Nutritional Medicine Journal

Inflammatory Bowel Disease: Towards a Model for Personalised Nutritional Therapy

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Abstract

Inflammatory bowel disease (IBD) has a complex multifactorial aetiology involving interactions between environmental factors (including diet), the microbiome, genetics and the immune system, leading to dysfunctional immune responses and chronic inflammation. Dietary factors and gut dysbiosis have emerged as important treatment targets in the management of IBD as they are involved in the initiation and perpetuation of inflammation, and subsequently disease development and progression. Specific dietary approaches and nutritional interventions have some, albeit limited, clinical evidence to suggest they can modify gene expression, have anti-inflammatory effects, induce mucosal healing, normalise intestinal microbiota, reduce disease activity and/or help maintain remission. This review uses evidence from nutritional science to propose a theoretical pragmatic model for the personalisation of nutritional therapy in patients with active or latent IBD, incorporating disease-modifying dietary recommendations and nutrient-based supplements, primarily as adjuvant therapies, with the intention to stimulate further investigation and research.

Cite as: Brown, B. (2022) Inflammatory bowel disease: towards a model for personalised nutritional therapy. Nutr. Med. J., 1 (1), 32-59.
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Article history: Received 25 February 2022; Peer-reviewed and received in revised form 11 March 2022; Accepted 14 March 2022. Available online 31 March 2022
Published by: The Nutritional Medicine Institute

Introduction

Inflammatory bowel disease (IBD) refers to a group of chronic inflammatory autoimmune diseases, of which the most prevalent types are ulcerative colitis (UC) and Crohn's disease (CD), that have a frequency of > 0.3% of the population in industrialised countries.[1] UC primarily affects the colonic mucosa in a diffuse, continuous and superficial pattern.[2] In contrast, CD can affect any section of the gastrointestinal tract, including the small and/or large intestine, the mouth, oesophagus, stomach and anus.[3] Clinical symptoms of IBD include diarrhoea and/or constipation, passage of blood and/or mucus, abdominal pain and cramping, fever and signs of bowel obstruction, as well as diverse extraintestinal manifestations.[4]

The development of IBD involves an interaction between genetic influences, environmental factors, dysregulated immune responses and alterations of the gut microbiome.[5] Importantly, genetic factors only account for a small part of disease variance, emphasising the role of gut microbial factors, alterations in intestinal immune homeostasis and environmental influences in inducing gut inflammation.[6] Genetic backgrounds, life-long environmental exposures, microbial organisation and immune responses differ from person to person, and give rise to remarkably complex disease processes that are highly variable, suggesting that there are multiple disease subtypes or that each individual has a pathophysiology that is unique.[7] This biological heterogeneity and complexity may help explain why traditional therapeutic interventions that target chronic inflammation have limited effectiveness and ultimately fail.[8]

Drug therapy of IBD centres on induction and maintenance of remission. Common drug treatments include aminosalicylates, corticosteroids, thiopurines, methotrexate and anti-tumour necrosis factor (TNF) agents.[9] While drug therapy can help reduce symptoms and induce remission, 90% of people with UC and CD may experience a relapsing course of their illness.[10,11] Limitations of efficacy and toxicity of traditional drug treatments might be overcome with the development of personalised therapies based on advances in understanding of disease pathophysiology.[12]

A better model for the management of IBD could consider the multiple antecedents, triggers and mediators that interact to produce gut immune dysregulation and uncontrolled inflammation as opportunities for personalised interventions that target an individual's underlying pathophysiology.[13] This approach has been termed 'functional medicine', and developed as a clinical operating model that enables healthcare providers to leverage evidence-based integrative therapies in a highly personalised way.[14,15] Considerable research has provided evidence for modifiable environmental and lifestyle factors,[16] microbiota-targeted therapies,[17] dietary interventions,[18] and herbal and nutritional medicines[19] that could be individually tailored to improve acute treatment and maintenance of remission in patients with IBD.

The aim of this narrative review is to explore clinical evidence for nutritional interventions that may influence the disease course and thus be candidates for the treatment of active disease and maintenance of remission. Nutritional interventions are then organised into a pragmatic integrative model for personalised patient management that could be explored in further clinical research.

Dietary interventions

There are number of dietary risk factors for the development of IBD, many of which are typical of industrialised dietary patterns; high intakes of red meat, refined sugar, total fat and omega-6 fatty acids, and low intakes of dietary fibre, fruit and vegetables.[20] Diet is a potent modifier of gene expression, gut microbial composition and mucosal immunity, all of which play a fundamental part in both risk and the progression of IBD.[21] Observations from epidemiological and experimental studies have resulted in the formulation and evaluation of dietary interventions designed to halt disease

progression and maintain remission in patients with IBD with clinical evidence that dietary therapy plays an important role in disease treatment (summarised in Table 3).[22,23,24]

Healthy diets

A traditional Mediterranean-style diet (MED-DIET) modified to reduce inflammation and exclude foods that aggravate CD was found to result in a trend towards reduction in biomarkers of inflammation [C-reactive protein (CRP) and micronuclei numbers], a change in the expression of inflammation-relevant genes, and improvement in gut bacterial diversity after 6 weeks.[25] In this study, patients were provided with food items including salmon, organic avocados, sweet potato, a variety of vegetables, gluten-free bread, extra virgin olive oil, green tea, honey, and fish oil capsules. Another study assessed the multidimensional impact of a MED-DIET in patients with IBD over 6 months, and found the diet significantly reduced malnutrition-related parameters (improved body composition), liver steatosis, disease activity, and the inflammatory biomarkers CRP and faecal calprotectin.[26] Similarly, a MED-DIET improved nutritional status and reduced faecal calprotectin in paediatric patients with IBD.[27]

A low-fat, high-fibre diet (10% of calories from fat) was compared with an improved standard American diet (35–40% of calories from fat, with increased fruit and vegetable intake) in a parallel-group, crossover study of 17 patients with UC in remission or with mild disease over 4-week dietary intervention periods. Primary outcomes were quality of life, markers of inflammation, and faecal markers of intestinal dysbiosis. Although both diets improved quality of life, the low-fat, high-fibre diet decreased markers of inflammation and reduced several biomarkers of intestinal dysbiosis.[28]

