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Diet as a therapeutic option for adult inflammatory bowel disease

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Summary

There are many mechanisms to explain how food may drive and also ameliorate inflammation. Despite there being no consistent macronutrient associations with the development of IBD, many exclusion diets have been described in the medical literature and lay press: IgG-4 guided exclusion diet; semi-vegetarian diet; Low fat, fiber limited exclusion diet (LOFFLEX Diet); Paleolithic diet; Maker's diet; vegan diet; Life without Bread diet; exclusive enteral nutrition (EEN), the Specific Carbohydrate Diet (SCD) and the low FODMAP diet. The literature on diet and IBD is reviewed with a particular focus on EEN, the SCD and low FODMAP diet in IBD. Lessons learned from the existing observations and strengths and shortcomings of existing data is presented, along with recommendations for patients.

Keywords

Diet; Inflammatory Bowel Disease; Ulcerative colitis; Crohn's disease; Specific Carbohydrate Diet; Low FODMAP Diet; Exclusive enteral nutrition

INTRODUCTION

There is suspicion that the pathogenesis of inflammatory bowel disease (IBD) may involve the Western diet that is known to be high in fat, n-6 PUFA and red and processed meat and low in fruits and vegetables [1]. Westernization has become a global phenomenon, which may help to explain why there is a rising 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 affect 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 definitely effective in treating IBD.

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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 while approximately 80% believe diet is important in the overall management of disease [3]. And 40% of IBD patients have attempted various diet therapies often without the assistance of a physician or dietician [4]. There are now mechanisms posited to explain how foods can be both pro-and anti-inflammatory. 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.

In this review, we will try to highlight some aspects of dietary treatment of IBD and the current evidence. It is not possible to fit all preclinical data and its potential implications into a single short chapter; and it should be noted that current clinical data in dietary therapy of IBD is in its infancy. In many issues, highest level evidence such as randomized clinical trials are largely lacking. In the absence of such data, we will also present what we do in our clinics to generate a starting point/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 will be 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: IgG-4 guided exclusion diet; semi-vegetarian diet; Low fat, fiber limited exclusion diet (LOFFLEX Diet); Paleolithic diet; Maker’s diet; vegan diet; low carbohydrate diet [5–11]. This review will predominantly focus on exclusive enteral nutrition (EEN), which has the most robust evidence to support its use for the induction of remission in CD, and the Specific Carbohydrate Diet (SCD), which perhaps already has the largest following amongst IBD patients 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 IBD

The association of carbohydrates, protein, fats and fiber with IBD has been investigated, and the evidence primarily comes from epidemiological studies looking at dietary associations before the onset of IBD with only a few studies looking at flares in existing IBD patients. Several general and systematic reviews have also been previously written summarize these epidemiological associations with diet and IBD development [1, 12–15]. In this regard, many of the studies suffer from recall and selection bias, small sample size, short follow up periods, and the data can be 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 isn’t a consistent association amongst

macronutrients with development of IBD; it does not necessarily mean limiting a macronutrient cannot help alleviate symptoms or inflammation once the disease process has begun.

Western diet, high in carbohydrates and refined sugars, has been shown to induce dysbiosis in mouse models. Furthermore, a high processed sugar and carbohydrate diet can also lead to obesity, which is associated with a pro-inflammatory 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 prior to diagnosis and the accuracy of this data has been called into question. Most studies also did not subdivide carbohydrates into mono, di, oligo and polysaccharides. There have been many studies investigating the association of sugar, i.e. di and monosaccharides, with IBD with a trend towards 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 et al. addressed prior design weaknesses in a large prospective fashion utilizing the EPIC-IBD study cohort from eight European countries [20]. 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 to 4 controls who did not develop IBD. There was no association in univariate or multivariate analyses for any dietary pattern and carbohydrates and IBD risk in general, when adjusted for total energy intake, BMI 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 of the latter and the risk was present only if they had also low vegetables 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 may have a negative effect on colonocytes by inhibiting butyrate oxidation. The association between protein intake and development of IBD has been studied: In a study published by Reif et al using a pre-illness dietary questionnaire in newly diagnosed IBD patients in Israel did not show a statistically significant association with total protein intake [21]. Consumption of eggs did show a positive association with UC but not for 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 theoretical basis for playing a role in both driving and ameliorating inflammation in the intestine depending on the subtype. The mechanisms related to fat noted in the literature include the following: N-6 PUFAs such as linoleic acid are precursors for arachidonic acid, (which itself is a precursor of prostaglandins and leukotrienes); and dietary n-3 PUFA is a competitive substrate for n-6 PUFA metabolism

