to environmental triggers in individuals with a genetic predisposition to these diseases. Nearly 200 genetic loci have been linked to IBD,[1] yet little is known about the exact mechanisms by which these variants contribute to pathogenesis. Likewise, studies of environmental exposures as risk factors for IBD have been the focus of scientists for decades. Some environmental exposures have been associated repeatedly with risk of IBD, such as smoking, which increases the risk of CD and reduces the risk of UC.[2] However, similar to genetic variants, the mechanism whereby these environmental exposures contribute to the etiology of IBD is a mystery. In the past 2 decades, major breakthroughs in DNA sequencing and other technologies have opened new avenues of investigation into the mechanisms by which environmental factors, such as diet and the gut microbiome, contribute to the development and progression of IBD.

By using modern sequencing techniques to characterize the gut microbiome, including those organisms that cannot be cultured easily, researchers found the composition of the gut microbiome in patients with IBD differs from that of patients without these diseases.[3] Similarly, dietary patterns have been associated with the composition of the intestinal microbiome in healthy individuals as well as in those with gastrointestinal and hepatic disorders.[4–8] We discuss the effects of diet on initiation and progression of IBD, and the basic processes that underlie these associations, focusing on the link between diet and the gut microbiome.

Epidemiology of Diet and IBD

The incidence of IBD has increased worldwide—first in developed nations and subsequently in developing nations, indicating a role for environmental factors in pathogenesis.[9,10] Moreover, children of immigrants from countries of low incidence who move to regions with a higher incidence

Abbreviations used in this paper: **CD, Crohn's disease; EEN, exclusive enteral nutrition; FGS, functional gastrointestinal symptom; FODMAP, fermentable oligo-, di-, and monosaccharides and polyols; GPR43, G-protein–coupled receptor 43; HFD, high-fat diet; H_2S, hydrogen sulfide; IBD, inflammatory bowel disease; IL, interleukin; MCT, medium-chain triglyceride; PEN, partial enteral nutrition; PUFA, polyunsaturated fatty acids; SCD, specific carbohydrate diet; SCFA, short-chain fatty acid; SRB, sulfate-reducing bacteria; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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have the same risk of developing IBD as children of families who have resided in the high-incidence region for many generations.[11] Interestingly, when both parents were immigrants from the same country, the incidence of IBD has been observed to be lower in their children, perhaps suggesting that a cultural factor is related to the risk of IBD. Similarly, immigrants from Latin America to South Florida develop IBD at a much later age than non-Hispanic whites, yet within 1 generation, US-born Hispanics develop IBD at a similar age as non-Hispanic whites.[12] In general, data from epidemiology studies of migrants to higher-IBD-prevalence countries show an increasing incidence of IBD, leading to the hypothesis that environmental factors such as diet affect risk of IBD.

Early Diet

The earliest diet is either breast milk or infant formula. The association between breast feeding and risk of subsequent IBD has been studied repeatedly. Some, but not all,[10] studies have suggested a lower risk of childhood-onset IBD among children who were breastfed.[13,14] Mothers with IBD are less likely to breastfeed their infants than mothers without IBD.[15] It is not clear whether mothers with IBD who breastfeed reduce the risk for IBD in their children to the same extent as mothers who do not have IBD and breastfeed.

In the first few years of life, the bacterial microbiome and virome are labile.[16,17] Although vaginal vs Cesarean section delivery affects the infant microbiome,[18] the cessation of maternal IgA in breast milk is more likely to induce characteristics of an adult-like microbiome, dominated by Firmicutes and Bacteriodetes, than feeding of solid food.[19,20]

Dietary Patterns Before IBD

Although breast feeding or formula feeding almost always is initiated before the onset of IBD, a major challenge in studying the association of a diet of table food and new-onset IBD is the need to collect dietary information before the onset of the disease. Otherwise, even subtle preclinical symptoms of the disease may alter the person's dietary patterns. Fortunately, several large longitudinal studies have been able to provide data to study dietary patterns as risk factors for IBD. The results of these studies have been relatively consistent, pointing to a lower risk of IBD among people who consume more fruits and vegetables, and a higher risk in people who consume less of these and more animal fats and sugar.[10,21–23] The positive association between fat consumption, particularly transunsaturated fats[23] and n-6 fatty acids,[24] has been most evident for UC.

Studies of fatty acids can focus on select groups of fatty acids, such as n-6 or n-3, or on the relative ratio of n-3:n-6 fatty acids. For example, Ananthakrishnan et al associated a higher ratio of n-3:n-6 fatty acids with a lower risk of UC.[23] Studies in animal models have indicated that iron and sulfur amino acids, which similar to fats are found in high concentrations in meats, are also risk factors for IBD.[25–30] In contrast to fats, a diet high in fruits and vegetables is associated with a reduced risk of CD more than UC.[10] Interestingly, dietary intake of zinc, of which meat is also a major source, has been associated inversely with the risk of CD but not UC.[31] Because most foods contain many different nutrients, it is challenging to isolate the effect of individual nutrients in observational research.

Notably, dietary patterns 20 years or more before the onset of disease have been associated with the risk of IBD, particularly CD. For example, in the Nurses' Health Study, greater self-reported consumption of a prudent diet, characterized by a higher intake of fruit, vegetables, and fish, while in high school was associated with more than a 50% lower risk of adult-onset of CD.[31] Early diet therefore might be as or more important than adult diet in determining risk for IBD.

Basic Research Findings

Given these epidemiologic associations, can basic science studies edify how these changes in diet may change susceptibility to IBD? Dietary factors may result in a susceptibility to IBD in a variety of ways. First, derivatives of food can affect intestinal permeability in ex vivo studies (using harvested intestines).[32] Dietary factors may serve as ligands for various host receptors. The aryl hydrocarbon receptor is expressed on intestinal dendritic cells and lymphocytes and helps maintain epithelial integrity, in part through induction of interleukin 22 (IL22).[33,34] The aryl hydrocarbon receptor has many ligands, some of which are present in foods. These include indole or tryptophan metabolites (derived from cruciferous vegetables), stilbenes (eg, resveratrol in red wine), carotenoids (present in yellow/orange/red vegetables), and flavonoids.[35] Innate immune receptors such as Toll-like receptors 2 and 4 are activated by saturated fatty acids but inhibited by omega-3 polyunsaturated fatty acids (PUFAs).[36,37] Specific factors in food therefore have direct effects on mucosal integrity and immune function.

In addition to these mechanisms that may contribute to the effect of diet on IBD, diet is linked directly to the intestinal microbiome and the generation of metabolites by the microbiota. Microbial colonization is required for the development of colitis in mice, indicating that the microbiome links diet with intestinal inflammation.[38] However, inflammation itself can alter the microbiome and therefore IBD-associated differences in the microbiome may be attributable to the presence of inflammation rather than causal.[39,40] For example, pediatric patients with CD have clear differences in the composition of their microbiome compared with children without IBD even before initiation of therapy.[41]

Mice have been used to assess the effect of diet on IBD susceptibility and the microbiome, allowing for precise timing of the onset of disease. Consistent with epidemiologic observations, in animal models, omega 3 (n-3) PUFAs and medium-chain triglyceride (MCT) oils are anti-inflammatory, whereas high-fat diets are inflammatory.