A semi-vegetarian high-fibre Japanese diet that includes a gradual transition from white to brown rice, eggs, milk, miso soup, vegetables, fruits, legumes, potatoes, pickled vegetables and plain yoghurt daily, with fish once a week and meat once every 2 weeks, was found to be effective at maintaining remission in adults with CD in a 2-year prospective study. Remission was maintained at 94% in the semi-vegetarian diet group versus 33% in controls, and relapse rates at 1 year and 2 years were 0% and 8% versus 33% and 75% in controls. Furthermore, the semi-vegetarian diet was associated with normal CRP in more than half of the patients.[29]

Several additional reports have subsequently supported the efficacy of the semi-vegetarian diet. In a case report, the semi-vegetarian diet was found to induce remission without medication in a patient with UC that developed after a low-carbohydrate weight-loss diet.[30] In another case report, the semi-vegetarian diet was used to successfully treat recent onset of UC during pregnancy.[31] A study examining the effects of the semi-vegetarian diet with infliximab for inducing remission in CD (n = 44) found that 100% achieved symptomatic remission in per-protocol analyses, with significant reduction in CRP and mucosal healing achieved in 46% of cases.[32] A second study of the semi-vegetarian diet and infliximab as first-line therapy for achieving remission demonstrated a high remission rate (76%; n = 17), low colectomy rate (6%), a significant decrease in CRP and erythrocyte sedimentation rate (ESR) at week 6 (9.42 mg/dl to 0.33 mg/dl, and 59 mm/hour to 17 mm/hour, respectively), and low 1-year remission rate (25%) and no additional colectomy cases.[33] Most (77%) patients with mild UC or UC in remission who received hospital-based dietary education had an improvement in symptoms at 2 weeks, and relapse rates were lower than those reported for medication over a median 3.6-year follow-up.[34] In a different cohort, patients with mild to severe active UC treated with the semi-vegetarian diet had a cumulative relapse rate of 14% at 1- and 27% at 5-year follow-up, considerably lower than those reported with conventional therapy (about 50% at 1 year).[35]

A diet low in sulphur-containing amino acids, particularly from red meat, dairy products and eggs, has been proposed to play a role

in the development and progression of IBD by increasing the intestinal concentration of hydrogen sulphide and impairing butyrate synthesis.[36,37,38,39] Possible adverse reactions to sulphite food preservatives E220–E228 also deserve consideration.[40] Meat is an important contributor to sulphide generation by bacteria in humans.[41] However, this theory is controversial as hydrogen sulphide has also demonstrated gastroprotective effects.[42] Similarly, experimental studies of sulphur-containing amino acids are equivocal. Methionine may contribute to IBD pathogenesis at high dietary intakes;[43] however, several studies have demonstrated gastroprotective effects of methionine and other sulphur-containing amino acids.[44] Interestingly, hydrogen sulphide production may be independent of dietary sulphate and suppressed by prebiotic fibre.[45]

A prospective study of patients with UC in remission found that higher consumption of meat, especially red and processed meat, total protein, sulphur and sulphate were associated with disease relapse when compared with lower intakes.[46] Also, a small uncontrolled pilot study assessing a low-sulphur diet [avoiding eggs, cheese, whole milk, ice-cream, mayonnaise, soya milk, mineral water and sulphite-containing drinks (wine and cordials), nuts, cruciferous vegetables, and red meat] in patients with UC suggested better maintenance of remission after 56 months versus medication with evidence of marked histological improvement, reduced number of bowel movements (from 6 to 1.5 per day) and reduced medication requirement.[47] Additional evidence from semi-vegetarian diet studies discussed above suggests that a vegetarian or semi-vegetarian diet may be a feasible approach, but whether it is due to restriction of dietary sulphur or some other factor(s) is unclear.[48] Dietary changes used in these studies are complex, and attributing their effects to a simple mechanism such as reduced sulphur intake may be overly simplistic and difficult to substantiate.

The IBD-AID

A multi-component, multi-functional IBD-targeted diet simplistically termed the anti-inflammatory diet (IBD-AID) was developed for the treatment of IBD, and has some evidence to suggest it is an effective regime. The aim of the diet is to induce and maintain remission, and it restricts the intake of lactose, and refined or processed carbohydrates. Foods include soluble fibre, leeks, onions and fermented foods, red meat is replaced with fish high in omega-3 fatty acid content and chicken, olive oil is used in cooking and coconut oil in baking. The diet is also personalised to account for nutritional deficiencies and food intolerances, and stages the textures of the foods to improve absorption of nutrients and minimise intact fibre depending on the symptomology of the patient. In a case series report, 60% of patients with UC and CD treated with IBD-AID had either a good or very good clinical response after reaching compliance with a large reduction in symptoms scores, and all patients could discontinue at least one of their prior IBD medications.[49] In a subsequent clinical study, patients with CD were randomised to IBD-AID plus prebiotic fructooligosaccharides (FOS), FOS alone, or a placebo and control diet. The subjects were followed until either they had a flare or for up to 12 months. No subject flared in the IBD-AID group, while 31% flared in the FOS group, and 21% flared in the placebo group. There was a trend for longer survival without flare in the diet intervention group, and examination of the 16S rDNA sequencing data demonstrated significant increases in the mean abundance of the beneficial gut bacteria Roseburia after the diet intervention.[50]

The autoimmune protocol (AIP) diet

An AIP diet developed for IBD management was tested in patients with UC and CD. The aim of the diet was to reduce intestinal inflammation, dysbiosis and/or symptomatic food intolerance, and the regime consisted of a 6-week elimination phase (staged elimination of grains, legumes, nightshades, dairy, eggs, coffee, alcohol, nuts and seeds, refined/processed

sugars, oils and food additives) followed by a 5-week maintenance phase (during which no food group reintroduction was allowed). Nutritional deficiencies in iron and vitamin D were also treated with supplementation. Clinical remission was achieved by week 6 by 11/15 (73%) of study participants, and all 11 maintained clinical remission during the maintenance phase of the study. At the end of the study period, symptom scores, quality of life and faecal calprotectin were all significantly reduced, and endoscopic improvements were noted in those who underwent follow-up endoscopy. However, CRP did not significantly change during the study, and two participants with CD with ileal strictures developed either worsening disease activity or partial small bowel obstruction.[51,52] Overall, this study suggests potential benefits in UC, but the benefit and safety in CD is uncertain.