[24]. DHA can alter expression of COX-2 in the GI tract and thus inhibit LTB4/PGE2 release and inhibit angiogenesis [25, 26]. Lipoxins derived from n-6 PUFA and resolvins derived from n-3 PUFA are anti-inflammatory and can inhibit dendritic cell function and LTB4 production [27, 28]. N-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 [31, 32]; reduce inflammation via the NF-KB and PPAR alpha pathways [33, 34]; and can bind to receptors such as GPR20 (G-protein-coupled receptor) causing anti-inflammatory effects in macrophages [35]. Long-chain triglycerides can produce increased lymphocytes fluxes and enhanced proliferative response in intestinal lymph [36], whereas medium chain triglycerides can suppress IL-8, a neutrophil chemottractant expressed in high levels in actively inflamed mucosa of both CD and UC [37, 38]. Fats can also alter the microbiome [39–41] that can lead to upregulation of TLR and NOD mediated inflammation [42–44] and increased intestinal permeability from altered tight junction proteins [45, 46]. 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 IL10 knockout mouse models [47–48]. Dietary fat can activate mast cells which can indirectly affect gut permeability via regulation of transcellular and paracellular transport [49, 50].

Studies of the association of fat with IBD have similar methodological shortcomings: Most studies have been retrospective case control, are subject to bias in determining pre-illness diet and fail to account for confounders [51–56]. Though some studies have shown an association of CD with total fat, MUFA, total PUFA, total omega-3 fatty acid and omega-6 fatty acids, there are also other studies that show no such association [23, 57 – 61]. For UC, there have been associations with total fat, MUFAs, total PUFA and omega-6 fatty acids [21, 23, 58, 62, 63] and also studies that show no such association [61, 64]. Negative and positive associations with omega-3 fatty acids have been reported [55, 58, 62]. Two studies have shown a statistically significant decrease in the risk of UC with high intake of DHA [55, 62]. One of the only prospective studies published utilized the Nurses' Health Study cohort and found that there was no association of total fat, saturated fat, total MUFA, or total PUFA with risk of IBD [65]. There was an association with high intake of trans-unsaturated fatty acids and UC but not CD. There was an inverse association between long-term intake of n-3 PUFA, particularly DHA and EPA, and risk of UC but not CD. Unfortunately, randomized controlled trials have shown utilizing fish oil or n-3 PUFA in those already diagnosed with IBD is not a very effective strategy [66, 67].

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 [68]. 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 NF-KB. Certain soluble plant fibers have also been shown to inhibit translocation of E coli across M-cells in Peyer's patches [69]. The retrospective study published by Reif et al showed that fiber had a negative association with IBD though this did not reach statistical significance [21]. A prospective study using the Nurses Health Study cohort 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 [70]. Li et al. published a meta-analysis of case-controlled studies which 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 [71]. Though 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 [72].

VITAMINS AND MICRONUTRIENTS

There is a separate chapter on vitamins and trace elements in this volume, so the reader is referred to that chapter for further detail. 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 system [73, 74]. Polymorphisms of the vitamin D receptor have been identified as a genetic factor in IBD patients. Patients with IBD, particularly CD, are more likely to be vitamin D deficient. A higher serum level is associated with improved outcomes [75–80]. However, vitamin D deficiency can be a cause or consequence of IBD, and therapeutic trials in CD have yielded only modest results [81–83]. A low vitamin D level may also be a proxy for northern latitude, reduced UV light exposure and a disrupted circadian rhythm which may be associated with dysbiosis and increased IBD-related hospitalizations [84, 85]. Abnormalities vitamin D absorption have also been identified especially when IBD is active, suggesting that simple mega-dose 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 [86]. The prevalence of zinc deficiency in IBD ranges from 15 to 40% [87–90]. A low serum zinc level has also been associated with hospitalization, operation or other complications in CD patients [91]. Ulcerative colitis patients with low serum zinc level also have increased hospitalizations and a trend towards increased complications. The accuracy of serum zinc levels has been called into question since acute illness can diminish plasma levels and shift zinc stores into the liver [86]. Despite this limitation, serum zinc levels may still have clinical value; and normalization of zinc levels in those IBD patients who are deficient have been associated with improved outcomes.

