# Diet as a Therapeutic Option for Adult Inflammatory Bowel Disease

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**KEYWORDS**

• Diet • Inflammatory bowel disease • Ulcerative colitis • Crohn's disease
• Specific carbohydrate diet • Low FODMAP diet • Exclusive enteral nutrition

**KEY POINTS**

- Diet can have an impact on inflammatory bowel disease (IBD) through multiple mechanisms.
- Exclusive enteral nutrition can be used to induce remission in adult Crohn's disease patients when corticosteroids are contraindicated.
- There is preliminary evidence to suggest efficacy of the Specific Carbohydrate Diet and the low FODMAP diet in IBD.

## INTRODUCTION

There is suspicion that the pathogenesis of inflammatory bowel disease (IBD) may involve the Western diet which is known to be low in fruits and vegetables and high in fat, n-6 polyunsaturated fatty acids (PUFA) and red/processed foods.[1] Westernization has become a global phenomenon, this may explain why there is an increasing incidence of IBD in countries where it was previously rare.[2] Diet has not traditionally been part of the gastroenterologist's armamentarium against IBD that affects adults. In fact, many patients are informed that diet likely does not play any part in the development or perpetuation of inflammation, and there is no one particular diet that has been shown to be effective in treating IBD. Patients are often told, "Eat what you can tolerate." Despite this refrain, approximately 40% of patients with Crohn's disease (CD) believe that diet can control symptoms and approximately 80% believe diet is important in the overall management of disease.[3] In addition, 40% of patients with IBD have attempted various diets, often without the assistance of a physician or dietician.[4] There are now mechanisms posited to explain how foods can be both

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proinflammatory and antiinflammatory. The resistance to adopting diet amongst gastroenterologists is multifactorial. It partly stems from lack of data demonstrating mucosal healing, which does not correlate well with perceived improvement in symptoms, particularly in CD. There is fear of causing more weight loss in a patient population that may already be malnourished, and implementing a dietary protocol may be too time consuming in a clinic setting. The belief that patients will jettison evidence-based medical therapy and instead adopt an unproven dietary intervention is particularly pervasive. These assumptions may be unsubstantiated. Diet deserves further consideration given the evidence assessed in this review.

It is not possible to fit all preclinical data and its potential implications into a single short article. It should be noted that current clinical data in dietary therapy for IBD is in its infancy, and randomized, clinical trials are largely lacking. In the absence of such data, we also present what we do in our clinics to generate a starting point or guide for clinicians who seek such information for their patients and for researchers coming into the field who are looking into new areas of investigation. Macronutrient associations with IBD are reviewed with an emphasis on the mechanistic basis behind how food contributes to intestinal inflammation. There are many diets described in the medical literature and lay press for IBD: the IgG-4 guided exclusion diet, the semivegetarian diet, the low-fat, fiber-limited exclusion diet, the paleolithic diet, the maker's diet, the vegan diet, and the low-carbohydrate diet.[5–11] This review predominantly focuses on exclusive enteral nutrition (EEN), which has the most robust evidence to support its use for inducing remission in CD, and the Specific Carbohydrate Diet (SCD), which perhaps already has the largest following among patients with IBD, and has some preliminary evidence published to support its efficacy. The Low FODMAP diet is also discussed because of its current widespread use in the IBS patient population and similar mechanism to the SCD.

## MACRONUTRIENT ASSOCIATIONS WITH INFLAMMATORY BOWEL DISEASE

The association of carbohydrates, protein, fats, and fiber with IBD has been investigated. The evidence primarily comes from epidemiologic studies looking at dietary associations before the onset of IBD with only a few studies looking at flares in existing patients with IBD. Several general and systematic reviews have been published summarizing these epidemiologic associations of diet and IBD development.[1,12–15] Many of the studies suffer from recall and selection bias, small sample size, and short follow-up periods. The data is often conflicting and inconclusive. The current body of literature tends to consider only the macronutrient in question and does not attempt to control for confounders, which understandably would be a difficult undertaking. It is also premature to dismiss diet as a therapeutic tool just because there is not a consistent association among macronutrients with development of IBD; it does not necessarily mean limiting a macronutrient cannot help to alleviate symptoms or inflammation once the disease process has begun.

The Western diet, high in carbohydrates and refined sugars, has been shown to induce dysbiosis in mouse models. Furthermore, a diet composed of highly processed sugars and carbohydrates can lead to obesity, which is associated with a proinflammatory state and increased bowel permeability. There have been several studies published from the 1970s through the 1990s investigating the association between various classifications of carbohydrates and CD, and the results have been conflicting.[16] Unfortunately, almost all of these were retrospective, case-control studies subject to recall and selection bias. Patients were often asked to remember diets eaten years before diagnosis, and the accuracy of this data has been called into question. Most studies also did not subdivide

carbohydrates into monosaccharides, disaccharides, oligosaccharides, and polysaccharides. There have been many studies investigating the association of sugar, that is, disaccharides and monosaccharides, with IBD with a trend toward showing a positive association, more so with CD, but also with ulcerative colitis (UC) to a lesser extent.[17–19] A much larger study by Chan and colleagues[20] addressed prior design weaknesses in a large prospective fashion using the EPIC-IBD study (Emerging Practice in IBD Collaborative) cohort from 8 European countries. The cohort of initially healthy subjects was given a validated food frequency questionnaire at recruitment to measure intake of carbohydrate, sugar, and starch during the previous year. Cases were identified as those subjects who subsequently developed IBD. Each case was compared with 4 controls who did not develop IBD. There was no association in univariate or multivariate analyses for carbohydrates or any dietary pattern with IBD risk when adjusted for total energy intake, body mass index, and cigarette smoking. However, in a subgroup analysis, there was a positive association between a "high sugar and soft drinks" pattern and UC when comparing the highest and lowest consumers, and the risk was present only if they also had low vegetable intakes.

