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## Diet, nutrition and inflammatory bowel disease

Diet may play an important role in the development, complications and therapy of inflammatory bowel disease (IBD). Dietary components, such as fatty acid and carbohydrate content, may increase the risk of developing IBD in a genetically predisposed host. Intake of fruit, vegetable fiber and omega-3 fatty acids have been associated with a decreased risk of development of Crohn's disease, whereas a high dietary intake of meat and fatty foods may increase the risk. Although protein-calorie malnutrition is uncommon in IBD, micronutrient deficiencies are common and may increase the risk of osteoporosis, thrombotic complications and poor wound healing. Enteral therapy is efficacious for the induction of remission in Crohn's disease, although it may be less effective than corticosteroids and difficult to tolerate. Dietary supplementation of omega-3 fatty acids and slowly fermentable dietary fiber have biologic plausibility as a treatment of IBD; however, the current data do not demonstrate a significant benefit. Herbal therapies, such as curcumin, have potential benefit in IBD, although larger studies are required to prove the efficacy and safety.

**KEYWORDS:** Crohn's disease ■ curcumin ■ defined diet ■ diet ■ inflammatory bowel disease ■ micronutrient ■ nutrition ■ ulcerative colitis

Jason K Hou<sup>†</sup>

& Joseph H Sellin

<sup>†</sup>Author for correspondence:

Baylor College of Medicine,  
1709 Dryden Road, Suite 8.35,  
Houston, TX 77030, USA

Tel.: +1 713 798 0950

Fax: +1 713 798 0951

[jkhhou@bcm.tmc.edu](mailto:jkhhou@bcm.tmc.edu)

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the intestinal tract that encompasses Crohn's disease (CD) and ulcerative colitis (UC). Conversations regarding diet are one of the most frequently discussed points between doctors and patients. The interrelationships between IBD and diet are complex, and are an area of great interest and confusion among both physicians and patients. There is a dietary intellectual divide between clinicians and patients. Physicians tend to focus on the nutritional complications of IBD, while patients are interested in diet as either a cause or cure of IBD. There are a great deal of objective data outlining the nutritional complications caused by IBD, but in the area of cause or cure, information is sparse, anecdotal and often conflicting. Although nutritional complications are common, they are often underappreciated. Nutritional complications of IBD are usually viewed as protein-energy malnutrition. Protein-energy malnutrition has been reported to be prevalent in 20–85% of patients with IBD; however, this is based on hospitalized patients from several decades ago [1,2]. Although occasional patients with CD will present with significant cachexia, this is increasingly uncommon. A recent case-control study from Canada reported that the most prevalent form of nutritional abnormality in CD patients in remission was excess body weight [3]. Despite the excess body weight, deficiency of micronutrients, such

as folate, iron, selenium, zinc, and vitamins B, C, D, E and K were common. In addition to malnutrition, diet may play an important role in the etiology and treatment of IBD. Dietary intake of carbohydrates and long-chain triglycerides has been implicated as a risk factor for the development of IBD. Patients view diet as a contributing factor to disease activity. Up to 65% of IBD patients report food intolerances and up to 28% of patients maintain a dairy-free diet, although there are little data to support this practice [4]. Several reports have demonstrated no difference or an even lower prevalence of lactose intolerance in UC patients compared with non-IBD controls but an increased prevalence in CD [5–7]. Enteral nutrition has been demonstrated to be efficacious in the treatment of CD. Further understanding of the role of dietary intake and inflammation suggests more practical methods of using diet as a treatment of IBD. In this article, we discuss the role of diet in the etiology of IBD, the importance of micronutrient deficiency and the potential role of diet as treatment for IBD.

### Diet as etiology

The incidence of IBD is rising. Observations that the incidence of IBD increases in migrant populations to the adopted population suggest the environment as a causative factor [8]. Changes in the western diet and its global spread have been implicated as one of many theories

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contributing to the rising incidence worldwide. Most diet studies in IBD are case-control studies and prone to heterogeneity and recall bias. Attempting to isolate single nutrients or even patterns of nutrient intake is a daunting task, fraught with potential methodological pitfalls. Although evidence is far from definite, certain recurrent themes emerge.