Mice with ileitis or colitis (caused by genetic manipulation or exposure to chemicals) fed a high-fat diet (HFD) have increased small intestinal or colonic inflammation and barrier dysfunction.[42–45] Studies have shown that the stool phospholipid profile changed with a HFD and with inflammation.[46] These changes also were associated with changes in bacterial taxa, indicating complex interactions between the host and the microbiome in response to fat intake. Furthermore, a diet high in milk fat (saturated fat) alters the microbiome, with an increase in a sulfite-reducing pathobiont *Bilophila wadsworthia*, and induces inflammation in IL10-knockout mice.[47] Although mice without disruption of *Il10* also had outgrowth of the *B wadsworthia*, they did not develop inflammation. These data indicate that the diet's effect on the microbiome leads to inflammation in genetically susceptible animals.

It is not clear whether microbiome changes are a cause or effect of IBD. One of the goals of the ongoing multinational Genetics, Environment and Microbiome study is to identify factors that increase risk for IBD.[48,49] This study has associated age, sex, being breastfed, and environmental factors such as living in a large city with the composition of the microbiome in this cohort, which is at high risk for IBD. However, the study has not associated IBD-related genetic polymorphisms with the composition of the intestinal microbiota.[50] Similar correlations have been observed in a large Dutch cohort.[8] Total carbohydrate intake and features of a Western diet, including higher caloric intake and consumption of sugar-sweetened beverages, were associated negatively with microbiome diversity. In contrast, features of a Mediterranean style diet such as consumption of fruits, vegetables, and red wine were associated with increased diversity. Red wine consumption also was associated with increased *Faecalibacterium prausnitzii* abundance, which has been proposed to have anti-inflammatory properties in patients with IBD.

Dietary Interventions and Patient Management

Flares Caused by Dietary Factors

Although dietary patterns correlate with the development of IBD, there is little information about which foods induce flares. Most patients believe that diet can induce symptoms, so they avoid certain foods or avoid eating. However, only approximately half of patients have ever received advice from a dietitian.[51–53] By using food frequency questionnaires in patients with UC, investigators identified that a high intake of meat, especially red and processed meat, protein, alcoholic beverages, sulfur, and sulfate increased the likelihood of a flare.[54] Similar results also were obtained from short-term food questionnaires.[55] In patients with CD, a diet higher in total fat, saturated fat, monounsaturated fatty acids, and a higher ratio of omega-6:omega-3 PUFAs was associated with disease relapses.[56–58]

Oral administration of iron sulfate or heme in dietary iron, which is present in meat, increases the severity of chemically induced colitis in mice and rats.[44,59–63] In animal models, administration of iron negated the anti-inflammatory effects of green tea extracts.[64] Oral iron also has a strong effect on gut bacteria in patients with CD.[29,65] For example, adherent entero-invasive *Escherichia coli* have been reported to perpetuate CD. Adherent invasive *E coli* express genes for iron acquisition and require iron for growth and perpetuation in macrophages, so this could be an additional mechanism by which oral iron exacerbates CD.[66] Although a high percentage of all iron-deficient patients (with or without IBD) tolerate oral iron poorly, only a small percentage of patients with IBD have disease flares in response to oral iron.[67]

Exclusive and Partial Enteral Nutrition With Defined-Formula Diets

Children and adolescent patients with IBD often consume an inadequate number of calories and do not meet their daily requirements for vitamins.[68] If dietary patterns contribute to the etiology of IBD, it is logical to consider altering the diet as a therapeutic strategy. The most widely studied dietary intervention has been the use of exclusive enteral nutrition (EEN) with elemental, semi-elemental, and defined formula diets. These approaches are used commonly in the treatment of pediatric CD, particularly in Canada, Japan, and Europe.[69–71] The currently marketed formulae improve symptoms, intestinal inflammation, and nutritional status in CD.[72–74] In direct comparison, EEN generally performed less well than corticosteroids.[74] This has been attributed in part to increased discontinuation rates in the EEN arms of these trials, perhaps because of poor tolerance of the therapy. Many of these trials were conducted in adults. In contrast, in a recent randomized trial, steroids and EEN each reduced symptoms, but only EEN reduced mucosal inflammation.[72] This provides evidence that the therapeutic benefit of EEN extends beyond just improving symptoms. It is not clear whether mucosal healing also would occur in adults; EEN has been reported to produce lower rates of clinical response in adults than steroids.

For maintenance of remission, a diet in which half of the daily calories came from an elemental supplement reduced the rate of CD relapse by nearly 50% compared with a regular diet.[75] This finding indicates that less-extreme dietary interventions could be beneficial. Moreover, several observational studies have examined the effects of EEN in conjunction with tumor necrosis factor (TNF) antagonists. These studies found the combination to be more effective than TNF antagonists alone.[76] Findings from these studies provide evidence to support the use of EEN as a bridge therapy for CD—particularly for patients wishing to avoid exposure to corticosteroids. It should be noted that the studies showing the greatest benefit of EEN were conducted in children. In contrast, meta-analysis of EEN studies in adults showed variable results, possibly because of poor adherence to the therapy.[77]

There have been few studies of the use of EEN in the management of patients with UC.[78] One small clinical trial of patients with moderately to severely active UC receiving corticosteroids compared EEN with parenteral nutrition.

The study found no statistically significant difference in rates of remission, but a higher proportion of patients receiving parenteral nutrition developed postoperative infections.[79] Although it is possible that EEN could be effective in patients with UC, further studies are needed. Studies should address whether EEN could be used in place of steroids as a bridge to maintenance therapy. Given the challenges of initiating EEN, such a study might need to be conducted among hospitalized patients or those with mildly active UC.

Prior head-to-head studies of different EEN formulations and EEN vs partial enteral nutrition (PEN) whereby the formula is used to provide approximately 50% of the patient's calories may lend insight into the mechanism(s) of action. Elemental formulas with fully hydrolyzed protein are not more effective than partially hydrolyzed formulas or formulas with intact protein.[74] Although this finding might contradict the reduced antigenicity hypothesis, it is important to remember that a diet of a single formula contains far fewer antigens than a usual diet of table food. However, the effectiveness at improving symptoms and reducing inflammation appears greatest when used as EEN rather than PEN.[73,80] Therefore, some component of table food could contribute to the inflammatory process in patients with CD, even if it is not fat content or protein.

Compared with TNF antagonists, EEN and PEN therapy is less likely to normalize fecal levels of calprotectin in children.[80] These observations have been used to assess the impact of inflammation and EEN on the microbiome (Figure 1).[7] Shotgun meta-genomic sequencing showed distinct patterns associated with inflammation and after treatment.[7] Similar to a previous study of children with CD, antibiotic exposure was associated with increased dysbiosis, as was corticosteroid use. The proportion of fungus increased with active disease and with antibiotic use. Dietary therapy reduced inflammation and led to changes in the microbiome within 1 week. Unlike TNF antagonists, however, the changes in the microbiome induced by EEN did not lead to a microbiome resembling that of healthy individuals. A difference in microbiome was seen in patients who responded to EEN vs those who did not and could be seen within a week; this observation may allow for early recognition of responders and nonresponders. A change in the microbiota was not seen in children receiving PEN, despite receiving almost the same amount of enteral formula, suggesting that the change seen with EEN was largely owing to exclusion of table foods.