Other common deficiencies in IBD, more notably in CD than UC, include vitamin B1, B6, B12, D, K, folic acid, selenium and iron [92]. There is some evidence to suggest that oral iron may modify the microbiome, and enable adherent invasive E. coli (AIEC) penetration and survival in macrophages and is associated with increased intestinal inflammation [93, 94], whereas such effects have not been associated with iv iron formulations.

Taking into account the above evidence, we currently recommend a multivitamin with trace elements to our IBD patients, especially those on dietary therapy 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 which have a GRAS (Generally Regarded As Safe) status by the FDA are being used in common foods, and could potentially have an impact on IBD. Although few clinical studies have been conducted with IBD patients, we generally recommend avoidance of food additives in IBD patients, 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 gastrointestinal inflammation. Additionally, most food additives do not enhance the nutrient content of the food that they have been added to, and are not essential components of a healthy diet. So, doing without them is not expected to bring about any physical harm and has the potential advantage of replacing processed foods with higher intakes of whole/naturally occurring foods, which typically have also a 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; non-dairy milks that are derived from soy, rice, and nuts like almonds; cottage cheese, mayonnaise, sour/cooking/whipping cream, ice cream, lunch meats (even turkey) and rotisserie chicken, and even infant formula can have added carrageenan. Estimates of intake can vary from 20 mg to several grams/day with an estimated mean of 250 mg/day [95,96]. Since carrageenan is derived from seaweed, it is considered ‘natural”; this illustrates that a label on the food packing as “natural” does not guarantee lack of food additives. Preclinical evidence clearly demonstrates that carrageenan can cause colitis, when given to animals in sufficient quantities in multiple models (e.g. guinea pigs, rats, mice, etc.) which share similarities with human IBD [95,96]; this inflammation can be ameliorated by antibiotics and is partially driven by the gut microbiota [97,98] but inflammatory signals can also occur in the absence of gut microbiota[98]. Multiple in-vitro studies using human colonic tissues also attribute inflammatory effects to carrageenan [95]. In a pilot, randomized, placebo-controlled clinical trial, 12 UC patients were maintained on a carrageenan free diet and were administered either placebo or carrageenan containing capsules at a low dose (200 mg/day which is less than the estimated intake in the US diet). There were no relapses in those UC patients who were carrageenan free and taking placebo capsules, whereas 3 patients taking carrageenan capsules relapsed sooner, creating a significantly earlier relapse associated with elevated fecal calprotectin levels and elevated inflammatory cytokines such as IL-6 [96].

Another ubiquitous additive is maltodextrin and is used as a thickener and is derived from corn starch and other starches, and therefore is considered “natural”. Its use over the past few years appears to have grown and is correlated to the rise in CD incidence [99]. 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, etc. 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 [99]. In humans, IBD patients appear to have a microbiome enriched in the metabolism of maltrodextrin, and E.coli including AIEC strains from CD patients forms thicker biofilms and enhanced adhesion in the presence of maltodextrin, suggesting that this compound may be increasing colonization of pathogenic bacteria in IBD [99,100]. Furthermore recent studies also suggest that maltodextrin may be deregulating cellular and mucosal barrier related host antibacterial defenses [99].

Other additives with potentially adverse effects on IBD are as follows: 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 [101]. Polysorbate 80 and carboxymethyl cellulose have been shown to induce colitis in IBD mouse models [102,103]. Polysorbate 80 is an emulsifier found in processed foods that enhances *E.* coli translocation across M cells and human Peyer's patches in CD [104]. Carboxymethyl cellulose is found in industrialized milk products, breads, sauces and sausages and has been shown to enhance bacterial adherence to epithelium and distend spaces between villi leading to bacterial infiltration in IL-10 gene-deficient mice [97,105].