■ Role of dietary fats

High fat intake is one of several components of the western diet. The quantity and quality of fat intake has been associated with the increased risk of IBD. Long-chain omega-3 polyunsaturated fatty acids (PUFA), such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and docosapentaenoic acid, are metabolized into anti-inflammatory compounds, such as leukotriene B5 in the gut. Omega-6 PUFA, such as linoleic acid, are converted to arachidonic acid and its proinflammatory metabolites, prostaglandin E2, leukotriene B4 and thromboxane B2 (FIGURE 1). Increased levels of these proinflammatory metabolites have been observed in the colonic mucosa of patients with UC [9,10]. Omega-3 and omega-6 PUFA both utilize lipoxygenase and cyclooxygenase in a competitive manner, with increases in availability of omega-3 PUFA inhibiting the metabolism of omega-6 PUFA and *vice versa*. The intake of PUFA may influence the risk of IBD and disease activity at a genetic level. Guerreiro *et al.* reported that single-nucleotide polymorphisms of *TNF-α* 857 and *IL-6* 174 were associated with dietary fat intake, risk for IBD and disease activity. An increased ratio of omega-6 PUFA:omega-3 PUFA intake was associated with higher disease activity and polymorphism in *TNF-α* 857 [11].

In a case-control study of pediatric patients in Canada, Amre *et al.* used a validated food-frequency questionnaire in newly diagnosed CD patients to evaluate their dietary intake in the year prior to CD diagnosis, and to compare them with orthopedic control patients [12]. There was no association of omega-3 or omega-6 PUFA as a class effect with the risk of developing CD. However, they observed a dose-dependent protective effect of long-chain omega-3 PUFA, including EPA, docosapentaenoic acid and DHA for CD (odds ratio [OR]: 0.44, 95% CI: 0.19–1.00, *p* < 0.001). There was no association of omega-6 PUFA or arachidonic acid with risk for CD; however, the ratio of long chain omega-3 PUFA:arachidonic acid was protective for CD, more so than long-chain omega-3 PUFA alone (OR: 0.32, 95% CI: 0.14–0.71). Vegetable, fruit, nut, fish and dietary fiber intake were protective against the development of CD in a dose-dependent manner. In the same pediatric population, D'Souza *et al.* categorized the dietary intake into specific food patterns [13]. The 'western' diet pattern, characterized by meat, fried food, fast food, snacks and dessert was positively associated in girls with the development of CD (OR: 4.7, 95% CI: 1.6–14.2, *p* < 0.0006). A 'prudent' diet pattern, characterized by vegetables, fruits, dairy products, eggs, olive oil, dark breads, grains, fish and nuts was protective for CD in both girls and boys (OR: 0.3, 95% CI: 0.1–0.9 and OR: 0.2, 95% CI: 0.1–0.6, respectively). Other studies have also implicated a positive association between a fast-food type of diet and the development of CD in girls [14,15]. The finding of positive associations with diet patterns, but not one factor, independently suggests a multifactorial role of diet in the pathogenesis of IBD.

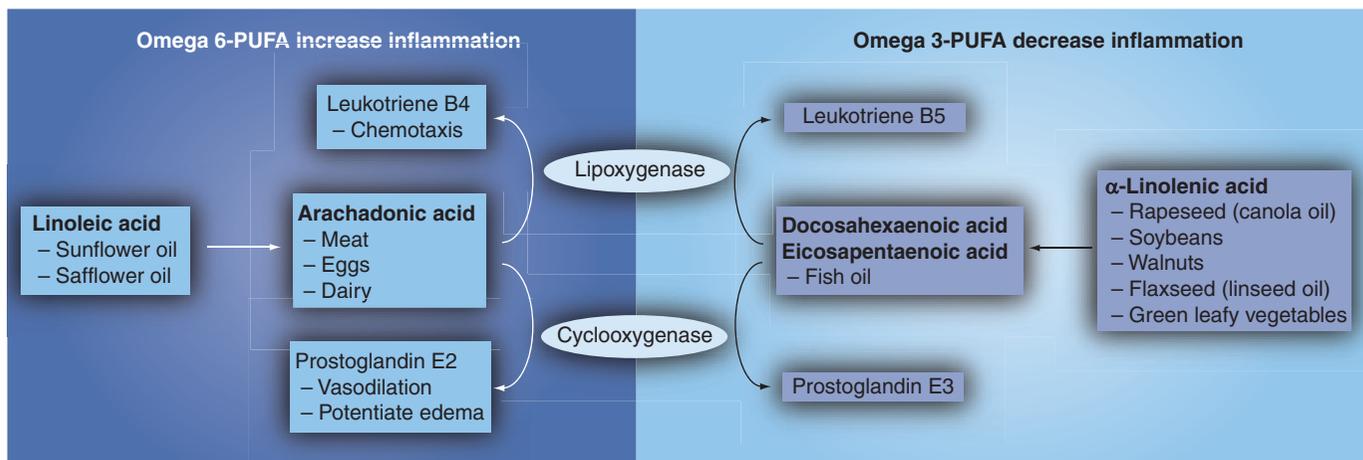


Figure 1. Metabolism of omega-6 and omega-3 polyunsaturated fatty acids. PUFA: Polyunsaturated fatty acids.