Protein derived from meat, cheese, milk, fish, nuts, and eggs provides colonic bacteria with sulfate and sulfite, which are fermented to form hydrogen sulfide. This combination may have a negative effect on colonocytes by inhibiting butyrate oxidation. The association between protein intake and development of IBD has been studied. Reif and colleagues[21] used a preillness dietary questionnaire in newly diagnosed patients with IBD in Israel to show there was no statistically significant association with total protein intake. Consumption of eggs did show a positive association with UC but not CD, and there was no association with fish and both types of IBD. Another epidemiologic analysis of CD incidence in Japan showed a positive correlation with animal and milk protein intake, but there was no correlation with fish protein. There was a negative correlation with vegetable protein.[22] A prospective cohort study of middle-aged French women showed an association between risk of IBD and total protein intake, specifically with meat and fish but not eggs or dairy.[23]

Dietary fat has a substantial theoretic basis for playing a role in both driving and ameliorating inflammation in the intestine depending on the subtype. n-6 PUFAs such as linoleic acid are precursors for arachidonic acid (which itself is a precursor of prostaglandins and leukotrienes), and dietary omega-3 PUFA is a competitive substrate for n-6 PUFA metabolism.[24] Docosahexaenoic acid (DHA) can alter expression of cyclooxygenase-2 in the gastrointestinal (GI) tract and thus inhibit LTB4/PGE2 release and inhibit angiogenesis.[25,26] Lipoxins derived from n-6 PUFA and resolvins derived from omega-3 PUFA are antiinflammatory and can inhibit dendritic cell function and LTB4 production.[27,28] The omega-3 PUFA can inhibit T-cell proliferation and decrease antigen presentation,[29,30] and can modulate chemotaxis of immune cells by inhibiting IL-8 and ICAM-1 expression[25,31]; reduce inflammation via the nuclear factor-κB and peroxisome proliferator activated receptor alpha pathways[32,33]; and can bind to receptors such as GPR20 (G-protein–coupled receptor) causing antiinflammatory effects in macrophages.[34] Long-chain triglycerides can produce increased lymphocytes fluxes and enhanced proliferative response in intestinal lymph,[35] whereas medium chain triglycerides can suppress IL-8, a neutrophil chemottractant expressed in high levels in actively inflamed mucosa of both CD and UC.[36,37] Fats can also alter the microbiome,[38–40] which can lead to upregulation of Toll-like receptor and NOD-mediated inflammation,[41–43] as well as increased intestinal permeability from altered tight junction proteins.[44,45] Milk-derived saturated fats can alter the bile acid composition and allow for growth of sulfate-reducing bacteria such as *Bilophila wadsworthia*, which produce toxic hydrogen sulfide and can aggravate colitis in IL-10 knockout

mouse models.[46,47] Dietary fat can activate mast cells, which can indirectly affect gut permeability via regulation of transcellular and paracellular transport.[48,49]

Studies of the association of fat with IBD have similar methodologic shortcomings. Most studies have been retrospective case control, are subject to bias in determining pre-illness diet and fail to account for confounders.[1,50–54] Although some studies have shown an association of CD with total fat, monounsaturated fatty acids, total PUFA, total omega-3 fatty acid, and omega-6 fatty acids, there are also other studies that show no such association.[23,55–59] For UC, there have been associations with total fat, MUFAs, total PUFA, and omega-6 fatty acids[21,23,52,56,60]; however, there are studies that show no such association.[59,61] Negative and positive associations with omega-3 fatty acids have been reported.[52,53,56] Two studies have shown a statistically significant decrease in the risk of UC with high intake of DHA.[52,53] One of the only prospective studies published used the Nurses' Health Study cohort and found that there was no association of total fat, saturated fat, total monounsaturated fatty acids, or total PUFA with risk of IBD.[62] There was an association with high intake of transunsaturated fatty acids and UC but not CD. There was an inverse association between long-term intake of omega-3 PUFA, particularly DHA and EPA, and risk of UC but not CD. Unfortunately, randomized, controlled trials have shown that using fish oil or omega-3 PUFA in those already diagnosed with IBD is not a very effective strategy.[63,64]

A lower intake of fiber may change the microbiome and lead to diminished production of short-chain fatty acids (SCFA),thereby reducing their expected immunoregulatory effects.[65] SCFAs, particularly acetate and propionate, are the only known ligands for a G-protein–coupled receptor GPR43 expressed on neutrophils, eosinophils, and activated macrophages. Another SCFA butyrate is the main energy source for colonocytes and helps to maintain the epithelium. SCFAs also inhibit histone deacetylases and can inhibit nuclear factor-κB. Certain soluble plant fibers have also been shown to inhibit translocation of *Escherichia coli* across M-cells in Peyer's patches.[66] The retrospective study published by Reif and colleagues[21] showed that fiber had a negative association with IBD, although this did not reach statistical significance. The prospective Nurses' Health Study cohort study showed an association between the highest quintile of cumulative dietary fiber intake and reduced risk of developing CD but not UC. Fiber from fruits and vegetables reduced risk of CD, but this was not true for fiber from whole grains or legumes.[67] Li and colleagues[68] published a metaanalysis of case-controlled studies that showed an inverse relationship between vegetable consumption and UC but not CD. A subgroup analysis did show an inverse relationship between vegetable consumption and CD only in European studies, but not Asian studies. There was an inverse relationship between fruit consumption for both UC and CD. Although the overall negative association between fiber intake and IBD is relatively consistent, these conclusions have been questioned in CD; it is possible that patients could have intentionally limited fiber during a prolonged, symptomatic period preceding the official diagnosis of CD.[69]