Personalised elimination diets

The use of empirical elimination re-challenge diets to identify food intolerances and construct a personalised exclusion diet has been well studied in CD.[53] Typically the re-challenge phase is preceded by induction of remission with an elemental diet (a liquid nutritional formula providing essential nutrients and hypo-allergenic protein as free amino acids). In one such study, 84% of patients with active CD achieved clinical remission within 14 days of commencing an elemental diet, and were then assigned to either glucocorticoids or an elimination re-challenge diet (reintroduction of foods). Remission lengths were significantly greater in the diet group (3.8 versus 7.5 months), with 45% remaining disease-free for at least 2 years.[54]

Immunoglobulin G (IgG) antigens against foods have been reported to be significantly higher in patients with CD than in healthy controls, and IgG-based testing has been used with some success as a guide for an elimination diet in patients with CD.[55,56] A 6-week intervention study in patients with CD found improvements in stool frequency, abdominal pain, general well-being and IFN gamma secretion of T-cells when compared with a sham diet.[57] In another study, 90% of patients with CD reported symptomatic improvement, with a reduction in inflammatory biomarkers and IgG titres for the excluded foods.[58] More recently, treatment of CD with an IgG-based exclusion diet resulted in significant improvements in symptoms and a reduction in faecal calprotectin in those with more severe disease.[59] This approach may help maintain remission, with an IgG-based exclusion diet resulting in better control of inflammatory biomarkers and a disease relapse rate of 12.5% versus 25% in controls.[60]

In one study of patients with UC, an IgG-based exclusion diet for 6 months significantly reduced symptoms scores, resulted in greater reduction in extraintestinal complications, greater improvements in body composition and albumin, and improvements in quality of life when compared with a control group.[61] Although most research of IgG-based exclusion diets has been in patients with CD, this report suggests a potential benefit for UC that requires further investigation.

Gluten-free diet for non-coeliac gluten sensitivity and coeliac disease

Non-coeliac gluten sensitivity (NCGS) may be more frequent in patients with IBD and could contribute to disease activity, although more research is needed to clarify the role of gluten-free diets. A majority (65.6%) of patients with IBD who have initiated a gluten-free diet independent of a diagnosis of coeliac disease report symptom improvement, and nearly 40% report fewer disease flare-ups.[62] In patients with IBD, NCGS has been shown to be more frequent than in irritable bowel syndrome (IBS) and dyspeptic controls, and has been associated with more severe clinical symptoms and stricturing disease.[63] Of relevance, NCGS may be related to an autoimmune phenotype with higher proportions of patients developing autoimmune disorders, positive for antinuclear antibodies, and with DQ2/DQ8 haplotypes compared with patients with IBS.[64] In a case report, a patient with severe treatment-resistant UC and absence of coeliac disease achieved

full clinical remission (including severe bloody diarrhoea) and improvement in laboratory data (including ESR) within 12 weeks of a gluten-free diet, with symptom exacerbation on subsequent exposure to gluten that again resolved with a gluten-free diet.[65]

Patients with coeliac disease have been reported to have a three–10 times higher prevalence of IBD compared with those without coeliac disease in some studies.[66,67,68] Currently there are no prospective controlled studies of a gluten-free diet for patients with IBD with coeliac disease.[69] However, several case reports have described important clinical improvements in patients with IBD and coeliac disease treated with a gluten-free diet and medication.[70,71,72,73,74] The presence of coeliac disease should be ruled out, and in cases of confirmed coeliac disease a gluten-free diet should be initiated.

Additive-free diets

Industrial food additives such as bulking agents, colourings, emulsifiers, enzymes, flavour enhancers, preservatives, stabilisers and sweeteners have been suggested to play an important role in the development of autoimmune diseases including IBD.[75] In experimental studies, several food additives have been linked to alterations in the gut microbiome, intestinal inflammation and/or the development of IBD, including the emulsifiers polysorbate-80 and carboxymethylcellulose,[76,77,78] the thickener carrageenan,[79] non-caloric artificial sweeteners including sucralose,[80] acesulfame potassium[81] and saccharin,[82] the polysaccharide maltodextrin,[83] the whitener and anti-caking agent titanium dioxide[84], ethylenediaminetetraacetate (EDTA)[85], and the widely-used (yet typically undisclosed on product labels) enzymes, microbial transglutaminases.[86] Dietary exposure to such additives, in particular maltodextrin and carrageenan, has been estimated to be frequent in children with CD, although this was not related to disease severity.[87] A carrageenan-free diet has been examined in patients with UC in remission. The study had two arms, a carrageenan-free diet with either placebo capsules or carrageenan capsules (200 mg/day), to tease out the effects of carrageenan exposure. Despite being a relatively small study group of 12 people, and the carrageenan capsules providing less than average daily dietary exposures, the results were striking. At the end of the study, three patients who received carrageenan-containing capsules relapsed, while none of those who received placebo-containing capsules had a relapse. And laboratory tests showed increases in the inflammatory markers interleukin (IL)-6 and faecal calprotectin in the carrageenan-exposed group, but not in the placebo group.[88] Although evidence for adverse effects of carrageenan are limited, so too are safety data, and avoiding or eliminating exposure to this food additive would be advised in general.[89]

A diet containing low levels of oxides of titanium, aluminium and/or silicon was found to accelerate disease remission in patients with CD treated with corticosteroids in a pilot study.[90] However, a subsequent large, multi-centre, double-blind trial failed to replicate these findings.[91] More investigation is needed to clarify their contribution to IBDs.[92]

Maltodextrin is estimated to be found in about 60% of all packaged food products, with most people consuming foods containing maltodextrin at least twice a day.[93] Experimental evidence suggests that maltodextrin impairs defences against pathogenic gut bacteria, and increases the proximity of such bacteria to the epithelium.[94] Importantly, analysis of mucosa-associated bacteria in people with CD showed increased prevalence of a gene essential for maltodextrin metabolism.[95] However, clinical trials of maltodextrin-free diets are lacking.