European Investigation into Cancer and Nutrition (EPIC), a prospective cohort study of 203,193 patients across Europe, reported associations with fatty-acid intake with the development of UC. Hart *et al.* reported a case-control study within EPIC of 126 incident cases of UC [16]. Linoleic acid was positively associated with development of UC in a dose-dependent manner (OR: 2.49, CI: 1.23–5.07 in the highest quartile of intake). The positive association barely failed to meet statistical significance when adjusted for the intake of other fatty acids (OR: 2.31, 95% CI: 0.97–5.36). They demonstrated a dose-dependent protective effect of DHA in UC (OR: 0.23, 95% CI: 0.06–0.97). Interestingly, they observed trends towards a positive association in the intake of two other long-chain omega-3 PUFA,  $\alpha$ -linoleic acid and EPA, but these were not statistically significant. Sakamoto *et al.* performed a hospital-based case-control study evaluating the role of diet in IBD in Japan [17]. They observed a positive association with both omega-3 and omega-6 PUFA in the risk of developing CD (OR: 3.24, 95% CI: 1.52–6.88 and OR: 2.57, 95% CI: 1.24–5.43, respectively), and a trend towards a positive association of both omega-3 and omega-6 PUFA with the development of UC, although this was not statistically significant. These studies suggest that the importance of the specific fatty acid and the effects in IBD may not be class-specific for either omega-3 or omega-6 PUFA.

#### ■ Role of dietary carbohydrates

The consumption of refined sugars has also been associated with an increased risk for the development of IBD [18–20]. The increase in highly fermentable, but poorly absorbed, short-chain carbohydrates and polyols (fermentable oligo-, di- and monosaccharides and polyols [FODMAPS]) have been hypothesized to increase susceptibility to CD [21]. Intake of FODMAPS may increase bacterial overgrowth in the distal small bowel resulting in increased intestinal permeability and triggering CD in a genetically susceptible host. Sakamoto *et al.* observed a positive association in the intake of ‘confectionaries’ with the development of UC and CD (OR: 2.86, 95% CI: 1.24–6.57 and OR: 2.83, 95% CI: 1.38–5.83, respectively) [17]. However, carbohydrate intake overall demonstrated trends towards being protective of IBD, although, this was not statistically significant. A sugar industry-sponsored critical review by Riordan *et al.* argues that the data regarding refined sugars and the risk of IBD is inconclusive.

Although the majority of published studies support the association of carbohydrate intake and increased risk of IBD, the studies of higher quality demonstrate no association [22]. Refined sugars have been assumed to be a surrogate for a ‘westernized’ diet, this may not entirely be the case. Some have pointed out the discordance between high sugar intake and low rates of IBD in the Middle East [23]. There are a limited number of intervention trials that have, at best, demonstrated mixed results [20]. A confounding factor in evaluating carbohydrate intake and IBD risks is that certain carbohydrates, such as FODMAPS, may increase intestinal permeability and increase risk for IBD, whereas other carbohydrates, such as slowly fermentable fiber, may decrease risk. Future studies will need to differentiate fast and slow fermentable carbohydrate intake to determine the role of carbohydrates in IBD risk.

#### ■ Role of microparticles

Microparticles are ingested nonbiologic bacteria-sized particles, such as titanium, aluminum and silicon, and have been hypothesized to predispose to IBD. Initially thought to be linked to toothpaste, microparticles have crept into modern food processing. Microparticles have been observed to accumulate in lymphocytes in Peyer patches and may modulate inflammation and predispose or trigger IBD [18,24]. Microparticles are thought to activate inflammatory responses by interacting with bacteria and inducing a granulomatous response [25]. *In vitro* studies demonstrated increases in IL-1 in colonic tissue and peripheral blood mononuclear cells from IBD patients exposed to lipopolysaccharide and titanium dioxide [26]. However, a recent study by Thoree *et al.* demonstrated no alteration of inflammatory phenotype in cells containing microparticles [27]. Lomer *et al.* observed a statistically significant decrease in CD activity index in patients on a low microparticle diet compared with controls in a small, randomized, double-blind study in 20 CD patients [28]. However, in a larger multicenter randomized trial in 83 patients, comparing a low microparticle diet to a control diet, no benefit was observed. [24]. Whether microparticles play a role in the pathogenesis or on-going inflammation in IBD is still unclear and further studies are necessary.

