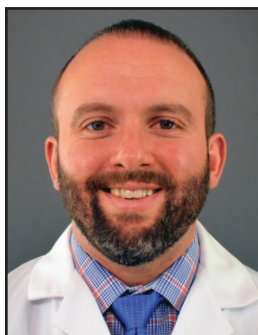


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## Diet and Inflammatory Bowel Disease: What is the Role?



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**Patients often question the role of diet in inflammatory bowel disease (IBD). Despite the interest in this topic, little consensus exists on how to address diet in patients with IBD. Animal studies and population-based human studies serve as the knowledge base for IBD risk associations. Such studies have demonstrated the potentially positive effects of omega-3 fatty acids, amino acids, plant polysaccharides, vitamin D, fiber, fruits, vegetables, and fish, in addition to the potentially deleterious effects of high total fat, red meat, omega-6 fatty acids, food additives, and a general Western diet. Exclusive enteral nutrition, the most studied dietary therapy in IBD, has demonstrated benefit in pediatric patients with Crohn's disease. Less studied diets, including the specific carbohydrate diet, anti-inflammatory diet, and the low-FODMAP diet, may be of some potential benefit.**

### INTRODUCTION

In a recently proposed hierarchy of needs of patients with inflammatory bowel disease, there is discordance between patient needs and the focus of the physician, especially when it comes to the role of diet.<sup>1</sup> Clinicians tend to focus on defining and achieving therapeutic targets while patients often are concerned with what they can eat and if any diets are helpful or harmful with respect to IBD. Though the role of diet in IBD is becoming increasingly discussed, there is limited, if any, consensus on the topic. In this article, we

aim to review several aspects of the function of diet in IBD including its role in the changing epidemiology, disease pathogenesis, and risk of IBD. We will also examine several defined diets that have been proposed and studied as potential therapies for IBD.

### Epidemiology

The incidence and prevalence of both Crohn's disease (CD) and ulcerative colitis (UC) have increased over time, and it is suggested that diet may play a role. Though the incidence and prevalence of IBD remains the highest in industrialized areas of North America and western Europe,<sup>2,3</sup> there has been a rise in previously low-prevalence areas,

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including parts of Asia, South America, and the Middle East.<sup>2</sup> The reasons for this changing global landscape are unclear, but several factors have been proposed,<sup>4</sup> including infection, hygiene standards, medications, and pollutants. Notably, diet has also emerged as a possible key contributor to this increasing incidence of IBD in the developing world, largely due to the rise of the Western diet throughout the world.<sup>5</sup> Furthermore, emigration from a low-prevalence region to a high-prevalence region has been shown to increase the risk for developing IBD and has recently been associated with changes in microbiome composition.<sup>6,7</sup> It is likely that diet and the other factors noted are similarly involved with this risk. Furthermore, obesity has been proposed as a diet-related lifestyle factor that may be associated with an increased risk of IBD.<sup>8</sup> These parallel observations suggest that diet likely plays a role in the changing global epidemiology of IBD.

### **Diet in the Pathogenesis, Risk, and Outcomes of IBD**

The interplay between diet and IBD has largely been investigated through animal models of intestinal inflammation and epidemiologic studies on IBD risk associations. Animal models have been used to study the potential pathogenesis of specific dietary components in causing intestinal inflammation. In addition, several large, population-based cohorts have been utilized to investigate IBD risk associations with specific dietary components. With the limited amount of clinical trial data in the area of diet and IBD, these studies provide an important framework for better understanding the interplay between diet and IBD.

### **Studies Involving Animal Models of Intestinal Inflammation**

When it comes to the pathogenesis of diet and IBD, several contributing factors have been proposed, including dysbiosis, altered intestinal barrier function, and effects on innate immunity.<sup>9</sup> It has been suggested that diet-related changes in the intestinal microbiome lead to decreased production of short-chain fatty acids (SCFAs).<sup>9</sup> This may disrupt the intestinal barrier and lead to bacterial translocation and deleterious downstream effects

on the innate immune system.<sup>9</sup> This proposed mechanism is largely based on animal studies of diet-derived factors, such as macronutrients, vitamins and minerals, and food additives.<sup>10</sup>