The fat concentration in the formula does not seem to affect efficacy in human beings.[74] However, the type of fat in EEN has been evaluated in animal models. In comparing supplementation of an elemental formula with either MCT vs long-chain triglycerides in rats, researchers found the MCT-rich formula to have a greater anti-inflammatory effect than long-chain triglyceride–rich EEN.[81] Similarly, combining MCT with n-3 supplementation in EEN in an animal model was more beneficial than n-3 alone and better than n-6 alone as the comparator.[82]

The Specific Carbohydrate Diet

Given that EEN may work by eliminating some component(s) of table food, there has been interest in identifying other restriction diets that offer therapeutic benefit in CD (Table 1). A recent systematic review examined dietary

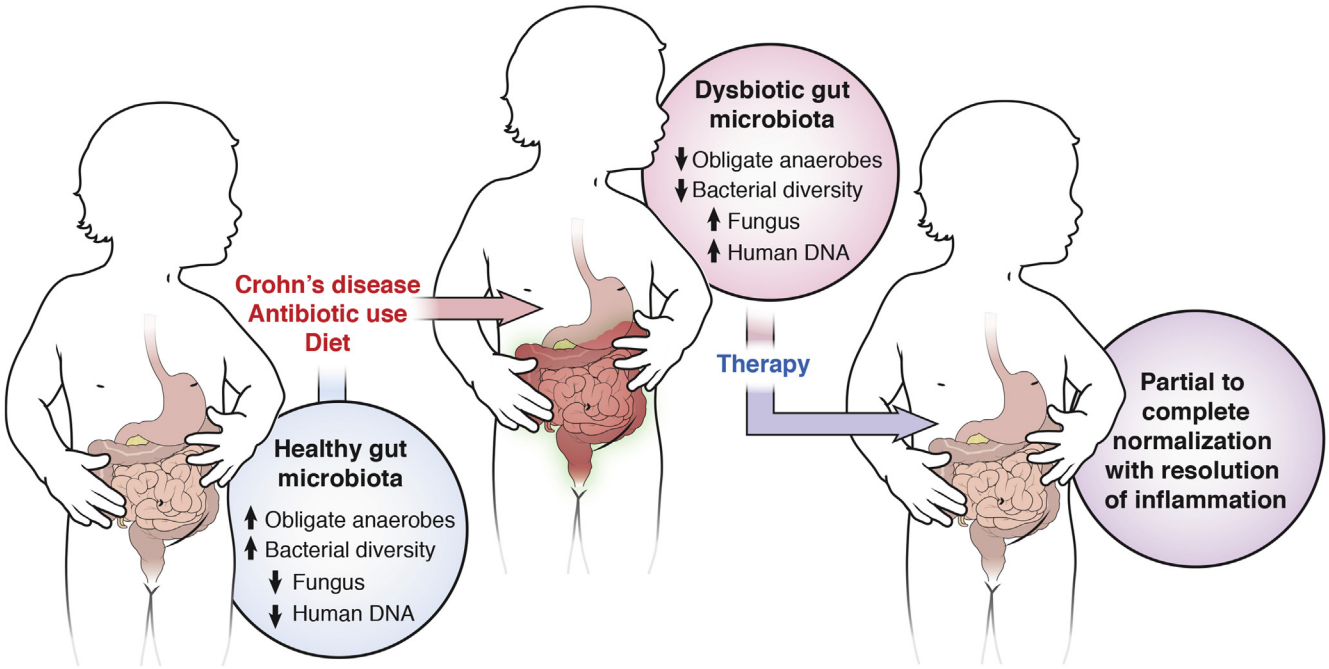

Figure 1. Effects of dietary and pharmacologic interventions on dysbiosis in patients with CD. Patients with CD have intestinal dysbiosis, with reduced diversity and relative proportions of bacterial and yeast species. Enteral nutritional or biologic therapy each lead to mucosal healing in some patients, accompanied by reductions in dysbiosis, which occurs more gradually with enteral nutrition than with biologic agents.[7] Levels of human DNA are used as markers of mucosal damage.

Table 1. Diets Commonly Used by Patients With IBD

	Low-FODMAP		SCD		Paleolithic diet		IBD-AID	
Basics	FODMAPs are grouped based on the length of their carbohydrate chains. Foods containing these forms of carbohydrates worsen the symptoms of IBS and IBD. They are poorly absorbed in the small intestine, are highly osmotic, and rapidly fermented by bacteria in the gut, which can increase IBS and IBD symptoms.		Disaccharide and polysaccharide carbohydrates are poorly absorbed in the gastrointestinal tract, causing bacterial and yeast overgrowth, resulting in overproduction of mucus. Limited to monosaccharides: glucose, fructose, and galactose.		The human gastrointestinal tract is poorly evolved to handle the modern diet, which has resulted from development of modern agricultural methods. Exposure to foods that were not present at the time of human evolution may result in modern diseases.		Loosely based on the SCD, but IBD-AID limits some carbohydrates such as refined sugar, gluten-based grains, and certain starches that are thought to stimulate the growth of inflammatory bacteria in the digestive tract, and adds prebiotics and probiotics to help restore an anti-inflammatory environment.	
Limitations	Based on few retrospective pilot studies and limited to symptomatic responses.		References only uncontrolled studies. Potential to contribute to vitamin D deficiency.		No research studies have been performed to test this diet with the IBD population. Potential to contribute to vitamin D deficiency.		Based on a small retrospective case study; further research needed to determine changes in microbiota composition.	
	Include	Avoid	Include	Avoid	Include	Avoid	Include	Avoid
Food group								
Grains	Gluten-free, oats, rice, quinoa	Wheat, barley, rye	None	All cereal grains	Cereal grains	All others	Oats	Gluten-based grains
Fruits	Banana, blueberry, cantaloupe, clementine, grape, kiwi, lemon and lime, mandarin, melons (variety), orange, passion fruit, pineapple, raspberry, strawberry	Apple, applesauce, apricot, blackberries, canned fruit, dates, dried fruit, grapefruit, mango, nectarine, pear, peach, plum, prunes, watermelon	All but canned or frozen	None	All	None	Most allowed if pureed and seeds are strained out	Fruits with seeds

