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The Role of Diet in Inflammatory Bowel Disease

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Abstract
Purpose of Review Diet may play both a causal and therapeutic role for inflammatory bowel disease (IBD). Physicians caring for patients with IBD are often asked to make dietary recommendations. However, there are no well-established guidelines on the use of diet as a treatment of IBD. In this review, we describe the evidence supporting diet as a potential cause for IBD, patient-perceived symptoms based on diet, current research on various diets as a treatment for IBD, and areas of future research.
Recent Findings New studies in murine models suggest that dietary emulsifiers may trigger the gut inflammatory cascade. New studies of restriction diets in patients have shown a relationship between dietary intake, symptoms, and bowel inflammation.
Summary Until several ongoing clinical trials are completed, a reasonable approach to dietary recommendations for patients with IBD is to propose a well-balanced, healthy (low-fat, low-sugar) diet prepared from fresh ingredients, such as the Mediterranean diet, with exclusions of self-identified foods that worsen or trigger IBD-related symptoms.

Keywords Inflammatory bowel disease · Diet · IBD therapy · IBD pathogenesis

This article is part of the Topical Collection on *Inflammatory Bowel Disease*

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Introduction

The incidence of inflammatory bowel disease (IBD) has been increasing worldwide, and the cause for this is not clear. Both Crohn's disease (CD) and ulcerative colitis (UC) are more common within industrialized countries, and the highest incidence and prevalence have been noted in North America and Europe [1, 2]. However, increasing incidence of IBD has been noted in previously described low-incidence regions of the world such as Asia as these countries become more westernized [1]. Similarly, individuals emigrating from a low IBD prevalence region to a higher prevalence region are at a higher risk for developing IBD than those who remain living in low prevalence regions [2].

The cause for the increased IBD incidence is currently unknown, but the answer may be related to the complex relationship between the environment and genetics. Given the higher incidence rates observed in industrialized nations, many have hypothesized that sanitation, microbial exposure, diet, pollution, and medications may be involved [3]. This hypothesis has prompted studies of diet as both a cause of and treatment for IBD [4].

In this review, we aim to describe the mechanism of diet as a potential cause for IBD, patient-perceived symptoms based on diet, current research on various diets as a treatment for IBD, and areas of future research.

Mechanism of Diet on IBD

There are multiple hypotheses on how diet may play a causative role in IBD, and basic science studies have elucidated a few of these possible mechanisms [5–7]. Diet may directly affect the microbiome in order to cause IBD [5]. Diet affects the production of metabolites by organisms that live in the gut, and these small molecules may initiate the inflammatory

cascade. For instance, mouse models have shown that microbial colonization is required for the development of colitis [7]. However, the cause and effect relationship between inflammation and the microbiome is still under investigation since inflammation itself can change the microbiome [8]. Additionally, dietary antigens may trigger an immune response. For example, innate immune receptors (e.g., Toll-like receptors 2 and 4) can be activated by saturated fatty acids, but they are inhibited by omega-3 polyunsaturated fatty acids (PUFAs) [7]. Therefore, animal model studies have been consistent with epidemiologic observations in that omega 3 PUFAs and medium-chain triglycerides are anti-inflammatory while high-fat diets are pro-inflammatory [7]. Finally, diet may have a direct impact on the mucous layer of the gastrointestinal tract, which functions to protect the epithelium from luminal content [9•].

Mouse models have also shown that high-fat diets increase the severity of colitis in mice [6]. In addition to fatty acids, specific amino acids such glutamine and arginine may affect the inflammatory cascade. Glutamine and arginine have been shown to improve clinical parameters of chemical-induced colitis when added to the diet of mice; dietary histidine, from which histamine is derived, can decrease symptoms of immune-mediated colitis in mice [6]. Threonine may enhance barrier function by augmenting intestinal mucus production [6].

Additionally, plant polysaccharides and poorly digestible plant fibers have been implicated in controlling the severity of colitis in murine models. These have been shown to decrease colitis via increased production of short-chain fatty acids (SCFAs), which serve as a source of energy for colonic cells and can stimulate immune tolerance by increasing production of T-regulatory cells. The effects of curcurmin, green tea, fermented grains, and polyphenols such as resveratrol have also been studied for their anti-inflammatory activity [6, 10, 11].