## VITAMINS AND MICRONUTRIENTS

The reader is referred in Fayez K. Ghishan and Pawel R. Kiela's article, "Vitamins and Minerals in IBD," for a discussion of vitamins and trace elements in this issue. Briefly, vitamin D is a fat-soluble vitamin that, in addition to regulating bone, calcium, and phosphorus metabolism, can regulate the adaptive and innate immune systems.[70,71] Polymorphisms of the vitamin D receptor have been identified as a genetic factor in patients with IBD. Patients with IBD, particularly CD, are more likely to be vitamin D deficient. A higher serum level is associated with improved outcomes.[72–77] However,

vitamin D deficiency can be a cause or consequence of IBD, and therapeutic trials in CD have yielded only modest results.[78–80] A low vitamin D level may also be a proxy for northern latitude, reduced ultraviolet light exposure, and a disrupted circadian rhythm, which may be associated with dysbiosis and increased IBD-related hospitalizations.[81,82] Abnormalities in vitamin D absorption have also been identified, especially when IBD is active, suggesting that simple megadose supplementation strategies may not be adequate or appropriate in active disease, especially in those who are not calcium replete.

Zinc is an essential micronutrient and deficiency has been associated with excessive loss of GI secretions from chronic diarrhea or fistula drainage. It is an enzyme cofactor involved in wound healing, cellular immunity, and growth.[83] The prevalence of zinc deficiency in IBD ranges from 15% to 40%.[84–87] A low serum zinc level has also been associated with hospitalization, operation, or other complications in patients with CD.[88] Patients with UC with low serum zinc levels also have increased hospitalizations and a trend toward increased complications. The accuracy of serum zinc levels has been called into question because acute illness can diminish plasma levels and shift zinc stores into the liver.[83] Despite this limitation, serum zinc levels may still have clinical value; normalization those in patients with IBD who are deficient has been associated with improved outcomes.

Other common deficiencies in IBD, more notably in CD than UC, include vitamin $B_1$, $B_6$, $B_{12}$, D, K, folic acid, selenium, and iron.[89] There is some evidence to suggest that oral iron may modify the microbiome, and enable adherent invasive *E coli* penetration and survival in macrophages, and is associated with increased intestinal inflammation,[90,91] though such effects have not been associated with intravenous iron formulations.

Taking into account this evidence, we currently recommend a multivitamin with trace elements to our patients with IBD, especially those on dietary therapy and following restricted diets. We do measure vitamin levels once a year and additionally replace the deficient trace element or vitamin as necessary based on the results.

## FOOD ADDITIVES

A significant variety of food additives that have a GRAS (Generally Regarded As Safe) status by the US Food and Drug Administration are being used in common foods and could potentially have an impact on IBD. Although few clinical studies have been conducted, we generally recommend avoidance of food additives in patients with IBD because substances that have been shown to be safe in a healthy individual may not be so in those individuals who are genetically and/or environmentally susceptible to GI inflammation. Additionally, most food additives do not enhance the nutrient content of food and are not essential components of a healthy diet. Excluding them is not expected to bring about any physical harm and has the potential advantage of replacing processed foods with whole and naturally occurring foods that have higher nutritional value.

One such food additive is carrageenan, which usually is used as a thickening, stabilizing, texturizing, or emulsifying agent in a variety of foods, even those that are regarded as “healthy” by the public. For example, dairy products such as chocolate milk; nondairy milks that are derived from soy, rice, and nuts like almonds; cottage cheese, mayonnaise, sour cream, cooking cream, whipping cream, ice cream; lunch meats and rotisserie chicken; and even infant formula can have added carrageenan. Estimates of intake can vary from 20 mg to several grams per day with an estimated mean of 250 mg/d.[92,93] Because carrageenan is derived from seaweed, it is

considered “natural”. Evidently the label ”natural” on food packaging does not guarantee a lack of food additives. Preclinical evidence clearly demonstrates that carrageenan can cause colitis when given to animals in sufficient quantities in multiple models (eg, guinea pigs, rats, mice), which share similarities with human IBD[92,93]. This inflammation can be ameliorated by antibiotics and is partially driven by the gut microbiota,[94,95] but inflammatory signals can also occur in the absence of gut microbiota.[95] Multiple in vitro studies using human colonic tissues also attribute inflammatory effects to carrageenan.[92] In a pilot, randomized, placebo-controlled clinical trial, 12 patients with UC were maintained on a carrageenan-free diet and were administered either placebo or carrageenan-containing capsules at a low dose (200 mg/d, which is less than the estimated intake in the US diet). There were no relapses in those patients with UC who were carrageenan free and taking placebo capsules three patients taking carrageenan capsules had earlier relapse associated with elevated fecal calprotectin levels and elevated inflammatory cytokines such as IL-6.[93]