Table 1. Continued

	Include	Avoid	Include	Avoid	Include	Avoid	Include	Avoid
Vegetables	Alfalfa, bean sprouts, bell pepper, bok choy, broccoli (≤1/2 cup), Brussels sprouts (≤ 2 sprouts) carrot, corn, cucumber, eggplant, green beans, kale, lettuce, potato, spinach, spring onion (only green top) squash, tomato, turnip, zucchini	Artichokes, asparagus, avocado, beetroot, cauliflower, cabbage, garlic, leek, mushrooms, onion, peas, shallots, snow peas, sweet corn, sweet potato	All but canned or frozen	Potatoes, yams, corn	All	Potatoes, corn, yucca, butternut squash, yam, beets	Most, with soft texture and well-cooked	Cruciferous vegetables in phase 1 and 2 studies
Protein	All	Breaded meat or made with high fructose corn syrup	All	Processed, canned, or smoked meats	Lean game meats, fish, shellfish	Domesticated meats	All fish, lean meats, omega-3 eggs	High-fat meats
Nuts, seeds, and legumes	Almonds (≤10 nuts), chia seeds, nut butters, macadamia, peanut, pecan, pumpkin seeds, walnuts	Beans, cashews, chickpeas, lentils, pistachios, soybeans	Lentils, split peas	Most legumes (eg, chickpeas, soybeans)	All nuts and seeds	All legumes, peanuts	Flax meal and chia seeds as tolerated, pureed nuts, and beans	Whole seeds and nuts
Dairy	Lactose-free yogurt and milk, almond, coconut, rice, or soy milk (from soy protein); hard and low-lactose cheese	Cow's, goat, sheep's, condensed, and evaporated milk, buttermilk, soy milk (from soybeans); soft cheese and creams	Lactose-free	All	None	All	Lactose-free, limited aged cheeses (made with active cultures and enzymes), fresh cultured yogurt, kefir	All
Beverages	Fruit and vegetable juices made with allowed foods (limit to 1/2 cup at a time), wine (5 oz), vodka, or gin (1.5 oz)	Coconut water, green tea, rum, soft drinks, sports drinks, white tea	Wine	Milk, instant tea, instant coffee, soybean milk, beer	All others	Soft drinks, alcoholic beverages, fruit juice	Not specified	Not specified
Other	Brown sugar, dark chocolate, maple syrup, golden syrup, stevia	Milk chocolate, sweeteners ending in "-ol," honey, high fructose corn syrup	Saccharin, honey, butter	Chocolate, margarine, corn syrup	Honey	Refined sugar, artificial sweeteners	Honey, stevia	Not specified
Reference	222		85		223		96	

IBD-AID, IBD anti-inflammatory diet; IBS, irritable bowel syndrome.

interventions broadly and concluded that exclusion diets such as the specific carbohydrate diet (SCD) and a diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) were the most promising.[11] This is consistent with systematic evaluations that have shown that the majority of patients believe diet affects the course of IBD.[83,84]

The SCD was popularized by Gottschall[85] in the book *Breaking the Vicious Cycle*. The SCD restricts all carbohydrates except monosaccharides: glucose, fructose, and galactose. Fresh fruits and vegetables are universally acceptable with the exception of potatoes, corn, and yams. Certain legumes, such as lentils and split peas, are permitted, whereas others, such as chickpeas and soybeans, are not. No grains are permitted. Saccharin and honey are permitted in addition to moderate use of sorbitol and xylitol. Canned fruits and vegetables are not permitted because of possible added sugars and starches. Unprocessed meats are permitted in the SCD without limitation. However, processed, canned, and most smoked meats are restricted because of possible sugars and starches used in additives. Milk is not permitted in the SCD because of lactose content. However, certain lactose-free cheeses are permitted, along with homemade lactose-free yogurt.

In a prior qualitative review, Hou et al[86] documented that most restriction diets had little clinical evidence to support their efficacy. However, several recent small studies have provided early evidence that the SCD reduces symptoms and bowel inflammation. Suskind et al[87] reported the effectiveness of the SCD in 7 children with CD who were not receiving any immunosuppressive therapies. All had clinical improvement by 3 months. In a follow-up study, this same group showed that fecal calprotectin level decreased from a mean of 685 mcg/g to 213 mcg/g at 2–6 weeks after starting the diet.[88] Cohen et al[89] used video capsule endoscopy to assess the effect of SCD in 10 children with CD. Video capsule endoscopy was completed at baseline and after 12 weeks of diet therapy; mucosal inflammation was quantified with the Lewis score. Four of 10 children achieved complete mucosal healing (Lewis score < 135), and 6 of 10 children achieved clinical remission. Therefore, similar to EEN, the SCD showed meaningful clinical improvement and mucosal healing in this uncontrolled study.

Several other uncontrolled trials of restriction diets also have shown improved disease activity and prolonged time to relapse.[90–96] Some of these were either derived from or have similarities to the SCD.[93,96] Sigall-Boneh et al[93] reported clinical remission in 33 of 47 (70%) children and young adults treated with a restriction diet with or without caloric supplementation with a defined formula diet, including 6 of 7 patients who used the diet without supplemental nutrition from a defined formula. Of patients with increased levels of C-reactive protein at baseline, 70% had complete normalization of levels; 11 of 15 (73%) with colonoscopy or small-bowel imaging showed mucosal healing. The restriction diet resembled the SCD because condiments, sauces, gluten, dairy, processed meats and foods, and canned foods all were forbidden. We have included a listing of the basic components of the IBD anti-inflammatory diet derived from the SCD[96] as well as the Paleolithic diet; both are popular with patients but there are few data to support their use (Table 1).

One might ask what SCD, other restriction diets, and EEN have in common and could these similarities help clarify the mechanism of action of these dietary therapies? Some similarities of these diets are avoidance of gluten and complex sugars. Patients frequently report improvement after a gluten-free diet. In an animal model of ileitis, gluten exacerbated inflammation independent of its effects on the microbiota.[97] Maltodextrin, a polysaccharide derived from starch hydrolysis, increased biofilm formation and epithelial invasion by adherent-invasive *E coli*, which could be another way in which consumption of polysaccharides may exacerbate CD.[98] Another similarity between the popular exclusion diets is the need to prepare all of one's food from fresh ingredients. It is possible that certain additives (discussed later) may promote inflammation and are avoided when meals are prepared from fresh ingredients.

A strategy of personalized exclusion diets has been proposed by several investigators. A recent study used IgG4 testing to guide exclusion of foods in the diet of patients with CD.[99] This 4-week study randomly assigned patients to a group whose diet excluded foods with the highest IgG4 response or a control group whose diet excluded foods with the lowest IgG4 response. Although quality-of-life measures improved with elimination of foods, no change in the level of C-reactive protein or fecal calprotectin was observed. Although the rationale for measuring levels of IgG4 as a means of personalizing diet changes may not be ideal, the findings show that nutritional interventions could benefit from personalization.

Link Between Sulfur-Containing Foods and UC

Restriction diets have not been as well studied for UC. The earliest studies of UC showed that removing foods such as milk, cheese, and eggs reduced symptoms in patients.[100] A prospective observational study examining the association of subjects' usual diets with risk of symptomatic relapse of UC associated a higher intake of eggs, red and processed meats, and alcohol with an earlier relapse of disease.[54]

One of the proposed mechanisms by which consumption of red meat and alcohol could exacerbate IBD is based on their high sulfur content. Red meat, eggs, and milk contain high levels of cysteine, which can be used as an efficient source for the generation of hydrogen sulfide (H_2S) by sulfate-reducing bacteria (SRB).[101–103] Colonic bacteria need to consume H_2 generated by primary fermentation of carbohydrates and proteins to maintain redox balance and continue to generate energy. SRB efficiently consume H_2 when sulfate is available as an electron acceptor. Dietary sources of sulfur include bread, preserved meats, dried fruit, and wine, which use sulfites as preservatives, or sulfate in the dietary supplement chondroitin sulfate or food additives such as carrageenan. In addition to direct diet sources, SRB also may extract sulfate from endogenous sources such as sulfated glycans in mucin or from taurocholic acid in bile. *B wadsworthia* is the only known intestinal microbe that uses taurine as an electron acceptor because it can liberate sulfite

from taurocholic acid using a taurine:pyruvate aminotransferase.[104,105] *B wadsworthia* increases inflammation in mice with colitis,[47] apparently because consumption of milk fat leads to an increase of taurocholic acid, providing a potential source of taurine for *B wadsworthia*.