DIETS FOR TREATMENT OF IBD

Exclusive Enteral Nutrition

Exclusive enteral nutrition (EEN) is as effective as steroids in inducing remission in children with CD [106]. Enteral feeds are also effective in the adult CD population but a meta-analysis showed that they were inferior to corticosteroids for inducing remission [107]. EEN has not been shown to be effective for UC [108]. EEN is 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 *F. prausnitzii* (a beneficial bacterium) and bacterial microbiota diversity (which are well recognized changes that characterize the dysbiotic microbiome in IBD). EEN associated fecal microbiota appears 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 AIEC [109, 110]. Open label trials have demonstrated endoscopic healing, decreased mucosal cytokine production and improved quality of life in CD patients [111–113].

Enteral feeds are classified based on their nitrogen content [107]. There are three types: elemental (amino acid based), semi-elemental (oligopeptide based) and polymeric (whole protein based). Elemental and semi-elemental formulas are hypoallergenic since 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 [107, 114]. A nonsignificant trend favoring very low fat and/or very low long chain triglyceride content

has been noted [107]. 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 non-inferior, may be more palatable and could be used as an alternative to steroids for inducing remission in adults. There still remains the concern regarding insufficient caloric intake when a patient drinks EEN by mouth versus utilizing a nasogastric or gastrostomy tube. EEN may additionally have insufficient vitamins and minerals such as vitamin D and zinc for IBD patients on steroids and with diarrhea, respectively [115]. 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 routinely be recommended [116–118]. Yamamoto et al. published a study demonstrating partial enteral nutrition with a low fat diet was associated with decreased post-operative recurrence of CD [119]. There is also data to suggest that partial enteral nutrition supplementation can decrease loss of response to infliximab [120, 121].

Lessons learned from these observations is that 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. It is most interesting to note that microbiome changes induced by EEN are not towards reversing many aspects of the dysbiosis seen in IBD such as reduced bacterial diversity, contrary to popular expectations; and yet this treatment can be effective in patients.

The Specific Carbohydrate Diet

The Specific Carbohydrate Diet (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* [122, 123]. Gottschall's theory is based on the assumption that carbohydrates have the most influence on the microbiota's maintenance and growth. She states IBD patients 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 the disaccharidases 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 occur with ulcerative colitis besides that of backwash ileitis. Gottschall likens the mechanism of action of the SCD to exclusive elemental nutrition since the principal carbohydrates in both are monosaccharides. However, as noted previously, the classification of elemental formula is based on nitrogen content and not carbohydrate content. Vivonex® Plus Essential and Peptamen®, both manufactured by Nestle 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,

excludes disaccharides and excludes 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 pseudo-grains and grain-derived flours, potatoes, okra, corn, fluid milk, soy, 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 since 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 since 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 [124].

Several studies have been published that suggest that SCD may be effective in IBD and most clinical observations have been in pediatric disease. These are reviewed in a separate chapter on diet and pediatric IBD. In adults, our group demonstrated that the fecal microbiome of IBD patients following the SCD may be different and more biodiverse than IBD patients following a Western diet based on 16 srRNA analysis of fecal microbiota composition [125, 126]. We also published a case series of fifty IBD patients on the SCD and showed that SCD-followers had decreased symptom scores and a high quality of life [127]. 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 ESR, CRP, calprotectin and Lewis score on capsule endoscopy; nevertheless, concomitant medication use in some of these patients is a potential confounder [128–130]. Results of an online survey of IBD patients following the SCD hints at the possibility of the diet helping to prevent IBD complications and hospitalizations though this is only patient reported and needs further study prospectively [124].