#### Nutritional deficiencies

Malnutrition in IBD was traditionally considered to be protein-energy malnutrition, as reported in older literature, in 20–85% of IBD

patients [1,2]. These studies were primarily performed on acute hospitalized patients, who may not reflect most patients seen in practice today. Guerrero *et al.* recently reported a case-control study in nonhospitalized adults in Canada, observing that the most prevalent form of malnutrition in CD was excess body weight [3]. Only 5.3% were considered moderately malnourished by subjective global assessment. CD patients had a lower BMI than healthy controls ( $p = 0.01$ ), but 32% of CD patients were overweight, 8% obese and only 2.6% were underweight. Despite the low prevalence of low BMI or malnutrition by subjective global assessment, they observed that CD patients had a lower intake of several micronutrients, including calcium, and vitamins C, D, E and K, with only a minority of patients reaching dietary references intake. Micronutrient deficiency, including vitamins A, B, C, D, E and K, magnesium, selenium, zinc and calcium, is well described in IBD patients at diagnosis and even in remission [29,30]. Geerling *et al.* observed lower plasma concentrations of  $\beta$ -carotene, magnesium, selenium, zinc and B12 in IBD patients at the time of diagnosis [30]. In CD patients in remission, Filippi *et al.* observed a lower intake of  $\beta$ -carotene, vitamins B1, B6, C and magnesium in CD patients with low plasma levels concentrations of vitamin C, copper, niacin and zinc [29].

Well-described complications attributable to nutritional deficiencies in IBD include osteoporosis from calcium and vitamins D and K deficiencies, and anemia from iron, folate and vitamin B12 deficiencies. Deficiencies in other micronutrients do not result in any clinically overt syndromes; however, they may affect hypercoagulability (folate) and the risk for neoplasia (antioxidant vitamins). Nutritional deficiencies are more relevant and frequent in CD owing to small-bowel involvement, although osteoporosis risk from glucocorticoid exposure and folate deficiency in UC are important.

#### ■ Food avoidance

The low intake of both macro- and micronutrients has been attributed to avoidance of certain foods owing to the perception of detriment to IBD by both patients and physicians; however, there are little data to support this practice. In a case-control study, 29% of CD patients excluded grains, 28% excluded milk, 18% excluded vegetables and 11% excluded fruits [3]. Similarly, Gerasimidis *et al.* reported that 28% of a pediatric population with IBD followed a dairy-free diet [4].

#### ■ Calcium & vitamin D

IBD patients have been observed, in population-based studies, to have 21–40% increased risk of fractures compared with the general population [31,32]. Glucocorticoid use is strongly associated with osteoporosis risk; however, other factors may influence osteoporosis risk, such as inflammation and nutritional deficiency [31]. Genetic differences may also play a role in osteoporosis in IBD. Several polymorphisms of the vitamin D receptor associated with IBD have been identified, although the clinical significance is as yet undetermined [33–35].

Glucocorticoid-induced osteoporosis mainly affects trabecular bone. Kuwabara *et al.* observed greater bone mineral density (BMD) deficiencies in the distal radius (cortical bone) compared with the lumbar spine (trabecular bone). This suggests factors other than glucocorticoid use (e.g., nutritional deficiency) as a contributing component to the osteoporosis burden in IBD [36]. van Staa *et al.* also demonstrated an increase in fractures after adjusting for corticosteroid use [37].

The frequency of vitamin D deficiency in IBD is difficult to determine as the optimal level of vitamin D is not clearly defined. Jahnsen *et al.* reported that 27% of CD and 15% of UC patients with low serum 25-hydroxyvitamin D (25-OH D) ( $<30$  mmol/l), but low 25-OH D levels did not correlate with low BMD [38]. By contrast, Leslie *et al.* reported on 101 IBD patients in Canada who were within 4 years of diagnosis. The mean age was 46.9 years with a prevalence of abnormal BMD of 9%. Serum 25-OH D levels correlated with BMD, and patients with gains in BMD over time positively correlated with serum 25-OH D [39].

Despite data to support the role of vitamin D and calcium in osteoporosis, early studies did not demonstrate improvement in BMD with oral calcium and vitamin D supplementation, although the supplementation of oral fluoride, in addition to calcium/vitamin D, was associated with an improvement in BMD [31,40]. Siffledeen *et al.* performed a randomized control trial (RCT) evaluating a bisphosphonate in addition to calcium and vitamin D supplementation [41]. No benefit was seen in the bisphosphonate group compared with the calcium/vitamin D supplement-alone group; however, both groups demonstrated improvements in BMD. Kitazaki *et al.* performed a small randomized trial of 39 patients with UC on glucocorticoids, comparing alendronate to alfacalcidol, demonstrating a significant improvement (4.1%) in BMD in the alendronate group at 6 and 12 months [42]. The 2003

American Gastrointestinal Association (AGA) guidelines for osteoporosis in gastrointestinal disease recommend that IBD patients with any of the following should be screened for osteoporosis with a dual energy x-ray absorptiometry (DEXA) scan: more than 3 months of corticosteroid use, low trauma fracture, postmenopausal female, male over 50 or hypogonadism [31]. All patients should be counseled regarding adequate vitamin D and calcium intake, smoking cessation, weight-bearing exercise and avoiding excessive alcohol intake. For patients with a T score between -2.5 and -1, who need to continue steroids, a bisphosphonate is recommended with a repeat DEXA scan in 1 year. For all patients with a T score below -2.5 or a history of vertebral compression fracture, a bisphosphonate is recommended [31].