Another ubiquitous additive is maltodextrin which is used as a thickener. It is derived from corn starch and other starches and therefore is considered natural. Its use over the past few years seems to have increased and is correlated with the increase in the incidence of CD.[96] It is found in many packaged foods (about 60% of all items), sugars, candy, beer, baby formula, cereal and health bars, nearly all flavored chips, and similar snacks. Maltodextrin has been shown to promote colonic inflammation in the form of necrotizing enterocolitis in young piglets and promotes growth of *E coli* in the ileum.[96] In humans, patients with IBD seem to have a microbiome enriched in the metabolism of maltodextrin. *E coli*, including adherent invasive *E coli* strains from patients with CD, form thicker biofilms and enhanced adhesion in the presence of maltodextrin. This suggests that this compound may be increasing the colonization of pathogenic bacteria in IBD.[96,97] Furthermore, recent studies suggest that maltodextrin may be deregulating cellular and mucosal barrier–related host antibacterial defenses.[96]

Sodium caprate is a medium-chain fatty acid constituent of milk fat that has been shown to increase paracellular permeability of the ileum in CD via dilation of tight junctions and disassembly of perijunctional filamentous actin.[98] Polysorbate 80 and carboxymethyl cellulose have been shown to induce colitis in IBD mouse models.[99,100] Polysorbate 80 is an emulsifier found in processed foods that enhances *E coli* translocation across M cells and human Peyer’s patches in CD.[66] Carboxymethyl cellulose is found in industrialized milk products, breads, sauces, and sausages, and has been shown to enhance bacterial adherence to the epithelium and distend spaces between villi, leading to bacterial infiltration in IL-10 gene-deficient mice.[94,100]

## DIETS FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

### *Exclusive Enteral Nutrition*

EEN is as effective as steroids in inducing remission in children with CD.[101] Enteral feeds are also effective in the adult CD population, but a meta-analysis showed that they were inferior to corticosteroids for inducing remission.[102] EEN has not been shown to be effective for UC.[103] EEN is the first-line therapy for CD in Asian countries. Its mechanism of action is not clear, but it may restore the epithelial barrier and correct dysbiosis. Other studies have shown that EEN paradoxically decreases *Faecalibacterium prausnitzii* (a beneficial bacterium) and bacterial microbiota diversity (which are well-recognized changes that characterize the dysbiotic microbiome in IBD). EEN-associated fecal microbiota seems to be farther away from that of a healthy

individual in compositional studies; therefore, it is plausible that EEN-related microbiota improvements are only in depleting the gut microbiome of potentially harmful bacteria rather than restoring a totally healthy microbiome. EEN may also work by excluding certain dietary components known to increase intestinal permeability and adherence of adherent invasive *E coli*.[104,105] Open-label trials have demonstrated endoscopic healing, decreased mucosal cytokine production, and improved quality of life in patients with CD.[106–108]

Enteral feeds are classified based on their nitrogen content.[102] There are 3 types: elemental (amino acid based), semielemental (oligopeptide based), and polymeric (whole protein based). Elemental and semielemental formulas are hypoallergenic; the amino acids or chains of amino acids are not long enough for antigen recognition or presentation. The nitrogen source likely is not relevant to therapeutic efficacy; there has not been a statistically significant difference in efficacy between different formulations.[102,109] A nonsignificant trend favoring very low fat and/or very low long chain triglyceride content has been noted.[102] The main criticism regarding the use of enteral nutrition is its lack of palatability; however, this mainly applies to elemental formula, which has a bitter aftertaste. Polymeric formulas, which again are noninferior, may be more palatable and could be used as an alternative to steroids for inducing remission in adults. There remains the concern regarding insufficient caloric intake when a patient drinks EEN by mouth versus using a nasogastric or gastrostomy tube. EEN may additionally have insufficient vitamins and minerals such as vitamin D and zinc for patients with IBD on steroids and with diarrhea, respectively.[110] EEN has successfully been used sequentially and also in combination with various exclusion diets to induce and maintain remission, but this method requires more research before it can be recommended routinely.[111–113] Yamamoto and colleagues[114] published a study demonstrating partial enteral nutrition with a low fat diet was associated with decreased postoperative recurrence of CD. There are also data to suggest that partial enteral nutrition supplementation can decrease loss of response to infliximab.[115,116]

There are probably multiple mechanisms through which dietary substances work to help IBD and these can vary from antigenicity of the foods to nutrient repletion. Paradoxically, the changes to the microbiome induced by EEN are not toward enriching bacterial diversity; nevertheless, this treatment can be effective in patients.

### *The Specific Carbohydrate Diet*

The SCD is one of the most popular diets for IBD available in the lay press. It was initially developed by gastroenterologist Dr Sidney Haas in 1951 and later popularized by biochemist Elaine Gottschall in the book *Breaking the Vicious Cycle: Intestinal Health through Diet*.[117,118] Gottschall's theory is based on the assumption that carbohydrates have the most influence on the microbiota's maintenance and growth. She states that patients with IBD have small bowel mucosal injury, which may be due to bacterial overgrowth leading to excessive fermentation of undigested carbohydrates. This leads to the formation of lactic, acetic, or other organic acids, which also may cause further injury to the small bowel mucosa. As a defense mechanism, the small intestine produces mucus that prevents the brush border intestinal enzymes from making contact with disaccharides and amylopectin, causing more maldigestion. Gottschall states, "The diet is based on the principle that specifically selected carbohydrates, requiring minimal digestive processes are absorbed and leave virtually none to be used for furthering microbial growth in the intestine." It is worth noting that, despite Gottschall's claim, there is no small bowel injury known to commonly occur

with UC besides that of backwash ileitis and rarely panenteritis following colectomy. Gottschall likens the mechanism of action of the SCD to exclusive elemental nutrition because the principal carbohydrates in both are monosaccharides. However, as noted, the classification of elemental formula is based on nitrogen content and not carbohydrate content. Vivonex Plus Essential and Peptamen, both manufactured by Nestle (Vevey, Switzerland) as elemental formulas, have maltodextrin and cornstarch listed as ingredients, which are not monosaccharides. Additionally, elemental and polymeric formulas are effective for only CD when the SCD claims to be effective for both UC and CD.