Though Gottschall recommends strict adherence to SCD, there is some data to suggest some liberalization may be possible with continued maintenance of remission [129], 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 IBD patients to explore their individual diet-disease relationship especially in the maintenance phase; and that patients could potentially conduct trial and error experiments on themselves with the aid of a health provider who can give objective dietary and clinical advice and can follow how they respond with preferably with objective assessments. Unfortunately, the appropriate time from diet initiation to liberalization is not clearly defined. Gottschall only 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 to 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 notice clinical food-symptoms correlations. We also recommend that during liberalization foods be introduced one at a time in small quantities over weeks rather than a few days. Another diet which is called the Anti-Inflammatory Diet for IBD (IBD-AID) and is based on the SCD encourages the use of omega-3 fatty acids, utilizes food-based pre and probiotics and uses a graded approach of food introduction based on food textures. The IBD-AID does include otherwise SCD "illegal" foods such as oatmeal, soy milk, flax/chia seeds, fenugreek and hummus though still has been successful in reducing Harvey Bradshaw Index in CD and the Modified Truelove and Witts Severity Index in UC symptomatically [131]. Currently there is an ongoing trial that is looking at the effectiveness of the SCD vs a Mediterranean-style diet in active CD funded by the Patient-Centered Outcomes Research Institute (PCORI) [132].

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 2–5 days. From there, the allowed foods are slowly liberalized. The efficacy of the SCD should be judged at the earliest in 1 month. We recommend formal assessment of symptoms using appropriate symptom scores and also markers of inflammation including CRP, 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 et al. discussed the nutritional deficiencies that can possibly occur with the SCD including folate, thiamine, vitamin B6/D/C/A, calcium and potassium deficiencies, though this is purely speculative [133]. 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 inflammatory bowel disease patient. It may not be practical for a CD patient with 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). Since most of the food consumed on SCD is prepared from scratch, ready access to fresh produce is necessary, and it may not be practical to follow the SCD if a patient lives in a "food desert" without access to transportation to a grocery or produce store, which 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 IBD patients 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 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 then after can have functional symptoms similar to those seen in IBS patients, for whom the 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 and bloating, abdominal pain and change In bowel habits. FODMAPs are osmotically active and can lead to more fluid delivery to the colon. They are also rapidly fermented resulting in acute gaseous distention. The low FODMAP diet specifically limits fructose, lactose, fructans, galactans and polyols and has been shown to be effective in improving IBS symptoms [134]. IBS is prevalent in the IBD population; ones study showed 57% and 33% of CD and UC patients respectively experienced IBS symptoms in the preceding week [135]. There is limited evidence that the low FODMAP diet may improve IBS symptoms in IBD patients. Gearry et al. published an uncontrolled study of 52 CD and 20 UC patients with inactive disease which showed approximately half had some response to the low FODMAP diet. [136] The diet was effective in alleviating abdominal pain, diarrhea, bloating and gas. There was a trend towards more constipation in UC patients, but this was not statistically significant. There is a theoretical concern that the low FODMAP diet excludes inulin, fructo-oligossacharides and fructose which are known prebiotics. This 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 since 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 IBD diet

We also have previously developed and tested an “anti-IBD” diet that restricts disaccharides; wheat and other grains except white rice; polyunsaturated fatty acids 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/avoided and foods were advised to be cooked (with all methods except rapid high-heat such as charring), since cooking with heat exposure reduces 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, also allows for bacterial toxins to survive small bowel transit, and thereby 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 acute or chronic necrotizing enteritis initially noted in the Papua New Guinea Highlanders who consume large amounts of foods that contain trypsin inhibitors (NEED REF).

In this diet, we encouraged 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 mono-unsaturated fats such as olive oil, which have been reported to be anti-inflammatory. Coconut oil shown to have some anti-inflammatory and anti-carcinogenic properties was the saturated fat alternative to 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 maintenance treatment in adult patients with Crohn’s disease, 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 three groups: 1) a prebiotic FOS intervention (receiving active FOS 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 (CDAI)) or upto 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 to placebo and an FOS 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 IBD patients compared to healthy individuals in multiple microbiome studies) increased at the end of treatment [138].