### ■ Folate & vitamin B12

Folate and vitamin B12 deficiency have been reported in IBD. In addition to causing anemia, deficiency of either vitamin may result in hyperhomocystinemia, which is associated with hypercoagulability and thrombotic complications. Folate is absorbed in the proximal jejunum. Dietary intake of folate has been observed to be lower than healthy controls [1,43]. Patients on sulfasalazine are at particular risk for folate deficiency as it decreases intestinal transport. Vitamin B12 is absorbed in the terminal ileum and dietary intake of vitamin B12 has also been shown to be lower in IBD patients than healthy controls [1]. CD patients with either terminal ileum disease or extensive small-bowel resection have a particularly increased risk of vitamin B12 deficiency. Historically, ileal malabsorption of vitamin B12 was diagnosed with a Schilling's test; however, owing to increasing unavailability of the appropriate isotopes, this elegant test of intestinal physiology is rarely performed today.

In regards to repleting folate stores, folate supplementation has been demonstrated to increase RBC folate stores at doses of 15 mg/day for 1 month and may reduce C-reactive protein levels [44,45]. Folate supplementation has been evaluated as a method of chemoprevention of neoplasia. Case-control and retrospective cohort studies have suggested a protective effect of folate on colon cancer in UC [46,47]; however, no prospective trials have demonstrated benefit as of yet.

### ■ Other micronutrients

Deficiencies in micronutrients, such as zinc, selenium and antioxidant vitamins have been reported [48-50]. The impact of these deficiencies in IBD is

speculative, but may be important. Zinc deficiency is reported in up to 40% of CD patients, although overt clinical manifestations are uncommon [51]. Acute zinc deficiency may be seen in patients on total parenteral nutrition without zinc supplementation and manifests as dermatitis, alopecia, diarrhea and mental-status changes. Chronic zinc deficiency may present as impaired wound healing, depressed cellular immunity, growth impairment, visual disturbances, impaired male fertility and fistula formation [52,53]. Selenium is a trace mineral required as a cofactor for the antioxidant glutathione peroxidase. Clinical manifestation from selenium deficiency has not been described, although studies in animals suggest it is protective against chemical-induced inflammation and may be protective against cancer [54,55].

### Diet as therapy

Diet as therapy for IBD is an appealing concept. There are several potential mechanisms by which diet may alter the course of IBD. Most directly, diet modification might remove a toxin or an antigenic stimulus. This may be the underlying mechanism for the benefits of elemental diets. Alternatively, a change in diet may alter the bacterial flora. Given the increasing recognition that the intestinal flora may have an important role in health and disease, and the enthusiasm for probiotic therapy, this is an attractive hypothesis. Indeed, prebiotics are a well-accepted mechanism of modulating the intestinal flora. Finally, dietary modification may alter intestinal fluid transport and gas production, minimizing symptoms, but has no direct effect on the disease itself.

Altered dietary patterns are common in patients with IBD. Googling 'diet therapy and IBD' results in over 100,000 hits. The reasons for dietary modification are multiple. It is unclear how often these changes are the result of symptom relief, beliefs in more natural therapies or the result of physician instruction. Altered diets may be due to intolerances to specific foods. There may be unique intolerances to a limited number of similar foods, but very frequently, especially if there appears to be an increasing number of avoided foods, it may not be the individual nutrient, but a reflection of ongoing activity of intestinal inflammation. In this situation, it is important to counsel patients to avoid needless restrictions of the spectrum of available foods.

Ballegaard *et al.* demonstrated that 65% of IBD patients reported food intolerances, compared with 14% of healthy controls. Food restriction was not related to high-fiber foods, but was common among all food groups [56].