Several vitamins and minerals have been implicated in the etiology of IBD. For instance, vitamin D has been shown to be involved in anti-inflammatory cascade, and to increase epithelial cell resistance to injury and to suppress the inflammatory response to gut antigens [6]. In contrast, iron may increase intestinal inflammation through the formation of oxygen radicals, which may lead to cellular injury and activation of pro-inflammatory transcription factors [6]. Invasive bacterial strains may use iron to promote inflammation. Finally, ingested iron has been shown to play a role in intestinal inflammation and alteration of gut microbiota in mice; dietary heme has been shown to increase the severity of colitis in rodents [6].

Western diets also include non-nutrient components such as preservatives and emulsifiers. It has been hypothesized that the increasing incidence of IBD and westernization of diets is related to commercially prepared foods [7]. Emulsifers contain both hydrophilic and lipophilic regions that can keep fats in liquid suspension in order to keep foods from separating and to improve food texture [7]. Emulsifers are therefore common in processed foods. Chassaing, et al. tested the hypothesis that disruption of the mucous layer in the gastrointestinal tract by two commonly used emulsifiers may cause gastrointestinal inflammation. In an IL-10 knockout mouse model, they found low concentrations of emulsifiers caused low-grade inflammation, a change in the gut microbiome, and colitis [9•].

Animal models of IBD are helpful to elucidate potential mechanisms whereby diet may lead to the onset or perpetuation of inflammation. However, these animal models do not fully reproduce the biology of IBD. As such, human studies are needed to guide dietary recommendations.

Patient Perceptions of Diet and Their Symptoms

Patients often attribute clinical symptoms of IBD to their diet. Several studies have provided information on patients' perceptions of symptoms as related to their dietary intake. In a self-reported survey of a large cohort of IBD patients, Cohen et al. found dietary patterns differed based on IBD subtype and history of surgery, but the foods that were perceived to either worsen or improve symptoms were consistent across all groups [12]. Yogurt and rice were found to improve symptoms within all groups of patients while bananas were found to more frequently improve symptoms in those patients with total colectomy and an ileal pouch [12]. The foods that worsened symptoms in most groups are as follows: non-leafy vegetables, spicy foods, fruit, nuts, leafy vegetables, fried foods, milk, red meat, soda, popcorn, dairy, alcohol, high-fiber foods, corn fatty foods, seeds, coffee, and beans [12]. As expected, patients tended to avoid foods that they reported as worsening their symptoms.

A French study from 2013 looked at dietary beliefs and behaviors in adult IBD patients [13]. 15.6% of patients (38/244) believed that diet could initiate disease while 57.8% (141/244) believed that food could play a role in relapsing IBD [13]. However, as opposed to the Cohen et al., patients in this cohort did not necessarily alter their diet based on their beliefs about diet and its role in IBD flares. For instance, even though 25% of patients believed that dairy products may worsen symptoms during a relapse, only 4% of patients adopted a dairy-free diet during a flare of their disease [13].

Nutrients and Risk of IBD

A recent systematic review was conducted to assess pre-IBD diagnosis dietary intake and risk of developing IBD [14•]. In general, the systematic review identified that diets high in fat were associated with a greater risk of IBD whereas those with higher fruit and vegetable consumption were associated with a

lower risk of IBD. For example, several studies included in the systematic review demonstrated an increased risk of CD with high total fat, MUFA intake, total PUFA intake, total omega-3 fatty acid intake, and high omega-6 fatty acids [15–17]. Five of seven studies of UC patients and dietary fat showed a positive correlation between high fat intake and increased risk of UC [16–22]; however, only one study was statistically significant and two prospective studies did not show a statistically significant association.

Carbohydrate intake was also studied in patients with CD and UC [14•, 15–18, 20, 22, 23]. A high intake of monosaccharides and disaccharides was associated with increased risk for CD in two studies, and one study was statistically significant; other studies showed that CD patients consumed significantly higher mono- and disaccharides compared to controls [24–26]. Three of four studies found high mono- and disaccharides associated with risk for UC but there were no consistent associations between UC risk and polysaccharide intake.