Animal studies investigating a high-fat diet have generally demonstrated a pro-inflammatory effect. One study in a Crohn's ileitis-like mouse model showed that a high-fat diet led to accelerated development of Crohn's disease via increased intestinal permeability and altered luminal processes.<sup>11</sup> Furthermore, in a dextran sulfate sodium (DSS)-induced colitis mouse model, a Westernized high-fat diet led to accelerated weight loss, an effect that was exaggerated by the addition of heme, an abundant component of red meat.<sup>12</sup> While these studies suggest a pro-inflammatory effect from a high-fat diet, omega-3 fatty acids have typically demonstrated an anti-inflammatory effect.<sup>13-17</sup>

Several amino acids have also been investigated for their role in intestinal inflammation. Glutamine and arginine are thought to have immunomodulatory effects<sup>18</sup> and have been shown to improve inflammatory measures in colitis-induced mouse models.<sup>19-22</sup> In addition, histidine, a precursor to histamine, inhibited pro-inflammatory cytokine production in a murine colitis model.<sup>23</sup> Threonine, likely through its beneficial effects on intestinal mucus production, and tryptophan have also been shown to reduce colitis in pig and mouse models.<sup>24,25</sup> Similarly, plant polysaccharides, in addition to fibrous plant products, have largely been shown to have an anti-inflammatory effect.<sup>26</sup> The proposed mechanism for this effect is increased production of SCFAs, which act to improve the barrier function and immune tolerance of colonocytes.<sup>27,28</sup> Other plant-based compounds, including curcumin, green tea, fermented grains, and polyphenols have also demonstrated anti-inflammatory properties in various animal models.<sup>10,29,30</sup>

Furthermore, several vitamins and minerals have been studied in the pathogenesis of IBD using animal models of intestinal inflammation. Vitamin D has notably been recognized as a regulator of immune pathways as demonstrated in several animal models.<sup>10,31</sup> In IL-10 knock-out mice, deficiency of vitamin D and vitamin D receptor were shown to accelerate IBD symptoms and death.<sup>32</sup> Vitamin D was also shown to maintain mucosal

integrity in a DSS-induced colitis mouse model by attenuating the effects of luminal antigens.<sup>33</sup> Calcium has been shown to have an important role in augmenting these effects of vitamin D on immune regulation.<sup>10,34</sup> In addition to vitamin D, dietary and supplemental iron has been shown to have a potential role in intestinal inflammation through oxygen free radical formation and also through alteration of the gut microbiome.<sup>10,35</sup> One Crohn's disease-like ileitis model showed that depletion of luminal iron had a preventative effect on inflammation.<sup>36</sup>

Lastly, food additives have generally demonstrated a pro-inflammatory effect in animal models.<sup>9</sup> Carboxymethylcellulose and polysorbate-80 have been investigated in IL-10 knock-out mice and have shown to disrupt intestinal barrier function, ultimately leading to increased intestinal inflammation.<sup>37,38</sup> Carrageenan and titanium dioxide (TiO<sub>2</sub>) have similarly shown to increase intestinal inflammation through disruption

of the intestinal barrier.<sup>39</sup> Malodextrin, a soluble dietary fiber, was shown to increase total intestinal IgA levels.<sup>40</sup> This effect was also associated with increased SCFA production, making it unclear if this effect is pro- or anti-inflammatory.

### **Human Studies on Dietary Risk Associations with IBD**

IBD risk associations with specific dietary factors have largely been studied using two large population-based cohorts, the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Nurses' Health Study.<sup>41-48</sup> Risk associations with fatty acid intake were investigated by both cohorts. In the EPIC cohort (n=203,193; 126 incident cases of UC), high intake of linoleic acid (omega-6 fatty acid found in vegetable oils) was associated with an increased risk of developing UC (OR=2.49, 95% CI 1.23-5.07, p=0.01).<sup>41</sup> Conversely, high intake of docosahexaenoic acid (omega-3 fatty acid found in fish oils) was associated with a