Other Diets for IBD

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 are noted in Table 1 for each of the

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

The IGG4 exclusion diet—Gunasekeera et al. published a randomized controlled trial of an IgG-4-guided exclusion diet for Crohn's disease [5]. IgG4 titers were drawn for the foods noted in Table 1. The foods corresponding to the four highest IgG4 titers were eliminated for four 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 (SIBDQT), Crohn's disease activity index (CDAI). Fecal calprotectin only improved in those with severe disease, i.e. CDAI > 150. A major lesson from the observations with this diet is that food can and perhaps should be personalized/customized for each IBD patient.

Semi-vegetarian (flexitarian) diet—Chiba M et al. described a semi-vegetarian diet for Crohn's disease as a departure from the Western diet known to be associated with the development of IBD [6]. 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 CD patients in medically or surgically induced remission showed that the semi-vegetarian diet may be effective for maintaining remission for up to two years of follow-up.

Others—The LOFFLEX 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 *The Paleo* Diet by Cordain), Maker's Diet (as described in *The Maker's Diet* by Rubin), vegan diet (as described in *Self Healing Colitis & Crohn's* by Klein) and low carbohydrate diet (as described in *Life without Bread* by Lutz) 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/Discussion

Diet remains a controversial but very promising treatment modality for adult IBD patients. Data on diet and IBD is full of contradictions, is sparse in terms of good quality clinical trials. While numerous mechanisms have been put forth to explain how dietary carbohydrates, fat and 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 [139]. Current data suggests limiting omega 6 PUFAs, saturated fats, animal protein and food additives while increasing fruits and vegetables. The SCD, one of the most popular diets already being used by IBD patients, 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 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 IBD patients 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. Further research in patients with IBD in the form of clinical trials are needed to answer many questions generated by patients and guide dietary therapies which have the potential to reduce flares in IBD patients.

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Key Points

- Diet can have an impact on 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

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 (i.e. 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, guargum, pectin, soy sauce
***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 consensed or evaporated milk, soft cheeses, sour/ 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, nectraines, pears, papaya, peaches, plums, prunes, persimmon, watermelon	Green beans, snow/blackeye/split peas, haricot/ kidney/mung/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
Semi-vegetarian diet	Bread, white rice (brown allowed)	Minced or processed meat, Fish allowed once a week, meat once every 2 weeks	Cheese	Margarine, butter	None	None	None	None	Carbonated beverages, juices, moderate or no alcohol	Desserts	Fast food, no eating between meals
***LOFFLEX Diet**	Wheat, oats, rye, barley	Pork, ham, bacon, eggs, processed meats	Cow, goat, sheep milk products, ice cream	Corn/vegetable and nut oil, margarine, butter	Corn, onions, sweetcorn, tomato	Citrus fruit, apples, bananas, dried fruit and marmalade	Peas, beans an lentils	Nuts and seeds	Tea, coffee, fruit squash, carbonated drinks, citrus/ apple/ tomato juice, alcohol		Pies, pâté, yeast, salad cream/ dressings, mustard, soy sauce

Food Restrictions	Grains	Meat	Dairy	Fats and Oils	Vegetables	Fruits	Beans and legumes	Nuts and seeds	Beverages	Sweeteners	Miscellaneous
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
*Maker's Diet	All grains	Pork (including sausage), bacon, ham, ostrich, emu, imitation meat, shellfish, eel, catfish, squid, fried/ breaded fish or chicken, lunch meat, imitation eggs	Soy/rice/almond milk, cow's milk	Safflower/ sunflower/ cottonseed/soy/ canola/corn oil, margarine, lard, hydrogenated oils	Corn, sweet and white potato	Apples, bananas, apricots, grapes, melon, peaches, oranges, pears dried fruit, canned fruit	Soy/black/navy/garbanzo/kidney/white/lima beans,	Honey-roasted nuts, macadamia nuts, hazelnuts, peanuts, cashews, walnut s, pecans brazil nuts, peanut butter, nuts or seeds dry roasted in oil	Alcoholic beverages, fruits juice, soda, chlorinated tap water, pre-ground commercial coffee	Sugar, heated honey, artificial sweeteners, sorbitol, xylitol	Tofu, protein powder from rice, soy, whey or cow's milk
*Vegan diet	All grains	All meat	All dairy	Heated/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 less than 72 grams in 24 hours

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