### ■ Enteral therapy

Enteral therapy has been described as beneficial for the primary treatment of CD. Although enteral therapy can avoid corticosteroid exposure, a major hurdle lies in the unpalatability of most formulations and subsequent difficulties with compliance or the requirement for nasogastric feedings to tolerate therapy. A *Cochrane review* of enteral therapy in CD concluded that enteral nutrition was beneficial but inferior to corticosteroids for the induction of remission in CD [57]. There was no difference in efficacy in elemental or nonelemental formulas, or in fat content or quality of formulas. A trend was observed favoring the response of very low-fat and very low-triglyceride enteral formulations compared with high-fat formulations; although, it was not statistically significant (OR: 1.55, 95% CI: 0.75–3.23). The authors add caution in making conclusions based on trends owing to the large heterogeneity of studies. The studies included in the article compared different fatty-acid content making general conclusions difficult. Bamba *et al.* performed a small, RCT of 10 patients comparing linoleic acid content within elemental diet therapy for CD [58]. They concluded that the addition of linoleic acid attenuated the therapeutic effect of an elemental diet in CD. By contrast, Sakurai *et al.* performed a randomized controlled study of 37 patients, comparing a low-fat elemental diet with a polymeric diet with a high amount of medium-chain triglycerides and linoleic acid, and demonstrated clinical remission in both groups (67 and 72%, respectively) with no difference of efficacy based on medium-chain triglycerides or linoleic acid content [59]. The study of long-chain triglycerides, given the highest weight in the *Cochrane review*, compared oleic acid with similar amounts of linoleic acid and demonstrated no difference between high and low oleic acid content in enteral formulations [60].

### ■ Nutritional supplements

A significant number of IBD patients take nutritional supplements, herbal medicines, and alternative and complementary medicines. Unfortunately, the data to support the use of many of these strategies are extremely limited. There are, however, some high-quality studies that have focused on nutritional supplements as a therapy in IBD. As described previously, omega-3 PUFA have a potential effect in decreasing inflammation in IBD. Belluzi *et al.* performed a randomized, double-blind placebo-controlled trial of omega-3 PUFA (40% EPA, 20%

DHA) for the maintenance of remission in 78 CD patients [61]. They observed a 33% absolute risk reduction of relapse in the omega-3 PUFA group. A subsequent RCT by Lorenz-Meyer *et al.* showed no clinical benefit [62]. Recently, two large RCTs evaluated the efficacy of omega-3 PUFA (50–60% EPA, 15–20% DHA) on CD, EPIC-1 and -2 [63]. They demonstrated a trend towards a benefit of omega-3 PUFA; however, this did not reach statistical significance. A *Cochrane review* on omega-3 PUFA and CD demonstrated a small pooled benefit for the maintenance of remission (RR: 0.77, 95% CI: 0.61–0.98); however, the authors concluded that there was probably no true benefit owing to the heterogeneity of studies and the likelihood of publication bias [64]. Another *Cochrane review* on omega-3 PUFA in the maintenance of remission in UC included three RCTs, none of which demonstrated benefit compared with placebo. All three studies were small (<100 patients), and two of the studies used olive oil as placebo, which may not be inert [65].

### ■ Dietary fiber

Dietary fiber has demonstrated promise as a therapy for UC. The mechanism of action of dietary fiber is potentially threefold. Dietary fiber is converted to short-chain fatty acids, which act as an energy source for colonocytes, modulate the local immune response (attenuate IL-6, IL-8 and TNF- $\alpha$ ) and modify the intestinal microbial balance towards nonpathogenic bacteria (prebiotic effect) [66]. Butyrate has been evaluated as a beneficial short chain fatty acid for the treatment of UC. A pilot study of topical butyrate in distal UC demonstrated benefit; however, a subsequent RCT demonstrated a trend towards benefit but did not reach statistical significance [67,68]. Dietary intake of fiber can increase colonic butyrate levels. Hallert *et al.* performed a pilot study demonstrating that an increase of dietary fiber intake of 60 g of oat bran daily can increase fecal butyrate levels by 36% [69]. They did not observe any exacerbation of symptoms in the 22 UC patients in remission with the increase of dietary fiber. Kanauchi *et al.* performed an open-label control trial of 18 patients with mild-to-moderate UC, treated with 20–30 g/day of germinated barley foodstuff [70]. A clinically significant benefit was observed in the germinated barley foodstuff-treated group and increased fecal concentrations of *Bifidobacterium* and *Eubacterium limosum* were detected. Not all dietary fiber may be beneficial. As described earlier, rapid FODMAPS have been

proposed as a risk factor for the development of IBD by increasing intestinal permeability when fermented in the terminal ileum or cecum.

### ■ Defined diets as therapy

Many IBD patients, seeking a dietary solution to their disease, will encounter numerous possibilities accompanied by explanations of the mechanisms of action and the expected testimonials. For several years, the most common of these have included the specific carbohydrate diet (SCD), the Maker's diet and a variety of 'juicing diets' [71,72]. Physicians will often feel uncomfortable providing opinion or feedback to their patients, especially as there is almost no evidence-based information. It is unlikely that any well-designed randomized studies will be forthcoming.