In one study of 18 patients with CD, a 6-week organic diet low in ‘environmental factors’ such as fertilisers, pesticides, preservatives

and food additives was found to result in significant improvements on either magnetic resonance imaging or endoscopy evaluation as well as sonography in patients with CD when compared with a control diet based on the same non-organically produced foods. However, disease activity scores were similar to the control group.[96]

Specific carbohydrate diet (SCD)

Originally developed for the management of coeliac disease symptoms in the 1950s,[97] the SCD was popularised with the book 'Breaking the Vicious Cycle' in the 1980s for the management of IBD.[98] The original premise for the diet was that restriction of complex carbohydrates and refined sugar from the diet would prevent malabsorption and symptom development, later the hypothesis was expanded to include the idea that malabsorbed carbohydrates could cause bacterial dysbiosis and contribute to the intestinal inflammation of IBD. Research partially supports this theory with the finding that the microbiome of patients with IBD following the SCD may become more biodiverse and characterised by higher levels of anti-inflammatory bacteria.[99,100] The SCD is a modified carbohydrate diet that excludes disaccharides and most polysaccharides, but allows consumption of monosaccharides. The diet is also supplemented with homemade yogurt.

Numerous case reports suggest important clinical benefits of the SCD in paediatric patients with IBD.[101,102] For example, in paediatric CD treatment with the SCD for an average of 14 months, clinical symptoms were resolved, and laboratory indices were improved or normalised, including serum albumin, CRP, haematocrit and stool calprotectin.[103] Also in an adult woman with UC refractory to medication, the SCD diet improved symptoms within 3–6 months and resulted in remission, determined through colonoscopy, within 2 years.[104]

In the first prospective clinical study of the SCD, nine children with CD were enrolled in dietary treatment over a 12-week period, then continued the programme for up to 52 weeks. Within the first 12 weeks there was a significant clinical and mucosal improvement, with seven of the children (60%) achieving clinical remission by 12 weeks. Sustained clinical remission was seen in six of the seven patients who remained on the diet for 52 weeks.[105] A subsequent 12-week study in paediatric patients with active CD compared a SCD diet with more flexible versions; a modified SCD with oats and rice (MSCD); or a whole-food diet (WF) eliminating wheat, corn, sugar, milk and food additives. All the diets were associated with 100% clinical remission and reductions in CRP and ESR, although reductions in these inflammatory biomarkers were greater in the SCD and MSCD groups, and all patients had changes in their microbiome.[106]

In adults with CD, an intervention trial comparing the SCD with the MED-DIET found similar clinical and inflammatory biomarker responses. Symptomatic remission at week 6 was 46% versus 43%, faecal calprotectin response was 34% versus 30%, and CRP response was 5% versus 3% for the SCD versus MED-DIET, respectively, suggesting that the MED-DIET, because it is less restrictive, may be preferred to the SCD with mild–moderate CD.[107]

Low-FODMAP diet

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (low-FODMAP diet) has been investigated in IBD, primarily for relief of IBS-like symptoms. In patients with IBS-like symptoms and IBD, either in remission or mild–moderate disease, a 6-week low-FODMAP diet significantly reduced IBS symptom scores and improved IBD-related quality of life.[108] A 6-week low-FODMAP diet was found to reduce IBD disease activity scores and reduce faecal calprotectin in patients with mild IBD or IBD in remission.[109] However, a subsequent clinical trial found improvement in IBS symptom scores but no reduction in inflammatory biomarkers.[110]

Genotype-guided diet

Genotype-guided personalised nutrition may have relevance in IBDs, with some evidence to suggest certain gene variations may be associated with food intolerance, and also help guide dietary interventions and nutritional supplementation.[111] Regarding food intolerances, patients with CD without the GSTT1 (–/–) variant of the GST gene were found to be less likely to tolerate the brassica vegetables broccoli, cauliflower and Chinese greens in a cohort from Auckland, New Zealand.[112] In the same cohort, patients carrying the G allele of FOXO3 were found to be less likely to tolerate mustard, wasabi, and raw and cooked tomatoes.[113] Those with the rs1050152 variant of the organic cation transporter gene OCTN1 were found to be significantly more likely to be intolerant to mushrooms.[114] Genetic lactase persistence as indicated by the T allele of rs4988235, the gene encoding for lactase-phlorizin hydrolase (lactase), had a higher risk of CD.[115] As these studies were carried out in a unique cohort from New Zealand, it is important to emphasise that the same results may not always apply to other populations.[116]

Functional foods

In addition to more complex dietary changes, the addition of certain foods to the diet of patients with IBD has been shown to reduce disease severity. Patients with UC who added 600 g of salmon per week to their usual diet for 8 weeks had significantly reduced symptoms scores and a tendency of decreased levels of CRP.[117] Patients with UC who consumed bilberries equivalent to 600 g a day of fresh berries for 9 weeks had a 90% treatment response, a 63% remission rate, a significant decrease in faecal calprotectin, and in colonic biopsies reduced pro-inflammatory and enhanced anti-inflammatory cytokines.[118,119] The addition of 60 g of oat bran daily to the diet of patients with UC for 4 weeks increased stool butyrate concentration by 36%, and reduced symptoms of abdominal pain and reflux.[120] Also, 50 ml of olive oil daily for 20 days decreased the inflammatory markers CRP and ESR, and improved gastrointestinal symptoms in patients with UC.[121]

Micronutrient deficiencies and therapy

Nutritional deficiencies are commonly associated with IBD, especially deficiencies in vitamins A, C, D, K, B3, B6, B12, folate, magnesium, calcium, iron, selenium, zinc and copper.[122,123] Medications can further contribute to deficiencies, for example corticosteroid therapy reduces absorption of calcium in the intestine,[124] and sulfasalazine and methotrexate increase folate requirement.[125] Although micronutrient deficiencies may not be associated with overt clinical symptoms of deficiency-related disease (e.g. scurvy), they are associated with extraintestinal complications, including anaemia, bone disease, cardiovascular complications, impaired wound healing and colorectal cancer risk.[126] Supplementation with micronutrients is not only important for treating deficiencies, in some cases micronutrients may help to reduce disease activity and maintain remission.[127] Although several experimental studies suggest important effects of various micronutrients on colonic inflammation in IBD, human studies exploring the effects of micronutrients on disease activity are limited.[128]