In the five studies that investigated high fruit intake, there was a consistent association with decreased risk of CD [14•]. In patients who consumed fruit more than once daily compared with those who consumed fruit less than once weekly and in patients who consumed fruit more than four times a day compared with those who consumed fruit less than once daily, these findings were statistically significant; high vegetable intake was associated with decreased CD risk in three studies but this was not statistically significant. Higher fiber diet was also shown to be associated with decreased risk for CD [14•]. On the other hand, studies on fruit intake and UC did not find any significant associations. Three of four studies showed a decrease in UC risk but none met statistical significance.

Consumption of certain nutrients and subsequent changes in diet have been implicated in the increased incidence of IBD in previous low incidence regions of the world. For instance, consumption of sugars/sweeteners, fats and oils, and total fat intake has been associated with more than a twofold increased risk of CD in a Japanese study, and similar associations were found in North American despite difference in genetic susceptibilities [3, 15, 16]. UC has also been associated with increased intake of monounsaturated and polyunsaturated fat consumption [3, 22].

Diet as Treatment for IBD

Most commonly used in the treatment of pediatric CD, exclusive enteral nutrition (EEN) is the most studied dietary intervention for the treatment of IBD. The tested formulas have been shown to improve symptoms and intestinal inflammation in CD [7, 27, 28]. One randomized control trial has shown that both steroids and EEN reduced symptoms but only EEN improved mucosal healing in pediatric patients [29]. On the other hand, most trials that have shown corticosteroids to be more beneficial than EEN in treatment of IBD have been performed in adults [7]. There are two leading hypotheses for the differences in the results of these trials among children and adults. The first is that children are more adherent to the EEN, often getting much of their nutrition via tube feeds while they sleep. Recent data supports the concept that nearly 100% exclusion of table food may improve the anti-inflammatory effects of EEN [30]. The alternative hypothesis is that EEN is more effective in new onset disease. The reason why diet would be more effective early in the course of the disease is not known.

Several diets that utilize whole foods are available to adult patients who are looking to treat their IBD with something other than or in addition to conventional medications. The diets include the specific carbohydrate diet (SCD), Paleolithic diet, low-fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet, and the anti-inflammatory diet (Table 1) [37]. Currently, there are no well-designed randomized trials evaluating the efficacy of these diets although patients may have anecdotal benefits.

The SCD diet was initially introduced to treat celiac disease. The diet theorizes that disaccharides and polysaccharides pass undigested into the colon, which causes bacterial and yeast overgrowth, thereby leading to an overproduction of mucus and intestinal injury [37]. Those who follow the SCD can only consume monosaccharides (i.e., glucose, fructose, and galactose) found in fruits and vegetables. Complex carbohydrates (i.e., disaccharides and polysaccharides) are excluded from the diet.

Suskind et al. conducted an anonymous online survey of IBD patients about their perceived benefits while on the SCD [31]. Close to half of all patients surveyed tried this diet to avoid medications, and 28% of patients started the SCD to supplement a partial response to standard medications. At baseline, 80% of patients had abdominal pain prior to starting the SCD. In contrast, most participants reported that the abdominal pain had resolved within 2 months. Additionally, there were improvements in the percentage of patients reporting diarrhea, blood in stool, weight loss, and limitations in activities as well. While 4% of patients reported they were in clinical remission prior to SCD initiation, 33 and 42% reported achieving clinical remission by 2 and 12 months, respectively. The majority of patients (96%) reported they were going to continue the SCD. While these are encouraging results, there is substantial risk of selection bias in those who agreed to complete the online survey.

Cohen et al. studied mucosal healing in pediatric CD patients who followed the SCD [32]. Based on capsule endoscopy and corresponding Lewis score, 4 of 10 patients achieved mucosal healing at week 12, and 8 out of 10 showed mucosal improvement; of the 7 patients who proceeded to the extension study, 2 of 7 patients achieved mucosal healing and 1 patient showed continued mucosal improvement. However, mucosal healing did not necessarily correspond to clinical

Table 1 Diet as therapy for inflammatory bowel disease (IBD)