**Table 1. Dietary Components and Summary of Evidence from Animal Studies**

Dietary Component	Summary of Evidence	Overall Effect on Inflammation
<b>General high-fat diet</b>	Accelerated development of CD in ileitis-like model <sup>11</sup> Accelerated weight loss in DSS-induced colitis model <sup>12</sup>	<b>Pro-inflammatory</b>
<b>Omega-3 fatty acids</b>	Generally anti-inflammatory-effect in animal models <sup>13-17</sup>	<b>Anti-inflammatory</b>
<b>Amino acids</b> Glutamine Arginine Histidine Histamine Threonine	Decreased inflammatory cytokine production <sup>18-22</sup> Improved intestinal mucus production <sup>23</sup> Improved measures of colitis <sup>24,25</sup>	<b>Anti-inflammatory</b>
<b>Plant polysaccharides</b>	Improved intestinal barrier function through production of SCFAs <sup>27,28</sup>	<b>Anti-inflammatory</b>
<b>Vitamin D</b>	Accelerated IBD symptoms and death in IL-10 knock-out mice <sup>32</sup>	<b>Anti-inflammatory</b>
<b>Iron</b>	Potential increase in intestinal inflammation through oxygen free radical formation <sup>10,35,36</sup>	<b>Pro-inflammatory</b>
<b>Food additives</b> Carboxymethylcellulose Polysorbate-80 Carrageenan Titanium dioxide Malodextrin	Disruption of intestinal barrier and increased total intestinal IgA levels <sup>37-40</sup>	<b>Pro-inflammatory</b>

CD: Crohn's disease; DSS: dextran sulfate sodium; SCFAs: short-chain fatty acids; IBD: inflammatory bowel disease; IL-10: interleukin-10

lower risk of developing UC (OR=0.59, 95% CI 0.37-0.94,  $p=0.03$ ).<sup>41</sup> Similarly, the Nurses' Health Study showed that an increased omega-3:omega-6 ratio was also associated with a lower risk for developing UC (multivariate HR 0.69, 95% CI 0.49-0.98,  $p=0.03$ ).<sup>42</sup> The Nurses' Health Study showed no association seen between fatty acid intake and risk of CD.<sup>42</sup>

The EPIC and Nurses' Health Study cohorts were also used to examine a variety of other dietary factors. A recent analysis from the EPIC study ( $n=401,326$ ; 104 incident cases of CD, 221 incident cases of UC) examined dietary fiber intake and showed no significant association between fiber intake and risk of CD or UC.<sup>43</sup> However, the Nurses' Health Study ( $n=170,766$ ; 269 incident cases of CD, 338 incident cases of UC), showed that the high fiber intake was associated with a 40% reduced risk of CD (multivariate HR 0.59, 95% CI 0.39-0.90) but not UC.<sup>44</sup> This protective association with CD risk appeared to be greatest for fiber derived from fruits. Furthermore, the Nurses' Health Study II cohort ( $n=39,511$ ; 70 incident cases of CD, 103 incident cases of UC) examined high school diet using a validated food frequency questionnaire and showed that a high school diet consisting of high intake of fruits, vegetables, and fish was associated with a decreased risk of CD but not UC.<sup>45</sup> It should be noted that these findings are subject to a high degree of recall bias. Lastly, the Nurses' Health Study cohort ( $n=165,331$ ; 261 incident cases of CD, 321 incident cases of UC) and EPIC cohort ( $n=262,451$ ; 193 incident cases of UC, 84 incident cases of CD) demonstrated no risk associations with dietary iron and heme intake<sup>46</sup> and alcohol intake,<sup>47</sup> respectively.

Vitamin D has become an increasingly recognized for its potential role in IBD and has shown associations with both IBD risk and IBD outcomes.<sup>48,49</sup> The Nurses' Health Study cohort ( $n=72,719$ ; 122 incident cases of CD, 123 incident cases of UC) showed an association between increased predicted plasma 25(OH)-vitamin D level and decreased risk of CD (multivariate HR 0.55, 95% CI 0.30-1.00,  $p=0.02$ ).<sup>48</sup> In addition, increased supplemental vitamin D intake was associated with a decreased risk of UC (multivariate HR 0.64, 95% CI 0.37-1.10,  $p=0.04$ ).<sup>48</sup> Furthermore, five-year follow-up data from a longitudinal IBD registry

showed that low-vitamin D levels were associated with more steroid usage, biologics, narcotics, hospitalizations, emergency department visits, and surgery ( $p<0.05$ ) among patients with CD and UC.<sup>49</sup> In aggregate, these findings support a potentially protective role for vitamin D in regards to IBD risk and IBD outcomes.

Dietary IBD risk associations were also investigated in a commonly-referenced systematic review by Hou et al., which included 19 studies, 2,609 IBD patients, and 4,000 controls.<sup>50</sup> Notably, high intake of total fats, PUFAs, omega-6 fatty acids, and meat were associated with increased risk of CD. In addition, high fiber and fruit intake were associated with decreased risk of CD, and high vegetable intake was associated with a decreased risk of UC.<sup>50</sup> While it is interesting that these findings are somewhat similar to findings from the EPIC and Nurses' Health Study cohorts, it should be noted that a majority of studies from this systematic review were not statistically significant and only reflected statistical trends.