Vitamin D deficiency is prevalent in the general population, and is 3.2 times higher in patients with IBD.[129] Vitamin D treatment may help reduce disease activity and maintain remission. A randomised placebo-controlled trial of 1200 IU (30 µg) of vitamin D3 daily in patients with CD showed improvement in serum 25(OH) levels after 3 months, and more than 50% lower rate of relapse compared with placebo.[130] Patients with CD treated with 1000 IU (25 µg) per day of vitamin D3 for 6 weeks had a reduction in disease activity scores and CRP.[131] Supplementation with up to 5000 IU (125 µg) per day of vitamin D3 for 24 weeks raised serum 25(OH)D3, and reduced disease activity scores and improved quality of life scores.[132] Notably, most patients required the maximum allotted 5000 IU of daily cholecalciferol to reach a serum 25(OH)D level of 40 ng/ml. Similarly, a clinical trial comparing a high [10 000 IU/day

(250 µg)] with a low dose (1000 IU) suggested a higher dose was necessary for optimising blood levels and maintaining remission in patients with CD.[133] Interestingly, clinical trials in patients with IBD suggest vitamin D treatment reduces ESR, high-sensitivity (hs)-CRP and TNF-α, increases cathelicidin (a precursor to an antimicrobial protein) gene expression, and increases gut bacterial diversity.[134,135,136]

Zinc has been shown to improve disease outcomes, reduce intestinal permeability and help to maintain remission. In patients with CD and UC, correction of zinc deficiency was associated with better disease outcomes, including a decrease in hospitalisations and disease-related complications compared with subjects who remained zinc deficient, over a 12-month period. Furthermore, patients with CD who normalised their zinc levels had a significant reduction in risk of subsequent surgeries.[137] In patients with CD in remission, supplementation with 25 mg of zinc three times daily for 8 weeks reduced intestinal permeability and relapse rate over a 12-month follow-up period.[138] Patients with active UC or ulcerative proctitis who were treated with 50 mg of zinc three times per day or placebo for 4 weeks as an adjuvant to drug therapy showed evidence of a modest improvement in clinical symptoms when compared with placebo, although this was not statistically significant.[139] The doses used in these studies may be unnecessary, with doses > 40 mg daily from food and supplements associated with copper deficiency and gastrointestinal side-effects.[140]

Thiamine may be useful for reducing fatigue in patients with IBD. Supplementation with 600 mg (for 60 kg adults) to 1500 mg (90 kg adults) of thiamine daily for 20 days completely alleviated symptoms of fatigue in 10 out of 12 subjects with UC and CD, and the remaining two also reported a significant improvement.[141] Notably there was an absence of blood thiamine deficiency, suggesting that conventional measurement may be insufficient for detecting deficiency, higher metabolic requirements or predicting treatment response. At this dose, thiamine may also be working as a pharmacological compound rather than to improve functional sufficiency.

Riboflavin has been found to have anti-inflammatory and antioxidant effects in CD. In an exploratory clinical trial, patients with CD of varying disease activity received 100 mg riboflavin for 3 weeks. Riboflavin supplementation was associated with reductions in the inflammatory biomarkers CRP, ESR, platelets and IL-2, an antioxidant effect indicated by an increase in the concentration of plasma free thiols, a reduction in clinical symptoms and an improvement in quality of life.[142]

Probiotics and prebiotics

Probiotics have been the subject of considerable research in IBD but, despite a strong theoretical basis for their use, clinical studies have provided sparse and conflicting evidence, with meta-analyses and systematic reviews generally concluding that there is little evidence for efficacy in CD, modest and inconsistent data for UC, and good support for probiotics in pouchitis.[143] All the clinical trials identified by the author are listed in Table 1. There is considerable heterogeneity in probiotic clinical trials related to probiotic strains, dose, duration and clinical outcomes (Table 1).

Table 1: Clinical trials of probiotics, synbiotics and fermented foods in IBD

Probiotic strain(s)	Dose	Duration	Subjects	Findings	References
Escherichia coli Nissle 1917	25 billion CFU daily	12 months	Active CD	Trend toward reduced relapse rate	Malchow *et al.* (1997)[144]
Escherichia coli Nissle 1917	25 billion CFU daily	12 months	Remission UC	Equivalence to mesalazine in remission	Kruis *et al.* (2004)[145]
Escherichia coli Nissle 1917	25 billion CFU daily	12 months	Remission UC	Equivalence to mesalazine in remission	Rembacken *et al.* (1999)[146]
Saccharomyces boulardii	1 g daily	6 months	Active CD	Significant reduction in relapse rate	Guslandi (2000)[147]
Saccharomyces boulardii	1 g daily	12 months	Active CD	No significant reduction in relapse rate	Bourreille *et al.* (2013)[148]
Saccharomyces boulardii	600 mg daily	3 months	Remission CD	Reduction in intestinal permeability	Garcia Vilela *et al.* (2008)[149]
Bifidobacterium longum plus inulin/oligofructose mix	200 billion CFU/6 g daily	6 months	Active CD	Significant improvement in CDAI scores	Steed *et al.* (2010)[150]
Lactobacillus rhamnosus GG	2 billion CFU daily	6 months	Active CD	No significant reduction in relapse rate	Shultz *et al.* (2004)[151]
Lactobacillus rhamnosus GG	20 billion CFU daily	up to 2 years	Active CD	No significant reduction in relapse rate	Bousvaros *et al.* (2005)[152]
Lactobacillus rhamnosus GG	18 billion CFU daily	12 months	Remission UC	Significant maintenance of remission	Zocco *et al.* (2016)[153]
Multi-strain (VSL#3)	720 billion CFU daily	12 weeks	Active UC	Significant achieved remission	Sood *et al.* (2009)[154]
Multi-strain (VSL#3)	720 billion CFU daily	8 weeks	Active UC	Significant reduction in disease activity	Tursi *et al.* (2010)[155]
Bifidobacterium longum 536	300 billion CFU daily	8 weeks	Active UC	Significant reduction in disease activity	Tamaki *et al.* (2016)[156]
Bifidobacterium breve plus galacto-oligosaccharides	1 billion CFU/ 5.5 g daily	12 months	Active UC	Improvement of endoscopic score	Ishikawa *et al.* (2011)[157]
Bifidobacterium breve, Lactobacillus casei, Bifidobacterium longum plus psyllium	75 billion/ 9.9 g daily	12 months	Active CD	Reduced disease activity and enhanced remission	Fujmori *et al.* (2007)[158]
Lactobacillus acidophilus La-5 and ***Bifidobacterium animalis*** subsp. lactis BB-12	150 billion CFU daily	12 months	Remission UC	No significant reduction in relapse rate	Wildt *et al.* (2011)[159]