Essential features of the SCD are as follows. It is primarily a modified carbohydrate diet, which allows consumption of monosaccharides and excludes disaccharides, and most polysaccharides (such as linear or branch-chained multiple sugars or starches). The diet is supplemented with homemade yogurt, fermented for 24 hours to free it of lactose. Recommended cultures include *Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, and *Streptococcus thermophile.* The SCD allows almost all fruits, vegetables containing more amylose (a linear-chain polysaccharide, rather than amylopectin, which is a branch-chained polysaccharide), nuts, nut-derived flours, low lactose dairy such as dry curd cottage cheese, meats, eggs, butters, and oils. It excludes sucrose, maltose, isomaltose, lactose, all true and pseudograins and grain-derived flours, potatoes, okra, corn, fluid milk, soy, and cheeses containing high amounts of lactose, as well as some food additives and preservatives. The SCD may be one of the most difficult diets available because it is several degrees more restrictive than the gluten-free diet and the author advises "fanatical adherence." Food labels for prepared foods are not to be trusted unless the company offers a letter in writing stating the ingredients are SCD legal. Juices from concentrate or with "natural flavors" are not allowed because Gottschall asserted these could still have illegal sugars added that are not listed on the label. Even small amounts of lactose, sucrose, or starch that can be fillers in medications or supplements are typically considered illegal. If a medication is essential, however, it is still allowed even with illegal ingredients. An online survey showed that 56% of patients continued to take medications along with the SCD.[119]

Several studies have been published that suggest that SCD may be effective in IBD and most clinical observations have been in pediatric disease. These studies are reviewed in Erin R. Lane and colleagues' article, "Dietary Therapies in Pediatric Inflammatory Bowel Disease: An Evolving IBD Paradigm," elsewhere in this issue. In adults, our group demonstrated that the fecal microbiome of patients with IBD following the SCD may be different and more biodiverse than patients with IBD following a Western diet based on 16srRNA analysis of fecal microbiota composition.[120,121] We also published a case series of 50 patients with IBD on the SCD and showed that SCD followers had decreased symptom scores and a high quality of life.[122] The majority of these patients had colonic CD and some were able to maintain clinical remission using diet without maintenance medications. There is also evidence that following the diet is associated with improvements in the erythrocyte sedimentation rate, C-reactive protein, calprotectin, and Lewis score on capsule endoscopy; nevertheless, concomitant medication use in some of these patients is a potential confounder.[123–125] Results of an online survey of patients with IBD following the SCD hints at the possibility of the diet helping to prevent IBD complications and hospitalizations, although this is only patient reported and needs further study prospectively.[119]

Although Gottschall recommends strict adherence to the SCD, there are some data to suggest some liberalization may be possible with continued maintenance of

remission,[124] and patients in our published case series and in our clinical observations have tolerated and done well with some of the "illegal" food items on an individual basis. This suggests that SCD is a starting point for patients with IBD to explore their individual diet–disease relationship, especially in the maintenance phase. Patients could potentially conduct trial and error experiments on themselves with the aid of a health provider who can follow how they respond with objective assessments. Unfortunately, the appropriate time from diet initiation to liberalization is not clearly defined. Gottschall recommends staying on the SCD for at least 1 year after the last symptom has disappeared, but there are no formal recommendations regarding how to liberalize from there. In our clinics, we suggest that an attempt at liberalization should occur preferably after the disease is well-controlled and is in the inactive phase. This allows the patient and the clinician to be able to better delineate clinical food–symptom correlations. We also recommend that during liberalization foods be introduced one at a time in small quantities over weeks rather than a few days.

The Anti-Inflammatory Diet for IBD is based on the SCD, encourages the use of omega-3 fatty acids, utilizes food-based prebiotics and probiotics, and uses a graded approach of food introduction based on food textures. The Anti-Inflammatory Diet for IBD does include otherwise SCD "illegal" foods such as oatmeal, soy milk, flax and chia seeds, fenugreek, and hummus, although it still has been successful in reducing Harvey Bradshaw Index in CD and the Modified Truelove and Witts Severity Index in UC symptomatically.[126] Currently there is an ongoing trial that is looking at the effectiveness of the SCD versus a Mediterranean-style diet in active CD funded by the Patient-Centered Outcomes Research Institute.[127]

There are also some practical considerations when implementing the SCD. The SCD is not simply a list of "legal" and "illegal" foods. There are many other rules regarding which foods to eat depending on presence of symptoms and duration of the SCD. For example, it would be incorrect for a patient with active cramping and diarrhea to start the SCD eating a salad, even if the ingredients of a salad were all technically "legal." With active diarrhea, fruits, raw vegetables, eggs, and large amounts of honey should be avoided. A patient is supposed to start off the SCD with the introductory diet consisting of dry curd cottage cheese, yogurt, eggs, apple cider or other juice, homemade gelatin, chicken soup, and broiled fish or beef patty for 2 to 5 days. From there, the allowed foods are slowly liberalized. The efficacy of the SCD should be judged at the earliest after 1 month of adherence. We recommend a formal assessment of symptoms using appropriate symptom scores and also markers of inflammation including C-reactive protein, fecal calprotectin, and possibly colonoscopy if clinically appropriate. If there are no improvements in symptoms and/or inflammation, it may be reasonable to discontinue the SCD. Hwang and colleagues[110] discussed the nutritional deficiencies that can possibly occur with the SCD including folate, thiamine, vitamin $B_6$, vitamin D, vitamin C, vitamin A, calcium, and potassium deficiencies, although this is purely speculative. It is reasonable for the patient's diet to be monitored by a dietician to assess for such potential deficiencies.