Nevertheless, it may be reasonable to become familiar with the outlines of some of these diets. SCD was developed by a biochemist after observing a beneficial response with colitis to a low-carbohydrate, gluten-free diet with the goal of changing the intestinal flora. The SCD is an extremely low carbohydrate diet, prohibiting sugar, fructose, high-fructose corn syrup, all grains, some legumes, starchy tubers (e.g., potatoes), bread, pasta, milk products, and canned fruits and meats. It does permit meats, poultry, fish, eggs, and fresh or frozen vegetables. Honey is allowed for sweetening. There clearly are internal inconsistencies in the SCD and major contradictions with other popular programs, such as the Maker's diet. Each of these diets has vociferous proponents and detractors. From our experience many patients will try one of these diets, some will experience a variable amount of benefit, but few will adhere to the diet over an extended period [HOU JK, SELLIN JH, UNPUBLISHED DATA]. Physicians should encourage patients to discuss their attempts at dietary modifications and ensure that basic nutritional requirements are being met.

### ■ Complementary & alternative medical therapies

The use of complementary and alternative medicines is commonplace in the general population and particularly in IBD. Over 30% of western populations and up to 50% of IBD patients report the use of complementary and alternative medicines [73,74]. Of complementary and alternative medicines, herbal therapies are the most commonly used. Several herbal therapies have demonstrated efficacy in clinical trials; however, the size and quality of studies to date do not yet endorse the routine use of herbal remedies in IBD (TABLE 1).

Curcumin is a natural compound from the plant *Curcuma longa* Linn and has been evaluated for use in both UC and CD. Curcumin exerts anti-inflammatory and antioxidant properties in animal models via suppression of the activation of NF- $\kappa$ B [75]. Holt *et al.* performed a pilot study of curcumin in five CD patients and five UC patients with four of five CD patients and all five UC patients clinically improving based on CD activity index and medication usage [76]. Hanai *et al.* performed a randomized, double-blind, placebo-controlled trial of curcumin in the maintenance of remission in UC [77]. A total 89 patients were enrolled with quiescent disease. All patients were given sulfasalazine or mesalamine but use of prednisone, immunologic therapy or biologic therapy was not permitted. Treatment patients received 1 g of curcumin twice daily. They reported a statistically significant benefit of the primary end point of maintenance of remission at 6 months, with 4.7% of patients in the curcumin arm and 20.5% of patients receiving placebo relapsing ( $p = 0.04$ ). They also observed a statistically significant improvement in both clinical activity index and endoscopic index in the curcumin arm but not the placebo arm at 6 months. They reported a 6 month follow-up after curcumin therapy was discontinued, demonstrating a convergence of relapse rate in both groups, again suggesting the benefit of curcumin. The potential benefit of curcumin and lack of significant adverse events cannot be ignored and warrants further investigation.

Small randomized trials have been performed with other herbal remedies for UC. *Aloe vera* is a derivative of *Aloe barbadensis* Miller and

**Table 1. Herbal medications demonstrating benefit in Crohn's disease and ulcerative colitis in clinical trials.**

	Common name	Clinical trials
<b>Crohn's disease</b>		
<i>Artemisia absinthium</i>	Wormwood	RCT (81)
<i>Boswellia serrata</i>	Frankincense	RCT (82)
<i>Tripterygium wilfordii</i>	Lei gong teng	Open, prospective (83)
<i>Pistacia lentiscus</i>	Chios mastic	Open, prospective (84)
<i>Curcuma longa</i> Linn	Curcumin	Open, prospective (74)
<b>Ulcerative colitis</b>		
<i>Curcuma longa</i> Linn	Curcumin	RCT (75)
<i>Aloe barbadensis</i> Miller	Aloe vera	RCT (77)
<i>Triticum aestivum</i>	Wheat grass	RCT (78)
<i>Oenothera biennis</i>	Evening primrose	RCT (79)
<i>Boswellia serrata</i>	Frankincense	Open, prospective (80)
RCT: Randomized controlled trial. Data taken from [1,87].		

contains numerous biologically active compounds that have possible anti-inflammatory and antioxidant properties [78]. *Aloe vera* was evaluated in a double-blind, placebo-controlled trial of 44 patients with active UC. At 4 weeks, patients treated with *aloe vera* demonstrated a statistically significant higher rate of response (47 vs 14%;  $p = 0.048$ ); however, no differences were detected for remission, endoscopic score or histologic score [79]. Wheat grass (*Triticum aestivum*) was also evaluated with a randomized, double-blind, placebo-controlled trial in 23 patients with active distal UC [80]. At 1 month follow-up, treatment patients demonstrated a statistically significant improvement in disease activity and a decreased severity of rectal bleeding. Evening primrose (*Oenothera biennis*) demonstrated improvement of stool consistency in a small RCT compared with placebo or fish oil in patients with stable UC; however, it did not show improvement in disease relapse or endoscopic scoring [81]. Frankincense (*Boswellia Serrata*) inhibits 5-lipoxygenase and has been shown to have similar efficacy to sulfasalazine for UC in a small, uncontrolled, prospective study [82].