Diet	Study author	Aim	Patients	Study endpoints	Results
SCD	Suskind [31]	Online survey to evaluate patients' perception of clinical benefit of SCD on IBD symptoms	417 patients; 47% CD; 43% UC; 10% indeterminate colitis	-Remission: patient perception -Maintenance of SCD	-Remission: 33% (week 2) and 42% (week 12) −96% reported continuing SCD at end of study
	Cohen [32]	Prospective study to evaluate clinical/mucosal responses to SCD in children	9 pediatric patients; active CD (PCDAI ≥15)	-MH: Capsule endoscopy findings and corresponding Lewis score <135	-MH: 40% (week 12); 28.5% (week 52) -Mucosal improvement: 80% (week 12); 14.2% (week 52)
IBD-AID	Olendzki [33]	Retrospective case series to determine clinical efficacy of IBD-AID	11 adult patients; 8 with CD; 3 with UC	-Remission: HBI ≤4 at week 4 for CD; MTLWSI ≤2 for UC -Response: HBI decrease ≥3 points for CD; Reduction from baseline in MTWSI of ≥2	-Remission: 100% CD patients (week 4); 67% UC patients (week 4)
Crohn's disease exclusion diet	Sigall-Boneh [34]	Prospective study to determine efficacy of PEN + SCD-based exclusion diet on remission in patients with CD	47 adult and pediatric patients;	-Remission: HBI ≤3 or PCDAI <7.5 at week 6 - CRP normalization (<0.5 mg/dL) -MH: Colonoscopic findings or MR-E + fecal calprotectin	-Remission 70.6% at week 6; 84.3% (27/32) at week 12 -CRP normalization: 70% (21/30) at week 6 - MH: 11/15 patients
Paleolithic diet	No formal studies to date				
Low FODMAP diet	Croagh [35]	Pilot study of low FODMAP on IBD patients with J-pouches or ileorectal anastomosis	7 adult patients; 5 J-pouch and 2 ileorectal anastomosis	-Patient report of symptom improvement	- 5/7 patients with improvement of symptoms (p = 0.02)
	Prince [36]	Prospective survey-based study to assess efficacy of low FODMAP in IBD patients	88 adult IBD patients; 39 with CD; 38 with UC; 11 with IBD-undefined	-Change in symptom severity (based on Gastrointestinal Symptom Rating Scale) - Improvement in stool consistency and frequency (based on Bristol stool chart)	- 78% with symptomatic improvement (week 6) - Compared to baseline, improved stool consistency (p = 0.002) and frequency (p < 0.001)

Abbreviations: *CD* Crohn's disease, *UC* ulcerative colitis, *SCD* specific carbohydrate diet, *IBD-AID* anti-inflammatory diet, *FODMAP* fermentable, oligo-di-mono-saccharides and polyols, *PCDAI* pediatric Crohn's disease activity index, *MH* mucosal healing, *MTLWISI* Modified True Love and Witts Severity Index, *HBI* Harvey Bradshaw Index, *PEN* partial enteral nutrition, *CRP* C-reactive protein

remission in patients. Mucosal improvement with SCD was seen in newly diagnosed patients in addition to those with flares of established disease.

The anti-inflammatory diet (IBD-AID) is a relatively new diet that was introduced based on the idea that dysbiosis is caused by certain carbohydrates that are substrates for pathogenic bacteria in the gut lumen [37]; this diet is based on the SCD. Therefore, carbohydrates such as refined sugar, gluten-based grains, and certain starches are eliminated [37]. In a small retrospective case series, all patients (n = 11) who followed this diet for at least 4 weeks reported reduced symptoms [33].

An exclusion diet with some similarities to SCD has been shown to be efficacious for clinical remission and normalization of inflammatory markers in a small cohort of patients (34 out of 47 were pediatric patients) when used with or without partial enteral nutrition with a defined formula [34]. Patients were not allowed to eat condiments, sauces, gluten, dairy products, animal fat, processed meats, products with emulsifiers, canned goods, and packaged products with an expiration date. Clinical remission was obtained in 70.6% of patients (33 out of 47), and normalization of CRP was noted in 21 out of 30 patients. Twenty-seven out of 32 patients with follow-up were still in remission at week 12, after a step-down phase that involved education on what to avoid based on suspected dietary factors causing inflammation, but no specific diet was provided by the research study. Ten out of 14 patients achieved mucosal healing; however, most of these patients were on immunomodulators for maintenance therapy.

The theory behind the Paleolithic diet is that our gastrointestinal tract has not evolved to consume the modern diet; rather, lean meats and noncereal, plant-based foods are preferred to avoid modern foods that may cause disease [37]. The Paleo diet suggests that lean protein should be 30–35% of daily caloric intake in addition to high-fiber (45–100 g daily) intake from

noncereal, plant-based sources. Evidence of efficacy of this diet for IBD is generally limited to anecdotes at this time.