The SCD is not an approach suited for every patient with IBD. It may not be practical for a CD patient with a significant amount of small bowel strictures because it can tend to be higher in fiber and may lead to an obstruction (although some of our patients have been able to juice to get part of the nutritional contents of fruits and vegetables rather than directly consuming them raw). Because most of the food consumed on SCD is prepared from scratch, ready access to fresh produce is necessary, and it may not be possible to follow the SCD if a patient lives in a "food desert" without access to transportation to a grocery or produce store that has reasonable pricing. At least a high

school education is likely necessary to be able to read the *Breaking the Vicious Cycle* book, implement the protocol, and trouble shoot the diet using online message boards. If eating out is an integral part of a patient's social life and/or happiness, the SCD may be too onerous, especially if disease activity is absent or mild, and other medical therapy is efficacious. In our experience, patients who have failed multiple medical therapies are more likely to find the restrictions of the SCD acceptable and worth the sacrifice, even though this patient population may not necessarily be the most likely to respond. We believe most patients with IBD should be notified that this and other exclusion diets exist so that they can make a personal decision if diet is the right strategy according to their circumstances. We also believe that all exclusion diets, including the SCD, should be adjunctive to clinically appropriate medical therapy.

Unfortunately, the nature of the SCD protocol makes some degree of orthorexia nervosa unavoidable. This syndrome is characterized by obsessive focus on food choice, planning, purchase, preparation, and consumption of food with the belief that this can control or reverse disease. The SCD's improvement in symptoms can increase quality of life and the restrictions can also decrease it. The gastroenterologist and patient should be vigilant in monitoring the net effect of this to determine if the SCD is helping and worth continuing. Cooking and preparing meals can be difficult for a patient who has significant disease activity, so family support is an important factor associated with success in implementing SCD in our experience. Websites do exist that offer ready-made food products that are SCD legal for purchase. If a patient has the financial means to pay for these foods, these websites can help to significantly reduce the time burden of cooking.

### *The Low FODMAP Diet*

Many patients in the active phase of IBD and also those in remission can have functional symptoms similar to those seen in IBS patients for whom the low FODMAP diet has been promoted. The theory behind the low FODMAP diet is partially similar to that of the SCD in that it tries to exclude poorly absorbed short-chain carbohydrates that can be fermented by intestinal bacteria resulting in gas, bloating, abdominal pain, and change in bowel habits. FODMAPs are osmotically active and can lead to more fluid delivery to the colon. The low FODMAP diet specifically limits fructose, lactose, fructans, galactans, and polyols, and has been shown to be effective in improving IBS symptoms.[128] IBS is prevalent in the IBD population; one study showed that 57% of patients with CD and 33% of patients with UC experienced IBS symptoms in the preceding week.[129] There is limited evidence that the low FODMAP diet may improve IBS symptoms in patients with IBD. Gearry and colleagues[130] published an uncontrolled study of 52 patients with CD and 20 patients with UC with inactive disease and showed approximately one-half had some response to the low FODMAP diet. The diet was effective in alleviating abdominal pain, diarrhea, bloating, and gas. There was a trend toward more constipation in patients with UC, but this difference was not significant. There is a theoretic concern that the low FODMAP diet excludes inulin, fructooligossacharides, and fructose, which are known prebiotics. This exclusion could potentially exacerbate the dysbiosis that is known to already exist in the IBD population; however, at this time there is no evidence that this does indeed occur.

Differing from the SCD, the low FODMAP diet limits certain sources of fructose (honey apples, dates, watermelon, and other fruits), fructans (onions, garlic), and galactans (beans, lentils, and legumes) that are otherwise allowed on the SCD. Another notable difference is that the low FODMAP diet allows use of sucrose, which is one of the main exclusions of the SCD. Overall, the low FODMAP diet is less restrictive because it is

also not as exclusionary of additives and preservatives, which makes eating at restaurants and eating processed foods easier. The dietary exclusions also tend to be more temporary, because reintroduction of FODMAPS after several weeks of strict adherence is encouraged.

### *Our Own Recommendations for an Inflammatory Bowel Disease Diet*

We have previously developed and tested an "anti-IBD" diet that restricts disaccharides; wheat and other grains except white rice; PUFAs and most saturated fats; processed meats and large amounts of red meats; and is devoid of all additives and preservatives. Additionally, foods that are rich in protease inhibitors (raw foods, nuts and seeds, uncooked root vegetables, etc) were reduced or avoided, and foods were advised to be cooked (with all methods except rapid high-heat such as charring), because cooking with heat exposure reduces the protease inhibitor content of foods. Protease inhibitors naturally occur in plants to neutralize digestive proteases in the intestinal lumen of the consuming person as well as those released by pests of the plant, and are a survival/defense mechanism of the plant. However, in the GI tract, neutralization of digestive proteases by large amounts of protease inhibitors within the food allows for bacterial toxins to survive small bowel transit and potentially create inflammation in the distal parts of the GI tract. One such example is a disease called pigbel, which is a clostridial bacterial toxin related to acute or chronic necrotizing enteritis initially noted in the Papua New Guinea Highlanders who consume large amounts of foods that contain trypsin inhibitors.[131]

In this diet, we encourage the consumption of all vegetables and fruits, replacement of red meat with fish high in omega 3 fatty acid content and chicken, and encouraged cooking with monounsaturated fats such as olive oil, which have been reported to be antiinflammatory. Coconut oil, which has been shown to have some antiinflammatory and anticarcinogenic properties, was the saturated fat alternative for the patients (especially for baking), and other fats were discouraged. Contrary to other diets limiting all grains, white rice was allowed, because very little of it is expected to be remaining in the distal small bowel or colon.