H_2S has been shown to have detrimental inflammatory effects in the colon, including increased DNA damage,[106–111] but also may promote wound healing in rats with colitis.[26] Approximately half the population carries SRB. In a reductionist mouse model in which gnotobiotic mice were reconstituted with a limited flora in the presence or absence of the most common SRB in human beings, *Desulfovibrio piger*, investigators found that mice fed a HFD (20%) and high simple sugar diet had the greatest expansion of *D piger*.[112] The largest production of H_2S and expansion of *D piger* occurred when mice were fed chondroitin sulfate, commonly used for osteoarthritis. Although *D piger* and increased H_2S were associated with lower levels of messenger RNAs encoding the tight junction protein claudin-4 and higher levels of matrix metalloproteinase-7, no inflammation was seen in the colons of these mice. These data indicate that it is not simply the ability to generate H_2S or the presence of SRB in the microbiota that determine the effect on inflammation, but the context.

Studies have examined the presence of SRB and H_2S production in patients with UC. Although some studies have found that patients have higher numbers of SRB and greater H_2S production,[102,113–116] it appears that mesalamine inhibit SRB growth and H_2S production.[114,117,118] These studies did not address whether simply reducing inflammation could affect H_2S production. Patients should be made aware that high-sulfur-containing foods and drinks may exacerbate symptoms. On the other hand, many patients are now following a popular diet, the Paleolithic (or paleo) diet. This diet highlights the consumption of lean, nondomesticated meats such as cattle, fish, and shellfish (30%–35% of daily caloric intake), and noncereal, plant-based foods high in fiber (45–100 g/day). Its effect on IBD may go beyond carbohydrate restriction because it promotes consumption of lean nondomesticated animals to reach a recommended polyunsaturated fatty acid omega-6 to omega-3 ratio of 2:1, which contrasts with the 20:1 or 30:1 ratio of the modern American diet.[119] Studies are needed to determine whether the high consumption of red meat in this diet leads to increased H_2S concentration, or SRB within the gut.

The Diet Low in FODMAPs

A high percentage of patients with IBD experience functional gastrointestinal symptoms (FGSs) even during remission, which are less likely to respond to anti-inflammatory therapy.[120,121] In patients with irritable bowel syndrome, reduced consumption of short-chain carbohydrates or FODMAPs can reduce FGS.[122] FODMAPs pass undigested through the small intestine owing to a lack of enzymes that digest specific oligosaccharides, disaccharides, and polyols; decreased lactase activity; and inadequate absorption of fructose. Once they reach the colon, FODMAPs can cause an osmotic effect that draws water into the lumen, resulting in intestinal wall distention, bloating, pain, and diarrhea, and/or are fermented by resident bacteria into different products including gases, which may be responsible for FGS. Patients with IBD following this diet also may have symptom improvement[120,121,123]; however, evidence that a low FODMAP diet reduces inflammation is lacking.[124] Rather, low-FODMAP diets have been observed to reduce the abundance of potentially favorable species such as *Clostridium* cluster IV and *F prausnitzii* and butyrate production.[124] Studies are needed to determine the long-term effects of low-FODMAP diets on the microbiome, metabolism, and inflammation in patients with IBD.

Dietary Supplements and Food Additives

Supplementing the diet with anti-inflammatory compounds is another appealing approach to therapy for patients. Several strategies have been tried, including supplementation with fiber, fish oil, vitamin D, and curcumin. On the other hand, there may be certain additives, especially in processed foods, that should be avoided.

Dietary Fiber Supplementation and the Effect of Short-Chain Fatty Acids

Dietary fiber generally refers to nondigestible complex carbohydrates belonging to 1 of 2 categories based on their solubility in water: insoluble fiber (ie, does not dissolve in water and usually is not fermentable; such as cellulose, lignin, waxes from plants), and soluble fiber (which dissolves in water and is mostly fermentable; such as pectins, β-glucans, β-fructans, gums, inulins, fructo-oligosaccharides, galacto-oligosaccharides, and dextrins) (Table 2). Soluble fibers include glucans, guar gum, some hemicelluloses, mucilage, pectin, inulin, acacia gum, partially hydrolyzed guar gum, oligofructose, fructooligosaccharides, and galacto-oligosaccharides.

Resistant starches are another complex carbohydrate that are not absorbed in the small intestine because their physical and chemical characteristics make them inaccessible to α-amylase. They have properties similar to soluble fiber, and therefore often are considered as such.[125]

Fermentable fibers and starches that are not digested and absorbed in the small intestine are metabolized readily by colonic bacteria into short-chain fatty acids (SCFAs) (ie, acetate, propionate, and butyrate), lactic acid, and hydrogen and methane gas. Both types of fiber have anti-inflammatory effects in animal models of colitis. The Academy of Nutrition and Dietetics,[126] the Crohn's and Colitis Foundations of America,[127] and the World Gastroenterology Organization[128] agree that dietary fiber should not be restricted in patient with IBDs in remission unless there is the presence of strictures. However, they recommend reducing high-fiber foods during flares. This latter recommendation is not evidence-based.

Some data suggest that high intake of fiber by patients with CD, but not patients with UC, may reduce the risk of

Table 2. Types and Sources of Fiber[125,224]

Classification based on solubility (ability to dissolve in water)	Viscosity (ability to hold water, thicken, and resist flow)	Fermentability (ability of colonic bacteria to digest, producing SCFAs)	Types of fiber	Food sources	Benefits
Soluble fiber	High	High	Glucans, guar gum, mucilages, pectin, some hemicelluloses	Bananas, apples, oranges, pears, strawberries, blueberries, grapefruits, peaches, concord grapes, cranberries, some legumes such as lentils, chickpeas, lima beans, okra, oats, oatmeal	Slows transit time Delays gastric emptying May help with diarrhea
	Low	High	Considered prebiotics: acacia gum, partially hydrolyzed guar gum, oligofructose	Asparagus, acorn squash, cucumbers, carrots	Results in SCFA production in colon
			Prebiotic FODMAPs: Inulins ($\geq$10 β 1–2 chain length) fructooligosaccharides ($<$10 β 1–2 chain length) Levans (β 2–6 bonds)	Wheat, garlic, rye, barley, pistachio, peach, watermelon, artichoke, beetroot, leek, pea, and onion	
			Prebiotic FODMAPs: galacto-oligosaccharides, including raffinose and stachyose	Lentil, bean, chickpea, cabbage, Brussels sprouts, chicory root, and onion	
	Low	High	Resistant starch	All starch degraded not absorbed by the small intestine; 4 types (RS1–4)	
			RS1: raw starch granules inaccessible to α amylase	Intact or milled grains, dry beans, pasta	
			RS2: raw crystals	Banana fruits, uncooked potatoes, maize	
			RS3: retrograded or gelatinized starch produced after heating and cooling of raw granules in water	Cooked potatoes and bread	
			RS4: chemically modified	Processed foods	
Insoluble fiber	Low	Low	Cellulose, lignin, some hemicelluloses	Brown rice, barley, bulgur, couscous, corn, celery, flax, fruit and vegetable skins, nuts, quinoa, rye, seeds, some legumes, wheat bran, whole grains	High in roughage Increases stool bulk Prevents constipation No gas byproduct

flares.[129] A systematic review examined the results of 23 randomized clinical trials of fiber supplementation in IBD.[130] Although meta-analysis was not possible owing to heterogeneity between the trials, the investigators concluded that the role of fiber is intriguing and merits further investigation in adequately powered clinical trials. These results are not surprising because there is wide variation in the types and the amounts of fiber supplementation in these studies. Moreover, the effects on UC vs CD and active disease vs a patient in remission can differ.