## Defined Diets in the Treatment of IBD

### Exclusive Enteral Nutrition

Exclusive enteral nutrition (EEN) is the most widely studied dietary intervention in IBD and has been most studied in the pediatric IBD population. It is more often used for the treatment of pediatric CD, especially in Canada, Japan, and Europe.<sup>51</sup> EEN consists of elemental, semi-elemental, or defined formula liquid diets. It is also one of the few dietary treatments in IBD that has been studied in prospective observational and randomized controlled trials,<sup>52-59</sup> albeit mostly in the pediatric population and a relatively small number of patients. One of the initial randomized controlled trials consisted of 50 pediatric CD patients and compared EEN to partial enteral nutrition (PEN).<sup>52</sup> This study showed remission rates [defined by pediatric Crohn's disease activity index (PCDAI) $<10$ ] of 42% for EEN vs. 15% for PEN ( $p=0.035$ ). Another trial of 37 pediatric CD patients that randomized patients to receive either a polymeric diet or corticosteroids in open-label fashion showed significantly higher mucosal healing rates with a polymeric diet compared to

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corticosteroids (75% vs. 33%,  $p < 0.05$ ).<sup>53</sup>

In addition, several non-randomized prospective studies have also demonstrated a potential benefit for EEN as a dietary therapy in IBD.<sup>54-56</sup> The GROWTH CD study prospectively followed newly diagnosed pediatric CD patients for 2 years and found EEN was associated with higher rates of remission compared to corticosteroids (63% vs. 46%,  $p = 0.036$ ).<sup>54</sup> In addition, an open-label study by Grover *et al.* prospectively followed 34 newly diagnosed pediatric CD patients who received EEN for a minimum of 6 weeks along with initiation of an immunomodulator.<sup>55</sup> This study showed a post-EEN clinical remission rate of 84% (defined by PCDAI < 10) and a complete mucosal healing rate of 21%. Furthermore, complete mucosal healing was shown to better predict sustained remission without need for corticosteroids, infliximab, or surgery.<sup>55</sup> More recently, a prospective observational study of pediatric Crohn's disease patients demonstrated similar clinical response rates of 88% for EEN compared to 84% for anti-TNF therapy ( $p = 0.08$ ).<sup>56</sup> However, in this study, EEN led to normalization of fecal calprotectin in only 45% of patients compared to 62% on anti-TNF therapy ( $p = 0.001$ ). This latter finding appears to challenge the results of Borrelli *et al.* which demonstrated a mucosal healing rate of 75%.<sup>53</sup> One proposed explanation for this that EEN therapy may be more effective in new-onset disease.

While studies in the pediatric population suggest a benefit of EEN as a dietary therapy for IBD, similar data in the adult population are lacking. Two early randomized controlled trials comparing corticosteroids to EEN in adult CD patients demonstrated improved CDAI scores<sup>57</sup> ( $n = 95$ ; EEN 41%, corticosteroids 72%,  $p < 0.05$ ) and improved remission rates<sup>58</sup> ( $n = 107$ ; EEN 55%, corticosteroids 74%,  $p < 0.01$ ) with corticosteroids compared to EEN. Another randomized controlled trial including two different fat formulations of EEN compared to corticosteroids also showed improved remission rates with corticosteroids (corticosteroids 79% vs. EEN 20% and 52%,  $p < 0.001$ ).<sup>59</sup> Furthermore, a recently updated systematic review of 27 studies included a meta-analysis of 8 trials comparing various types of enteral nutrition (EN) to corticosteroids in both

pediatric ( $n = 29$ ) and adult ( $n = 194$ ) CD patients.<sup>60</sup> Overall, there was no difference in remission rates between EN and steroids (RR 0.77, 95% CI 0.58-1.03). However, subgroup analysis by age showed that adults had a remission rate of 45% with EN compared to 73% with steroids (RR 0.65, 95% CI 0.52-0.82), and children had a remission rate of 83% with EN compared to 61% with corticosteroids (RR 1.35, 95% CI 0.92-1.97). It should be noted that more patients withdrew on EEN compared to corticosteroids, and children may be more adherent to EEN therapy than adults since it is given via naso-gastric tube during sleep.<sup>51</sup> This factor may account for the differences seen between the pediatric and adult populations.