We evaluated this diet as a maintenance treatment in adult patients with CD in a randomized, placebo-controlled, double-blind pilot study. We enrolled 54 subjects with quiescent CD, with medical induction of remission. Patients were randomized into 3 groups: (1) a prebiotic fructooligosaccharides intervention (receiving active fructooligosaccharides supplement + a placebo diet); (2) placebo (receiving placebo supplement + the placebo diet); and (3) diet intervention (receiving placebo supplement + the anti-IBD diet). The subjects were followed until either they had a flare (defined as the need for a new medication for treatment or a rise in the Crohn's Disease Activity Index) or up to 12 months. Flares, quality of life, compliance with treatments, and 16s DNA-based microbiome composition in colonic biopsy samples before and after the interventions were assessed. The results demonstrated that this anti-IBD diet resulted in a reduction of the flares compared with placebo and a fructooligosaccharides supplement with a moderate effect size (in fact, none of the subjects flared in the diet intervention group during the study); quality of life did not decline with the interventions; and beneficial bacteria such as *Roseburia* (which produce short chain fatty acids and are noted to be lower in patients with IBD compared with healthy individuals in multiple microbiome studies) increased at the end of treatment.[132]

### *Other Diets for Inflammatory Bowel Disease*

Several other diets have been described both in the medical literature and lay press for the treatment of IBD. A summary list of food exclusions is noted in **Table 1** for each of

**Table 1**
**Food exclusions for diets**

| Food Restrictions | Grains | Meat | Dairy | Fats and Oils | Vegetables | Fruits | Beans and Legumes | Nuts and Seeds | Beverages | Sweeteners | Miscellaneous |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SCD | All excluded | Processed meats | Lactose-containing dairy (ie, milk from animals, soft cheeses) | Margarine, but all other permitted | Potatoes, yams, parsnips, okra, corn, none in cans or jars | No additional sweeteners except honey | Chick peas, bean sprouts, soy, mung, fava, garbanzo beans; other beans need to be soaked and drained | Shelled peanuts, nuts in salted mixtures | Juice from concentrate, juices packed in boxes, lactose-free milk or with lactase enzyme, fortified wines | Refined sugar, molasses, corn or maple syrup, agave | Cornstarch, arrowroot, tapioca, sago starch, chocolate, carob, agar agar, carrageenan, guar gum, pectin, soy sauce |
| [a]Low FODMAP diet | Chicory root, inulin, with HFCS, wheat, flour tortillas, rye | No high FODMAP sauces or with HFCS | Buttermilk, cottage cheese, ice cream, sweetened condensed or evaporated milk, soft cheeses, sour cream, whipped cream, and yogurt | None | Artichokes, asparagus, beets, leeks, broccoli, Brussel sprouts, cabbage, cauliflower, fennel, mushrooms, okra, summer squash, garlic, onion | Avocado, apples, applesauce, apricots, dates, canned fruit, cherries, dried fruits, figs, guava, lychee, mango, nectarines, pears, papaya, peaches, plums, prunes, persimmon, watermelon | Green beans, snow peas, blackeye peas, split peas, haricot verts, kidney beans, mung beans, soy beans | Pistachios, cashews, coconut milk | Any with HFCS, high FODMAP fruit/vegetable juices, fortified wines | HFCS, agave, honey, molasses, sorbitol, mannitol, isomalt, xylitol | Soy products, carob powder |
| IgG-4 guided exclusion | Wheat, rice | Shrimp, egg, pork, beef, cod fish, lamb, chicken | Milk, cheddar cheese | None | Potato | Tomato | None | Peanuts | None | None | Yeast, soya |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Semivegetarian diet | Bread, white rice (brown allowed) | Minced or processed meat, fish allowed once a week, meat once every 2 wk | Cheese | Margarine, butter | None | None | None | None | Carbonated beverages, juices, moderate or no alcohol | Desserts | Fast food, no eating between meals |
| [a]LOFFLEX Diet | Wheat, oats, rye, barley | Pork, ham, bacon, eggs, processed meats | Cow, goat, sheep milk products, ice cream | Corn oil, vegetable, oil, nut oil, margarine, butter | Corn, onions, sweet corn, tomato | Citrus fruit, apples, bananas, dried fruit, and marmalade | Peas, beans, and lentils | Nuts and seeds | Tea, coffee, fruit squash, carbonated drinks, citrus juice, apple juice, tomato juice, alcohol | | Pies, pâté, yeast, salad cream/ dressings, mustard, soy sauce |
| Paleolithic diet | All grains | Processed meats | Milk from animals, cheese, ice cream | Butter | Corn, starchy tubers, manioc, potatoes, sweet potatoes, tapioca pudding, yams | | All beans, peas, lentils | Peanuts | Soda, colas, fruit drinks, candy | Sucrose | Miso, tofu |
| [a]Maker's diet | All grains | Pork (including sausage), bacon, ham, ostrich, emu, imitation meat, shellfish, eel, catfish, squid, fried or breaded fish or chicken, lunch meat, imitation eggs | Soy milk, rice milk, almond milk, cow's milk | Safflower, sunflower, cottonseed, soy, canola, corn oils; margarine, lard, hydrogenated oils | Corn, sweet and white potatoes | Apples, bananas, apricots, grapes, melon, peaches, oranges, pears dried fruit, canned fruit | Soy, black, navy, garbanzo, kidney, white, and lima beans | Honey-roasted nuts, macadamia nuts, hazelnuts, peanuts, cashews, walnuts, pecans brazil nuts, peanut butter, nuts or seeds dry roasted in oil | Alcoholic beverages, fruits juice, soda, chlorinated tap water, preground commercial coffee | Sugar, heated honey, artificial sweeteners, sorbitol, xylitol | Tofu, protein powder from rice, soy, whey or cow's milk |