Finally, fiber supplementation may increase the number of bowel movements, leading to a higher clinical disease activity score while reducing inflammation.[131]

Interest in soluble fiber supplementation relates mostly to the potential to increase the production of SCFAs via microbial fermentation.[132] SCFAs modulate cell proliferation, histone acetylation/gene expression, and immune responses.[133] Studies of fecal samples from adults with vs without IBD reported decreased levels of butyrate and acetate, so SCFAs might protect against IBD.[134] Butyrate protects against colon cancer and may protect against the development of UC.[135,136]

The type of SCFA generated in the intestine depends on the type of fiber or substrate consumed as well as the type of bacteria metabolizing it.[137,138] Resistant starch leads to more butyrate whereas pectin leads to more acetate and proprionate.[139] Figure 2 shows the relative amounts of SCFAs produced in response to specific types of carbohydrates and bacteria. Bacteria of the Bacteroidetes phylum produce high levels of acetate and propionate, whereas bacteria of the Firmicutes phylum produce high amounts of butyrate.[137] Within the Firmicutes phylum, the 2 most important groups of butyrate producers are *F prausnitzii*, which belongs to the *Clostridium leptum* cluster, and the *Eubacterium rectale/Roseburia* species, which belong to the *Clostridium coccoides* cluster.[138,140–143] The taxa-specific variability in SCFA production from fiber may explain the observed variability between populations to generate SCFAs when consuming high-fiber diets.[144]

The anti-inflammatory effect of SCFAs is mediated through binding the G-protein–coupled receptor 43 (GPR43, also known as FFAR2 [free fatty acid receptor 2]).[133,145–147] Loss of GPR43 exacerbates inflammation in models of colitis, arthritis, and asthma.[148] GPR43 is expressed on the colonic epithelium and could mediate the effects of SCFAs on proliferation and barrier function.[149,150] GPR43 also is expressed on immune cells and can mediate anti-inflammatory effects of SCFAs.[148] In animal models of IBD, providing acetate in the drinking water reduced colitis. In multiple animal models of IBD, supplementation of the diet with fructooligosaccharides, soluble fiber, or resistant starches (prebiotic) has been shown to reduce intestinal inflammation, with the effect of increasing SCFA production and/or changing the microbiome.[151–158] In certain studies, supplementation with prebiotics was effective only when combined with specific diets.[158,159] Findings from these animal studies provide insight into the mechanisms of the synergistic effects between a patient's diet and fiber supplements. These studies highlight how SCFAs may reduce inflammation in patients with IBD, although there is little clinical evidence to support their use. Small clinical trials of the efficacy of SCFA enemas in patients with distal UC came to different conclusions.[160–162]

Supplementation With Omega-3 Fatty Acids

Not only is the Western diet high in fat, but it also is high in dietary omega-6 fatty acids as a result of over-reliance on vegetable oils, such as corn, safflower seed, and cottonseed, resulting in a high omega-6 to omega-3 ratio. Omega-6 fatty acids, especially arachidonic acid and possibly linoleic acid, tend to be inflammatory, whereas omega-3 fatty acids, such as α-linolenic acid from plants and eicosapentaenoic acid and docosahexaenoic acid from fish, have strong anti-inflammatory effects.[163]

Two identical placebo-controlled clinical trials showed no benefit of omega-3 fatty acid supplementation for maintenance of remission in patients with CD.[164] However, epidemiology studies found a stronger association between fat intake and the incidence of UC than CD. Consumption of a high ratio of omega-6 fatty acid, which is inflammatory, to omega-3 fatty acid, which is anti-inflammatory, has been associated with an increased incidence of UC.[22,23,165] Whether supplementation with omega-3 fatty acids would provide benefit for UC currently is unknown. Similarly, there have been few studies of the effect of a Mediterranean-style diet, with a higher ratio of omega-3:omega-6, in patients with IBD.

Long-chain PUFAs that are n-3, provided as fish oil or plant-based oils, have been shown in a variety of animal models to be protective of colitis.[166–172] Mechanisms include improved barrier function, decreased expression of cytokines, inhibition of inflammatory eicosanoids (such as prostaglandin E_2 and leukotriene B4), decreased adhesion molecule expression, and changes in the microbiome. Conversely, feeding mice a diet high in n-6 PUFAs (eg, linoleic acid), such as corn oil, exacerbated colitis and caused enrichment in the microbiota with Enterobacteriaceae, segmented filamentous bacteria, and Clostridia species, which induce inflammation.[173] These effects could be mitigated by addition of n-3 PUFAs. In certain studies, plant-derived α-linolenic acid showed greater anti-inflammatory properties than fish oil–derived omega-3 (n-3) PUFAs.[174]

Supplementation of the diet with extra-virgin olive oil, which is higher in mono-unsaturated fats than PUFAs, protected against inflammation in the dextran sodium sulfate model of colitis.[175,176] Studies also have examined varying the ratios of n-6 and n-3 PUFAs in animal models[167]; inflammation could be attenuated significantly if rats were pretreated for months with one third of fat from n-3 and the rest as n-6 (linoleic acid: α-linoleic acid of 2). In this study, however, animals received only 10% of their calories from fat, which is much less than the typical American diet. The issue with translating many of these studies to our patients is that animal work generally involves pretreatment of rats/mice with a particular diet and does not clarify whether these fats help in established inflammation. Table 3 describes the types of fat and their dietary sources.