Studies on EEN for the treatment of ulcerative colitis are lacking. One small clinical trial randomized patients with moderate-severe UC to receive polymeric total enteral nutrition or total parenteral nutrition (TPN) for their nutritional support in addition to medical therapy.<sup>61</sup> This study showed no significant difference in readmission rate and colectomy rate between the two groups. However, enterally fed patients had less frequent and milder adverse events (9% vs. 35%,  $p = 0.046$ ) and less postoperative infections ( $p = 0.028$ ).

#### **Other Defined Diets and Dietary Interventions**

Other diets that have been proposed to have a potential therapeutic role in the treatment of IBD include the specific carbohydrate diet (SCD), gluten-free diet, anti-inflammatory diet, and the low-fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet.<sup>7,9</sup> It should be noted that most of these diets have not been evaluated in a randomized trial, and only anecdotal benefits have been reported.

The SCD includes only monosaccharides contained in fruits and vegetables and excludes disaccharides and polysaccharides contained in simple sugar and wheat-containing products.<sup>7,9</sup> It restricts carbohydrates and processed foods,<sup>9</sup> likely making it difficult to maintain adherence in the long-term. The SCD was initially used to treat celiac disease and proposes that undigested complex carbohydrates enter the colon and ultimately lead to intestinal injury through overproduction of bacteria, yeast, and mucus.<sup>7</sup> A recent online survey of 417 respondents (47% with CD, 43% with UC,

10% with indeterminate colitis) demonstrated a perceived clinical improvement with the SCD.<sup>62</sup> Prior to starting the SCD, 4% of patients reported clinical remission compared to 33% at 2 months and 42% at 6 and 12 months. Abdominal pain was present in 80% of patients before starting the SCD, and this proportion decreased to less than 10% at 12 months. Another study by Cohen *et al.* used capsule endoscopy to prospectively evaluate both clinical and mucosal responses to the SCD.<sup>63</sup> Nine pediatric CD patients completed the trial after 10 were enrolled. There were significant improvements in Harvey-Bradshaw Index ( $p=0.007$ ), PCDAI ( $p=0.011$ ), and Lewis score ( $p=0.012$ ). Despite these studies showing positive associations, a more recent study of 7 pediatric patients on the SCD for a median of 26 months showed no association with mucosal healing.<sup>64</sup>

Similar to the SCD, there has been limited investigation into the gluten-free diet in IBD patients, but gluten sensitivity is likely common among IBD patients. One single-center study of 102 IBD patients (55 CD, 46 UC) reported gluten

sensitivity in 23.6% and 27.3% of CD and UC patients, respectively.<sup>65</sup> A recent cross-sectional study investigated the gluten-free diet using a gluten-free diet questionnaire in 1647 IBD patients participating in a longitudinal internet-based cohort.<sup>66</sup> The findings showed that among 314 (19.1%) participants who attempted a gluten-free diet, 65.6% reported symptomatic improvement and 38.3% reported fewer or less severe IBD flares. The anti-inflammatory diet (IBD-AID) is based on the SCD and eliminates refined sugar, gluten, and select starches.<sup>7</sup> Clinical studies on this diet are lacking, except for a small case series of 11 patients who all reported symptom reduction with decreased bowel frequency after 4 weeks.<sup>67</sup>

The low-FODMAP diet reduces the amount of poorly-absorbed carbohydrates that are digested by gut bacteria to produce gastrointestinal symptoms.<sup>7</sup> With the significant impact of functional gastrointestinal symptoms on patients with IBD,<sup>68,69</sup> the low-FODMAP diet has been considered as a dietary intervention in IBD patients, especially in symptomatic patients with quiescent IBD.