Data also exist on the use of herbal therapies for CD. Wormwood (*Artemisia absinthium*) has been evaluated in a double-blind placebo-controlled trial to have a steroid-sparing effect [83]. Frankincense in CD, in a RCT of 83 patients, demonstrated noninferiority compared with mesalamine in a per-protocol analysis [84]. Lei gong teng (*Tripterygium wilfordii*), a traditional Chinese herbal remedy and Chios mastic (*Pistacia lentiscus*), a derivative of a Mediterranean evergreen shrub, have been demonstrated, in small, prospective series to have a potential benefit in CD [85,86].

### Conclusion

Diet plays an important role in IBD. Dietary components, such as linoleic acid and FODMAPS, may increase the risk of developing IBD in the genetically predisposed host. Vegetable, fruit, nut, fish, dietary fiber intake and omega-3 fatty acids may be protective from the development of CD. Although protein-calorie malnutrition is becoming less common in IBD, micronutrient deficiencies may predispose to complications, such as osteoporosis, hypercoagulability, malignancy and poor wound healing. Enteral formulas have a proven efficacy in inducing remission in CD; however, they are less efficacious than corticosteroids. The high prevalence and interest

level of patients for dietary supplements and herbal remedies to treat IBD make it necessary that physicians are aware of what is available, and what is potentially beneficial or harmful. Dietary supplementation of omega-3 fatty acids have biologic plausibility as a treatment of IBD; however, current studies do not demonstrate significant benefit. Further studies evaluating dose effect and formulations are necessary to determine efficacy. Slowly fermenting dietary fiber that increase colonic butyrate may be beneficial in UC. Curcumin and other herbal therapies have demonstrated potential efficacy in the treatment of IBD. Patients may embark on their own dietary modifications to control symptoms, minimize conventional medicines and, perhaps, minimize their disease.

The role of diet and nutrition in IBD are complex, overlapping, important and poorly defined. Despite considerable interest in these areas, there is not much definitive information. Global malabsorption that dominated the clinical presentation of IBD for decades has become less common. Instead, there are much more subtle deficiencies in specific nutrients that require careful attention by physicians caring for patients with UC and CD. Recognizing and replacing nutritional deficiencies is relatively straightforward, in comparison to delineating the role of discrete nutrients in either causing or treating IBD. There are some tantalizing threads of evidence that polyunsaturated fats and specific classes of carbohydrates may play a role in IBD, but the data are far from conclusive. Compared with the recent explosion in knowledge regarding the genetics of IBD, this area of research is challenged by the lack of elegant and precise methodologies to confidently define the role of diet and nutrition.

### Future perspective

Given the increasing interest in the role of diet and nutrition in IBD, this will no doubt be an area of increasing research. The challenge will be to design and execute studies that provide convincing evidence that a specific nutrient or type of diet has a major impact on the course of IBD. Epidemiologic studies may provide more clues as to the role of a 'westernized' diet in the changes in incidence of IBD in particular countries or demographic groups. However, these 'guilt by association' studies will need to be followed by more focused investigations that carefully delineate the potential mechanisms and/or benefit of a specific suspect. There are several promising dietary components, including

curcumin and wormwood, that should be tested in rigorous randomized controlled studies to determine whether they indeed have a role in treating IBD. Whether these studies ever come to fruition may depend on their ability to gather enough interest from pharmaceutical companies. Unfortunately, we will probably still be struggling to understand the impact of diet and nutrition in IBD in 2015.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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### Executive summary

- Diet plays an important role in inflammatory bowel disease (IBD).
- Dietary components, such as linoleic acid and fermentable oligo-, di- and monosaccharides and polyols, may increase the risk of developing IBD.
- Dietary components, such as fruits, vegetables and omega-3 fatty acids, may be protective against developing IBD.
- Micronutrient deficiencies are prevalent in IBD and may predispose to complications.
- Studies suggest that diet modification may be useful as therapy in IBD.
- Herbal therapies, such as curcumin, have been demonstrated to be effective in treating IBD in small, randomized trials.

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▪▪ of considerable interest

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