Benefits of Vitamin D Supplementation

Low vitamin D has been studied as a risk factor for IBD and supplementation has been shown to have potential therapeutic benefit. In general, distance from the equator (ie, latitude) is correlated positively with the incidence of IBD.[22,177] It has been proposed that this association results in part from lower sun exposure, leading to lower levels of

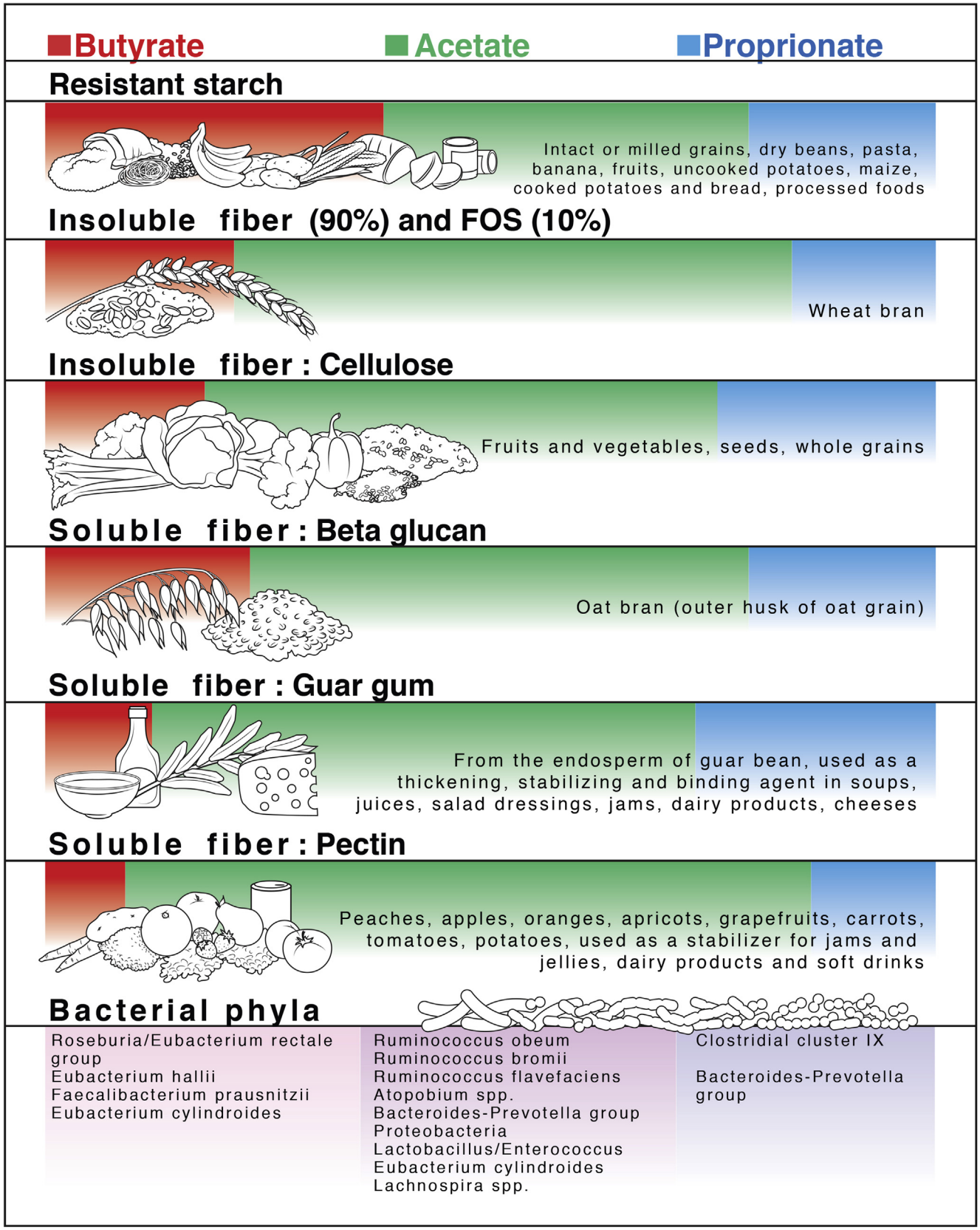

Figure 2. Generation of SCFAs from bacterial fermentation of fiber. Different types of fiber have different potentials to generate SCFAs, as do the microbiota that ferment the fiber sources.[139,218–221] Relative to other forms of fiber, resistant starch is preferentially fermented to butyrate, whereas pectin is preferentially fermented to acetate. Propionate production is relatively comparable among the different forms of fiber. Bacteria of the Bacteroidetes phylum produce high levels of acetate and propionate, whereas bacteria of the Firmicutes phylum produce high amounts of butyrate.[137]

Table 3. Types and Sources of Fat[225,226]

	Description			Recommended intake	Health impact
Dietary fats, recommendations, and health impact					
Total fat	Refers to all solid fats and oils Besides supplying calories, they help with the absorption of vitamins A, D, E, and K The chain length and saturation status determine their role in food and cooking as well as in health and disease risk			25%–35% kcal	If >35%, increased intake of SFA and energy. If <25%, then there is increased intake of carbohydrates and sugars, which, depending on the type, may exacerbate gastrointestinal symptoms (ie, fructose)
	Subtypes (name, abbreviation, nomenclature)	Animal Sources	Plant sources		
Solid fats: solid at room temperature					
SFA	LCT, >12 carbons Myristic acid (C14:0) Palmitic acid (C16:0) Stearic acid (C18:0) MCTs, 8–12 carbons Carprylic acid (C8:0) Capric acid (C:10:0) Lauric acid (C12:0)	Butter, lard, beef, pork, chicken fats, eggs	Palm oil Fully hydrogenated vegetable oils Cocoa butter Coconut oil Palm kernel oil Breast milk	<10% kcal	Increases inflammation High intake of saturated fat is associated with a higher risk of UC MCTs passively diffuse into the portal system (rather than lacteals) without requirement for modification similar to long-chain fatty acids In addition, MCTs do not require bile salts for digestion and thus are helpful in patients with IBDs with maldigestion Anti-inflammatory in animal models of IBD
Trans-fats	Elaidic acid (C18:1, t9) Vaccenic acid (C18:1, t11)	Butterfat, meat	Partially hydrogenated vegetable oils	<1% kcal Difficult to assess because foods with <0.5 g do not have to report it in the label Use of trans-fats in food products is banned in some states	Increases the risk for inflammatory diseases (cardiovascular disease, metabolic syndrome, or diabetes) Replacing these with PUFA is the most beneficial for health

Table 3. Continued

	Subtypes (name, abbreviation, nomenclature)	Animal Sources	Plant sources		
Oils: liquid at room temperature because of mono- and polyunsaturated fats, source of essential fatty acids and vitamin E					
Monounsaturated fatty acids	Have one double bond			<20% kcal, comprising most recommended total fat intake	Replacing SFA and carbohydrates with monounsaturated fatty acids lowers inflammatory responses related to cardiovascular risk Findings on the risk of IBD associated with intake of monounsaturated fatty acids are contradictory It is not beneficial if used to replace PUFA
	Palmitoleic acid (C16:1)	Product of palmitic acid metabolism in the body	Macadamia nuts, blue-green algae, sea buck		
	Oleic acid (C18:1), most abundant	Beef tallow, lard	Sunflower, canola, olive oil, peanut oil, avocado, almonds		
PUFAs	Have more than 1 double bond			Differs for each essential fatty acid	
	Long chain omega-3 (essential)			0.6%–1.2% kcal Use oils to replace solid fats when possible Increase the amount and variety of seafood, in place of poultry	Differs for each omega 3 Overall helps reduce inflammation Long-term intake of higher levels of omega-3 has been associated with lower risk of UC
	ALA, C18:3, most abundant		Flaxseed, walnuts, chia seeds, hemp seeds, canola oil	1.6 g/day for men 1.1 g/day for women	Anti-inflammatory in animal models of IBD
	Stearidonic acid (SDA, C18:4)		Genetically modified soybean oil	Not available	Not enough evidence to recommend in IBD
	EPA, C20:5 docosapentaenoic acid (DPA, C22:5) DHA, C22:6	Seafood, salmon, trout, herring, tuna, mackerel, sardines, anchovy, menhaden, seal meat, cod liver oil, krill oil, squid oil, or eggs, depending on diet	Algae functional foods (fortified): soy milk and juices, cooking oils	250–500 mg/day of EPA and DHA, as much as 3 g/day	EPA is an eicosanoid, which is a precursor for prostaglandins, thromboxanes, and leukotrienes EPA and DHA are precursors for resolvins and neuroprotectins, which are anti-inflammatory
	Long-chain omega 6 (essential)			5%–10% kcal Use oils to replace solid fats when possible	Differs for each omega-6 Some promote inflammation The American diet contains 11–25 times more omega-6 than omega-3