**Table 2. Dietary Factors and Summary of Evidence from Human Studies**

Dietary Factor	Summary of Evidence	Overall Association with IBD Risk
<b>Fatty Acid Intake</b>	Decreased risk of UC with docosahexaenoic acid (omega-3 fatty acid) <sup>41</sup>	<b>Omega-3 fatty acids associated with decreased UC risk</b>
	Increased risk of UC with high linoleic acid (omega-6 fatty acid) <sup>41</sup>	<b>Omega-6 fatty acids associated with increased UC risk</b>
	Decreased risk of UC with increased omega-3:omega-6 ratio <sup>42</sup>	<b>No associations with CD risk</b>
<b>Dietary Fiber</b>	No risk associations noted from EPIC cohort with UC or CD <sup>43</sup>	<b>Decreased risk of CD but not UC</b>
	Decreased risk of CD but not UC from Nurses' Health Study <sup>44</sup>	
<b>High school diet rich in fruits, vegetables and fish</b>	Decreased risk of CD but not UC from Nurses' Health Study <sup>45</sup>	<b>Decreased risk of CD but not UC</b>
<b>Dietary iron</b>	No risk associations from Nurses' Health Study <sup>46</sup>	<b>No associations with CD or UC</b>
<b>Alcohol intake</b>	No risk associations from EPIC cohort <sup>47</sup>	<b>No associations with CD or UC</b>
<b>Vitamin D</b>	Decreased risk of CD with increased predicted vitamin D level <sup>48</sup>	<b>Decreased risk of both CD and UC</b>
	Decreased risk of UC with supplemental vitamin D <sup>48</sup>	

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; EPIC: European Prospective Investigation into Cancer and Nutrition

However, few studies have investigated the low-FODMAP diet in IBD. One study of 32 patients with quiescent IBD and functional GI symptoms showed that challenge with fructan, a fermentable carbohydrate, led to exacerbation of pain, flatulence, and fecal urgency.<sup>70</sup> Another prospective study investigating the low-FODMAP diet in IBD (n=30), in addition to irritable bowel syndrome and celiac disease, showed improvement in Rome III criteria across all subjects, including IBD patients.<sup>71</sup> Another study used a prospective survey to assess clinical response to a low-FODMAP diet and showed symptomatic improvement in 78% at week 6 with improved stool consistency (p=0.002) and frequency (p<0.001) compared to baseline.<sup>72</sup> A recent meta-analysis and systematic review of 319 IBD patients (96% in remission) demonstrated significant improvement with the low-FODMAP diet in diarrhea (OR 0.24, 95% CI 0.11-0.52, p=0.0003), bloating (OR 0.10, 95% CI 0.06-0.16, p<0.00001), abdominal pain (OR 0.24, 95% CI 0.16-0.35, p<0.00001), and nausea (OR 0.51, 95% CI 0.31-0.85, p=0.009).<sup>73</sup> Lastly, one small study examined the low-FODMAP diet in patients after colectomy (5 J-pouch, 2 ileorectal anastomosis) and found symptomatic improvement in 5 out of 7 patients (p=0.02).<sup>74</sup>

Finally, it should be noted that older clinical trials have investigated fish oil supplementation as a potential diet-related IBD therapy.<sup>75-79</sup> An initial double-blind, placebo-controlled, cross-over trial of fish oil supplementation with omega-3 fatty acids showed no significant difference in clinical activity of CD and UC patients.<sup>75</sup> Two additional randomized controlled trials demonstrated no statistically significant benefit in ulcerative colitis disease severity based on histopathologic scores or mucosal cytokine levels<sup>76</sup> and in rate of corticosteroid-free remission.<sup>77</sup> However, a randomized controlled trial of an oral supplement enriched with fish oil, soluble fiber, and antioxidants was associated with improved clinical response and decreased corticosteroid requirement in 121 patients with UC compared to placebo (p<0.001).<sup>79</sup>

## CONCLUSION

As we learn more about the role of diet in IBD, signals from the available literature have demonstrated potentially positive and deleterious effects of several different dietary factors. Animal studies and human studies on risk associations suggest a possible protective role for omega-3 fatty acids, amino acids, plant polysaccharides, vitamin D, fiber, fruits, and vegetables. High total fat, red meat, omega-6 fatty acids, food additives, and a general Western diet may have potentially harmful effects. Exclusive enteral nutrition has been shown to be effective in inducing remission in pediatric CD, but is often impractical. Other defined dietary interventions in IBD have not been well studied and are not yet supported by a strong framework of scientific evidence. But perhaps this does not really address the most pertinent and practical matter of how to counsel patients in day-to-day practice. To this end, another defined diet not discussed previously in this review may play a key role—the Mediterranean diet—a non-restrictive diet with inclusion of potentially protective and exclusion of potentially harmful dietary factors.<sup>7</sup> A clinical trial to assess this diet in IBD patients is currently underway (NCT03058679). In the meantime, we might consider recommending the Mediterranean diet to our IBD patients, if not for its potential effects on IBD, then for its well-established benefit on cardiovascular risk.<sup>80</sup> ■

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