Multi-strain (Symprove)	10 billion CFU/50 ml daily	4 weeks	Remission CD and UC	Reduction in faecal calprotectin UC only, no reduction in symptoms	Bjarnason *et al.* (2019)[160]
Lactobacillus salivarius, Lactobacillus acidophilus and ***Bifidobacterium bifidus*** BGN4	Not specified	2 years	Active UC	Reduced disease activity	Palumbo *et al.* (2016)[161]
Multi-strain plus fructo-oligosaccharides	3 billion CFU/225 g daily	8 weeks	Active UC	Reduced disease activity	Kamarlı Altun *et al.* (2019)[162]
Bifidobacteria fermented milk	10 billion CFU/ 100 ml daily	12 months	Remission UC	Significant maintenance of remission	Ishikawa *et al.* (2003)[163]
Kefir (fermented dairy)	20 billion/ 400 ml	4 weeks	Remission/ active CD and UC	Reduced disease activity in CD only	Yilmaz *et al.* (2019)[164]

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CFU, colony-forming unit; UC, ulcerative colitis.

Overall, some species of probiotics have evidence of clinical efficacy in UC with less compelling data for CD, and they may be more appropriate for maintenance of remission than treatment of active disease.[165] Importantly, probiotics should be used with caution with immune-suppressant drug use, long-term corticosteroid treatment, damaged intestinal mucosa or in immunocompromised patients.[166] In active severe IBD with mucosal disruption, probiotics may be contraindicated as cases of bacteremia have been reported.[167,168] Thus, probiotic safety is better established in less severe disease activity or IBD in remission.[169]

Prebiotics have considerable experimental evidence to suggest that they could modify microbial composition and lower inflammation in IBD; in contrast, clinical studies are few but generally suggest that prebiotics are well tolerated and can improve bacterial composition and reduce disease activity in UC particularly.[170] The author lists all the clinical trials that they could identify in Table 2. Clinical trials of prebiotics have generally used doses of > 10 g/day for > 4 weeks (Table 2).

Table 2: Clinical trials of prebiotics and prebiotic fibres in IBD

Prebiotics	Dose	Duration	Subjects	Findings	References
Lactulose	10 g daily	4 months	Active CD and UC	No clinical benefits	Hafer *et al.* (2007)[171]
Fructo-oligosaccharides	15 g daily	3 weeks	Active CD	Reduction in disease activity	Lindsay *et al.* (2006)[172]
Oligofructose/inulin	7.5 or 15 g daily	9 weeks	Active UC	Reduction in disease activity with 15 g	Valcheva *et al.* (2019)[173]
Oligofructose/inulin	12 g daily	2 weeks	Active UC	Significantly decreased dyspeptic symptoms and calprotectin	Casellas *et al.* (2007)[174]

Oligofructose/inulin	15 g daily	4 weeks	Active CD	No clinical benefits, worse abdominal pain	Benjamin *et al.* (2011)[175]
Germinated barley foodstuff	20–30 g daily	4 weeks	Active UC	Significant reduction in symptoms	Bamba *et al.* (2002)[176]
Germinated barley foodstuff	20–30 g daily	4 weeks	Active UC	Significant reduction in symptoms	Kanauchi *et al.* (2002)[177]
Psyllium	10 g twice daily	4 months	Remission UC	Significant reduction in symptoms	Hallert *et al.* (1991)[178]
Psyllium	10 g twice daily	12 months	Remission UC	Equivalence to mesalazine in remission	Fernández-Bañares *et al.* (1999)[179]
Oat fibre	60 g oat bran (corresponding to 20 g dietary fibre)	3 months	Remission UC	Increased faecal butyrate, fewer gastrointestinal symptoms, no relapse	Hallert *et al.* (2003)[180]
Human milk oligosaccharide (2′-fucosyllactose)	2 g daily in a multi-component nutritional formula	6 weeks	UC (activity not specified, n = 4), IBS, coeliac disease	Improved quality of life	Ryan *et al.* (2021)[181]
Galactooligosaccharides	2.8 g daily	6 weeks	Active UC	Improvement for some symptoms, but no effect on clinical scores or inflammation	Wilson *et al.* (2021)[182]

CD, Crohn's disease; IBS, irritable bowel syndrome; UC, ulcerative colitis.

Overall, the clinical evidence suggests some prebiotics may be useful, primarily for UC, while others may not be effective, and some could worsen symptoms. Oligofructose/inulin > 12 g daily, and psyllium (Plantago ovata) husks have more compelling evidence, with the psyllium having considerable research for gastrointestinal disorders in general to support its safety and use.[183] Germinated barley foodstuff may also be useful, but the presence of gluten should be considered against the role of coeliac disease and NCGS in IBDs. Practical considerations are summarised in Table 3.

Butyrate

Butyrate is an endogenously produced short-chain fatty acid that plays a major role in the physiology of the colonic mucosa. In IBD, butyrate metabolism may be impaired, and may contribute to mucosal barrier dysfunction and inflammation.[184,185,186] Enteric-coated sodium or calcium butyrate salts have been used with some success in IBD.[187] In patients with mild–moderate UC, butyrate (4 g/day) plus mesalazine for 6 weeks reduced disease histology and symptoms scores better than mesalazine alone.[188] Similarly, in patients with mild–moderate UC who were poorly responding to mesalazine treatment, the addition of 921 mg butyrate and 750 mg inulin resulted in a marked improvement of symptoms and in the endoscopic appearance of mucosa.[189] The addition of butyrate to mesalazine in active UC for 28 days resulted in 85% experiencing a significant improvement in rectal bleeding and stool frequency compared with 55% with mesalazine alone. The butyrate group also had an increase in their faecal butyrate-producing bacteria pool, and reduced elevated baseline Bacteroides fragilis/Faecalibacterium prausnitzii ratio and lowered serum inflammatory biomarkers.[190] In patients with CD with mild–moderate disease activity who took butyrate (4 g/day) for 4 weeks, 69% responded to treatment with 53% achieving remission. Further, endoscopical and histological scores significantly improved, and inflammatory biomarkers were reduced.[191]