(*continued on next page*)

**Table 1**
**(*continued*)**

| Food Restrictions | Grains | Meat | Dairy | Fats and Oils | Vegetables | Fruits | Beans and Legumes | Nuts and Seeds | Beverages | Sweeteners | Miscellaneous |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [a]Vegan diet | All grains | All meat | All dairy | Heated and fried oils | Raw vegetables (except juiced), onion, radish, mustard green, garlic, chili pepper | Citrus fruits, pineapples, peaches, nectarines, berries (except blueberries), tomatoes, tomatillos, avocado | All legumes, soybeans | All nuts and seeds | Coffee, caffeinated teas, pasteurized drinks, soft drinks, sports drinks | Sucrose | Salt, spices, fermented products, chemical additives and preservatives |
| Low-carbohydrate diet | Limit bread, pastries, cereals, grains, pasta | N/A | N/A | N/A | Limit potatoes | Limit sweet fruits | N/A | N/A | N/A | Limit sweetened foods | Limit total carbohydrates to <72 g in 24 h |

*Abbreviations:* HFCS, high-fructose corn syrup; LOFFLEX, low-fat, fiber-limited exclusion; N/A, not applicable; SCD, Specific Carbohydrate Diet.

[a] These diets have foods listed that are initially excluded but later on there is some liberalization.

the exclusion diets; however, the many subtleties of their respective protocols are beyond the scope of this review.

### *The IGG4 exclusion diet*

Gunasekeera and colleagues[5] published a randomized, controlled trial of an IgG4-guided exclusion diet for CD. IgG4 titers were drawn for the foods noted in **Table 1**. The foods corresponding with the 4 highest IgG4 titers were eliminated for 4 weeks, and beef, pork, and egg were most commonly excluded, although exclusions varied for each person. There were significant improvements in the Short Inflammatory Bowel Disease Questionnaire and Crohn's Disease Activity Index. Fecal calprotectin only improved in those with severe disease, that is, a Crohn's Disease Activity Index of greater than 150. A major lesson from the observations with this diet is that food can and perhaps should be personalized and customized for each IBD patient.

### *Semivegetarian (flexitarian) diet*

Chiba and associates[6] described a semivegetarian diet for CD as a departure from the Western diet known to be associated with the development of IBD. The diet includes brown rice, miso soup, pickled and other vegetables, fruit, green tea, eggs, yogurt, potatoes, and milk. Meat and fish are limited but not completely excluded. Fast food, sweets, carbonated beverages, cola, juices, alcohol, margarine, butter, cheese, and bread are discouraged. An uncontrolled, prospective trial of patients with CD in medically or surgically induced remission showed that the semivegetarian diet may be effective for maintaining remission for up to 2 years of follow-up.

### *Others*

The low-fat, fiber-limited exclusion diet dietary protocol uses elemental formula to induce remission in CD and followed by a preliminary diet with exclusions noted in **Table 1**.[7] There is then a structured protocol for food reintroduction as the patient keeps a food diary to monitor for reactions. The Paleolithic diet (as described in *The Paleo Diet* by Cordain[8]), Maker's Diet (as described in *The Maker's Diet* by Rubin[9]), a vegan diet (as described in *Self Healing Colitis & Crohn's* by Klein[10]), and a low carbohydrate diet (as described in *Life without Bread* by Allan and Lutz[10]) are described only in the lay press with some associated anecdotal success, but no clinical trials or case reports have been published in peer-reviewed medical journals.[8–11]

## SUMMARY

Diet remains a controversial but very promising treatment modality for adult patients with IBD. Data on diet and IBD is full of contradictions and is sparse in terms of good quality clinical trials. Although numerous mechanisms have been put forth to explain how dietary carbohydrates, fat, protein, and other components can cause or reduce inflammation, many of these mechanisms pertain to mouse models, which are tools to enhance our understanding of diet–disease relationships, but cannot reproduce the full set of responses to inflammatory stresses in humans.[133] Current data suggest limiting omega-6 PUFAs, saturated fats, animal protein, and food additives may be helpful in IBD. The SCD, one of the most popular diets already being used by patients with IBD, instead restricts certain carbohydrates and pays little attention to the types of fat or protein consumed. Despite these contradictions, there is preliminary evidence that the SCD helps to improve symptoms, decrease inflammation, and may lead to increased biodiversity of the microbiome so should remain an option for the appropriate IBD patient in conjunction with appropriate medical therapy. Similarly, the low FODMAP diet focuses on excluding particular carbohydrates, is less

restrictive, and may be appropriate in patients with IBD without active disease to decrease IBS-like symptoms. EEN seems to paradoxically reduce the biodiversity of the microbiome, but can induce remission, which may be helpful when corticosteroids are contraindicated. Clinical trials are needed to answer the many questions generated by patients and guide dietary therapies that have the potential to reduce flares in patients with IBD.

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