Table 3. Continued

Subtypes (name, abbreviation, nomenclature)	Animal Sources	Plant sources		
Linoleic acid, C18:2, most abundant		Corn, soybean, safflower shortening	17 g/day for men 12 g/day for women	It can be elongated to ARA and thus synthesized into a variety of inflammatory eicosanoids
γ-linolenic acid, C18:3	Borage, evening primrose oil, black currant seed oil		Not applicable	Precursor of ARA There is some evidence that it can reduce inflammation
ARA, C20:4	Meat, poultry, eggs		Not applicable	Eicosanoid, which is a precursor for prostaglandins, thromboxanes, and leukotrienes; all of which are involved in promoting inflammation, vasoconstriction, and platelet aggregation
Conjugated linoleic acid (C18:2), double bonds in adjacent carbon	Ruminant meat and dairy		Not applicable	Little evidence on the benefits of conjugated linoleic acid

ALA, α-linolenic acid; ARA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LCT, long-chain triglyceride; SFA, saturated fat.

vitamin D.[178] Studies of dietary intake of vitamin D also support this hypothesis. For example, in the Nurses' Health Study cohort, women with the predicted highest vitamin D levels had a significantly lower risk of CD.[179] Following this hypothesis, Jorgensen et al[180] tested the efficacy of dietary supplementation with 1200 IU of vitamin D3 daily for 12 months in a placebo-controlled randomized trial of patients with CD in remission. Supplementation with vitamin D3 increased the participants' vitamin D levels modestly and reduced the proportion of patients with clinical relapse from 29% to 13%. Vitamin D reduced the severity of colitis in mice.[181,182] Further trials of vitamin D supplementation are warranted.

Vitamin D has multiple potential beneficial effects on intestinal inflammation through a variety of mechanisms. Vitamin D2 (plant sources) and vitamin D3 (animal sources and skin exposure to ultraviolet light) is transported by the vitamin D binding protein to the liver, where it is hydroxylated into 25-hydroxyvitamin D—the marker used to define deficiency. 25-Hydroxyvitamin D undergoes 1-α hydroxylation in the kidney and extrarenal tissues including intestinal macrophages into the active form, 1,25-dihydroxyvitamin D. This active metabolite binds to the vitamin D receptor in many different tissues, including immune cells, modulating gene expression. Vitamin D deficiency or impaired signaling worsens colitis through multiple effects and alters the gut microbiome.[183–193] A recent study found that in healthy volunteers, vitamin D supplements changed the gut microbiome in the upper gastrointestinal tract, increasing bacterial richness.[194] Before patients take vitamin D supplements, they should be calcium-replete because 1,25 OH mobilizes calcium stores from bone.[184,186,187,195–200]

Curcumin

There has been renewed interest in the use of curcumin as a therapy for IBD. Curcumin is a phytochemical (diferuloymethane) derived from the spice turmeric, which is common in Indian foods. Curcumin has been used as a complementary therapy for many immune-mediated and inflammatory conditions. Curcumin has been shown to have multiple effects that theoretically would be beneficial in IBD such as inhibition of nuclear factor-κB, signal transducer and activator of transcription 3, p38 mitogen-activated protein kinase, vascular adhesion molecule expression, and inflammatory cytokine expression in mice and human systems.[201–212] In IL10-knockout mice, which develop colitis, dietary supplementation with curcumin prevented tumorigenesis and increased the diversity of the gut microbiota.[213]

Two small, placebo-controlled, randomized trials of curcumin supplementation have shown promise for patients with UC. In a trial of 50 patients with active disease despite full-dose mesalamine therapy, the addition of curcumin 3 g/day was superior to placebo in induction of clinical remission and clinical response, and reduced mucosal inflammation (assessed by endoscopy).[214] Similarly, at a dose of 1 g twice daily, in combination with sulfasalazine or mesalamine, curcumin was superior to placebo in maintaining remission in patients with UC during 6 months of follow-up evaluation.[215] Additional large-scale trials are needed to confirm these results. It may be important to let patients know, however, that these studies have used pure preparations of curcumin. Patients need to be careful when purchasing curcumin, as some formulations can contain additives.[216]

Emulsifiers, Barrier Function, and the Intestinal Microbiome

A common feature of many of the popular diets used by patients with inflammatory bowel disease is the need to purchase raw ingredients and prepare one's own food. One hypothesis is that the increasing incidence of IBD is related to the availability of commercially prepared foods. Emulsifiers have emerged as a common additive in foods but can promote colitis in the right context. Emulsifiers are complex molecules that contain hydrophilic and lipophilic sections used to keep fats in liquid suspension or water-soluble foods in a hydrophobic medium to keep these from separating in foods and improving the texture of foods. These are ubiquitous in processed foods, including organic foods. IL10 knock-out mice fed emulsifiers, carboxymethylcellulose, and polysorbate-80 had thinning of the colonic mucus layer, invasion of bacteria into the lamina propria, a change in gut microbiome, and worsening of colitis.[217] Although the same changes in mucus occurred in mice without disruption of *Il10*, there was no evidence of gastrointestinal pathology. These observations support the importance of interactions between genetic and dietary factors.

It is hard to ascertain what concentrations of emulsifiers are consumed by patients with IBD because the validated diet surveys, such as most food frequency questionnaires, do not provide a way to quantify this. It is notable that EEN formulas routinely contain emulsifiers and are effective in patients with IBD.

Future Directions

The rapid increase in the incidence of IBD and other immune-mediated diseases indicates a role for environmental factors in pathogenesis. There is mounting evidence from basic and clinical research studies that diet could increase the risk of IBD in susceptible individuals, and that modifying diet could alter risk or disease development. A number of clinical trials are underway or in the planning stages that hopefully will lead to new approaches to therapy that, either alone or in conjunction with our expanding pharmacologic approaches, can change the course of these diseases. Until then, patients should be advised to eat a well-balanced diet, such as the Mediterranean-style diet, avoiding processed foods or foods that they self-identify as worsening their symptoms. Patients who are committed to attempting to manage their disease predominantly through dietary modification should be counseled about the importance of assessing for resolution of inflammation in addition to symptoms.

Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of the article. To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.10.019.

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Conflicts of interest
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