N-acetylglucosamine

N-acetylglucosamine (NAG) is an amino sugar and component of epithelial cells and mucus membranes of the digestive tract.[192] Experimentally, NAG has been shown to reduce intestinal inflammation and modulate the systemic immune system in autoimmunity.[193,194] Metabolism of amino sugars may be impaired in patients with IBD, but NAG appears to bypass this metabolic impairment and be preferentially incorporated into the intestinal mucosa.[195]

Clinical studies suggest that NAG may be useful. Treatment-resistant paediatric patients with IBD were given 3–6 g per day of NAG as an adjuvant to usual therapy, in addition to rectal administration in some children. Both oral and rectal administration of NAG resulted in clear clinical and endoscopic or radiological improvement.[196] In adults with IBD, treatment with 6 g NAG orally for 4 weeks resulted in an 88.1% response rate for overall clinical symptoms; a 58.8% response for abdominal pain with a 49% reduction in symptom score; a 64.7% response for diarrhoea with a 47% reduction in symptom score. There were also significant reductions in symptom scores for nausea, passage of mucus and rectal bleeding.[197]

Glutamine

Glutamine plays an important role in the integrity of the intestinal mucosa and regulation of the inflammatory response; however, despite its popularity as a dietary supplement for digestive health, the use of glutamine in IBD is controversial.[198] One study in patients with CD in remission found that glutamine (0.5 g/kg body weight) for 2 months reduced intestinal permeability and improved morphology.[199] However, other studies have not reported any benefit. Glutamine (21 g) for 4 weeks did not restore to normal the increased permeability seen in patients with CD, nor did it reduce disease activity or inflammatory biomarkers.[200] In children with CD, a glutamine-enriched polymeric (exclusive enteral nutrition) diet (8 g) for 4 weeks had no advantage over a standard low-glutamine polymeric diet for symptom reduction or reducing intestinal permeability, in fact symptom control was worse with glutamine.[201] Similarly, in adults with IBD, glutamine-enriched parenteral nutrition had no additional benefit.[202]

Creatine

The amino acid creatine is an energy precursor in the creatine kinase/phospho-creatine system, which is important for meeting the cellular energy demands of epithelial junction assembly and barrier integrity, and supplementation with creatine can restore energy synthesis and reduce disease activity in experimental models of colitis.[203] In a case report, a patient recently diagnosed with mild Crohn's ileitis started mesalamine and stopped taking a creatine supplement, after which symptoms progressively became more severe. The patient had noticed subjective improvement with creatine, they then stopped mesalamine and started creatine (1.5 g daily), after which symptoms significantly improved and mucosal healing was observed after 6 months of creatine monotherapy.[204] Subsequently it has been found that patients with IBD have lower levels of creatine messenger RNA compared with control.[205] The rationale for a clinical trial has been published with a suggested dose of 3–5 g twice daily.[206]

Phosphatidylcholine

Phosphatidylcholine is a major component of the mucus layer that forms a protective and functional barrier across the intestinal epithelium, is significantly reduced in IBD, and can be restored with phosphatidylcholine supplementation. Phosphatidylcholine comprises more than 90% of phospholipids in the mucus layer that prevents the invasion of bacteria into the intestinal epithelium from intestinal lumen, but in UC the mucus phosphatidylcholine content is reduced but as much as 70%.[207] Experimentally, phosphatidylcholine depletion via diminished luminal transport leads to low mucus phosphatidylcholine, bacterial invasion of the submucosa, inflammation and

IBD-like symptoms that are reversed with phosphatidylcholine administration.[208]

Human clinical trials of delayed-release (acid-resistant) phosphatidylcholine formulations have demonstrated important clinical benefit in active and steroid-refractory UC,[209,210,211] inadequate response to mesalazine,[212] and for maintenance of remission (1–4 g daily).[213] A series of clinical trials of a different phosphatidylcholine formulation (differences in delayed-release technology and phosphatidylcholine %) failed to demonstrate significant clinical effect, but this has been attributed to the formulation. Earlier trials using the 30% phosphatidylcholine-containing lecithin in a delayed intestinal release formulation were found to improve clinical and endoscopic outcomes, histological activity and quality of life in patients with UC when trials of the different formulation were excluded from a meta-analysis.[214] Dose–response analysis has demonstrated that optimal benefit occurs at > 1 g to 4 g daily.[213]

Coenzyme Q10

Coenzyme Q10 (CoQ10) or ubiquinone has shown promise in patients with mild–moderate UC. In a clinical trial, a patient with UC who received CoQ10 (200 mg daily) for 8 weeks had a significant reduction in symptom scores and blood pressure, and an improved quality of life compared with placebo.[215] It was also found that CoQ10 treatment reduced inflammatory biomarkers IL-17 and nuclear factor (NF)-κB, increased serum levels of the anti-inflammatory cytokine IL-10, and increased levels of the anti-microbial peptide cathelicidin.[216] Although the use of CoQ10 in UC is novel, a previous study in patients with functional gastrointestinal disorders also found an improvement in bowel movement frequency and quality of life with 150 mg of CoQ10 (as ubiquinol) daily.[217] Gastroprotective effects in experimental models of colitis have also been observed.[218,219]

Omega-3 polyunsaturated fatty acids

The omega-3 polyunsaturated fatty acids, especially, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have undergone considerable research in IBD, but despite several clinical trials exploring potential therapeutic effects the outcomes have been mixed. Poor clinical outcomes and null effects have been observed in some studies; however, others have found modest but clinically important benefits such as improved gut histology, decreased disease activity, reduced requirement of corticosteroids and lower rates of relapse.[220] A potential explanation for conflicting evidence of benefit is problems in study design, with two interesting possibilities being that dietary omega-3 to omega-6 ratio could impact treatment response, or that treatment could be personalised to people with biomarkers of inflammation.[221]