The low FODMAP diet's premise is that the types of carbohydrates that are grouped together are poorly absorbed in the small intestine, thereby are fermented by gut bacteria and lead to increased symptoms such as bloating, distension, cramping, and diarrhea [37, 38]. The diet is based on the idea of increased gut permeability as a potential cause of IBD. This diet is usually trialed for 6–8 weeks to assess symptom response. Then, foods can be reintroduced based on patient tolerance. Croagh et al. conducted a pilot study on the effect of low FODMAP diet in IBD patients with J-pouches and ileorectal anastomosis. They found 71% of IBD patients (5 out of 7) who undertook a low FODMAP diet reported improvement of stool frequency [35]. In a recent study of 88 IBD patients, 78% reported symptomatic improvement after following at least 6 weeks of a low FODMAP diet; also, patients reported significantly higher rates of normal stool form and frequency [36]. Dietary adherence has been the cornerstone to achieving efficacy in IBD patients.

While symptoms may improve on diets such as the IBD-AID and low FODMAP, it remains to be proven whether these diets also improve inflammation and whether the apparent effectiveness is greater than would be expected due to the cyclical nature of IBD. Larger prospective studies that include a control group are needed to establish both efficacy for symptoms and intestinal inflammation. Such studies also have the potential to advance our understanding of the effects of these diets, if any, on the gut microbiome.

Until such studies are completed, physicians, dieticians, and patients are left to ask what should a patient with IBD eat to minimize their symptoms and the frequency of relapses. One approach to this is to consider the common features of the many therapeutic diets described above. With the exception of EEN, all of the other diets require preparation of food from fresh ingredients. Thus, a simple recommendation would be to follow an otherwise healthy diet, similar to the Mediterranean diet, prepared from fresh ingredients, while avoiding foods that the individual believes worsens their symptoms [39]. Additionally, studies have shown a lower mortality rate associated with those who consume a Mediterranean diet [40, 41].

Future Directions

The field of diet and IBD is continuing to evolve. Despite significant advances in describing the clinical outcomes with diet-based therapies and in basic science studies to explore potential mechanisms, the mechanisms by which diet-based therapies improve symptoms in humans with IBD remain elusive. Studies of nutrigenomics, metabolomics and the microbiome may play an important role to identify the mechanisms by which diets are effective for control of symptoms and inflammation; thereby, diets could be formulated in a more specific manner and the issues of an excessively restrictive diet could be avoided. Alternatively, understanding the mechanisms behind the effectiveness of dietary interventions could allow for the development of targeted therapeutics. For example, if a food metabolite drives the inflammation, therapeutics could be developed to bind this metabolite or to block binding of it to the target cell.

Because the traditional diets discussed earlier may be overly restrictive, it is possible that the nutrigenomics, the study of diet on gene expression, could guide new therapeutic diets that specifically restrict inflammatory agents [42]. Marlow et al. conducted a small pilot study of patients who were maintained on 6 weeks of Mediterranean-inspired diet; they found a trend towards reduction of CRP and diversification of the gut microbiome. Also, gene expression was significantly affected, suggesting that this modality of study would be feasible to assess the effects of diet on genes regulating the inflammatory cascade.

There are limited data on the role of diet in combination with standard medical therapies [43–46]. Nguyen et al. conducted a meta-analysis to compare enteral nutrition therapy (elemental, semi-elemental, or polymeric) plus infliximab to infliximab monotherapy in patients with CD [47]. The combination of enteral therapy plus infliximab showed significantly improved odds of achieving clinical remission and long-term clinical remission at 1 year. In CD patients treated with infliximab, the number needed to treat using enteral nutrition to achieve long-term clinical remission after 1 year was found to be 4 patients [47].

Conclusion

The role of diet and IBD is complex, and this field of study is continuing to grow and to advance. As dietary changes can be cumbersome, a close working relationship between patient and dietician, if feasible, may be an important part of the multidisciplinary approach to IBD patients. Well-designed randomized controlled trials are needed to increase the science behind nutrition-based therapies for inflammatory bowel disease [48].

Compliance with Ethical Standards

Conflict of Interest Raina Shivashankar declares no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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