Supporting these possible limitations, an interesting clinical study examined the effect of 500 mg daily of EPA in patients with UC in remission, but with high elevated faecal calprotectin (≥ 150 µg/g). After 6 months, 63% of the intervention group had a 100-point reduction in faecal levels of calprotectin compared with 13.3% with placebo, and sustained clinical remission was achieved by 63.3% of patients versus 13.3% in the placebo group.[222] Also, a dietary intervention that modified the omega-3 to omega-6 ratio with foods, achieving about 1700 mg/day from EPA and DHA, plus supplementation of 7 ml/day of perilla oil, providing about 3400 mg/day of alpha-linoleic acid was able to show a significant association between higher omega-3 to omega-6 ratio and maintenance of remission in patients with UC and CD.[223] Omega-3 polyunsaturated fatty acids may be a useful addition to therapy, but could benefit from personalisation to inflammatory biomarkers (e.g. elevated faecal calprotectin) and may be more effective with improvement in dietary omega-3 to omega-6 ratio. The omega-3-index (erythrocyte EPA/DHA %) corelates

well with dietary EPA/DHA incorporation in gastrointestinal tissues, and may be a useful biomarker for personalising EPA/DHA therapy.[224]

Curcumin

Curcumin is a safe and effective therapy for improving maintenance of remission of UC when given as adjunctive therapy along with mesalamine or sulfasalazine.[225] Curcumin may also help reduce acute disease activity. In an open label study, patients with active IBD were treated with 1080 mg curcumin daily for 1 month and then 1440 mg daily for the remaining 2 months. All patients with proctitis improved, and four out of five patients with CD had lowered symptom scores and ESR.[226] Patients with UC who received curcumin, 1 g after breakfast and 1 g after the evening meal, plus sulfasalazine or mesalamine for 6 months had a lower rate of relapse (4.65%) compared with medication and placebo (20.51%), as well as lower symptom and endoscopic scores.[227] Patients with active UC who were not responding adequately to mesalamine were given 3 g of curcumin daily for 4 weeks. Curcumin was superior to placebo and mesalamine in inducing clinical and endoscopic remission.[228] Notably, a low dose of 450 mg curcumin daily was ineffective in inducing remission in mild–moderate UC.[229]

Boswellia

Frankincense *(Boswellia serrata)* has been used for centuries as a traditional medicine to treat inflammatory disorders, with some evidence to suggest it may help induce remission in IBD.[230] Patients with active UC who were given 1050 mg Boswellia gum resin daily for 6 weeks achieved a better rate of remission (82%) than sulfasalazine (75%).[231] Similarly in patients with chronic colitis, 900 mg Boswellia gum resin daily for 6 weeks was also found to be superior to sulfasalazine for induction of remission, with rates of 70% and 40%, respectively.[232] In patients with collagenous colitis and chronic diarrhoea, monotherapy with 1200 mg Boswellia gum resin daily for 6 weeks resulted in higher clinical remission (63%) compared with placebo (26%), but had no effect on histology or quality of life.[233]

An enhanced bioavailability and potency extract of Boswellia (250 mg of Boswellia/lecithin complex) reduced minor symptoms, the use of drugs and medical consultation, and faecal calprotectin in patients with UC in remission.[234] In patients with CD in remission, however, Boswellia was not found to be more effective for preventing disease relapse than placebo.[235]

Resveratrol

Resveratrol has prebiotic, immune-modulating, anti-inflammatory and antioxidant activity, with clinical evidence to suggest it can reduce clinical progression of several autoimmune diseases, including IBD.[236,237] In patients with active UC, supplementation with 500 mg resveratrol for 6 weeks significantly reduced clinical symptom scores and the inflammatory biomarkers TNF-α and NF-κB when compared with placebo.[238] Resveratrol also improved oxidative/antioxidative status, with a significant reduction in malondialdehyde, and an increase in superoxide dismutase and total antioxidant capacity.[239]

Aloe vera

Aloe vera juice has been shown to influence gastrointestinal health via promoting mucosal tissue repair, prebiotic effect, enhancing digestion, increasing absorption of nutrients and reducing inflammation.[240,241,242] Treatment of 100 ml twice daily with aloe vera inner-leaf gel for 4 weeks in active UC was more effective in inducing remission (30%) than the placebo (7%). Aloe vera also significantly decreased disease activity and histological scores.[243]

Silymarin

Silymarin (Milk thistle extract) may be useful to help maintain remission in UC. In one study, patients who were in remission received either 140 mg silymarin or placebo once daily for 6 months along with their standard therapy. At the end of the study, 98% (n = 38) of the silymarin group maintained remission compared with 65% for placebo (n = 32). Silymarin also reduced clinical disease activity scores and improved haemoglobin and ESR when compared with placebo.[244]

Discussion

This review highlights a wide range of therapeutic diets and nutrient-based supplements that have potential usefulness in the integrative management of IBDs. Adjuvant nutritional therapies could be used with conventional care or could be considered as alternative treatments in cases of drug intolerance or treatment resistance. Because IBDs typically have a relapsing disease course, adjuvant nutritional therapies have promise as relatively safe interventions that could significantly contribute to disease control and improved quality of life.[245] The use of nutritional therapies as alternative treatment options requires more research to establish use but, as evidenced in this review, there is clearly promise for specific interventions. Additionally, it is notable that most nutritional interventions have been studied in isolation; however, in clinical nutrition practice combinations of therapies could be personalised, may have additive effects, and may be more likely to enhance disease control and remission

Important limitations of some nutritional therapies for IBD include a lack of suitably controlled interventions that could help inform clinical decision-making, especially in the case of dietary interventions. An example is the comparison of the SCD and MED-DIET, which both performed equally well despite the SCD being considerably more restrictive.[109] Pragmatically, an easier to follow diet would be preferable, but unless such comparisons are made it may be difficult to prioritise one dietary approach over another. Mixed treatment outcomes were also frequently identified for nutritional interventions, indicating further research is needed to better understand the efficacy of candidate therapies. In the case of nutrients, many studies consisted of traditional randomised-controlled trials; however, clinical trials of nutrients would benefit from trial designs that appreciate their differences from pharmacological therapies. Unlike drugs, nutrients tend to have lower effect sizes, are influenced by background dietary intake, have dose–response curves, and benefit from personalisation.[246] Nonetheless, despite these limitations, the formulation of clinical considerations based on nutritional therapies with more compelling evidence related to the therapeutic diets and nutrient-based supplements reviewed here could inform clinical application (Table 3).

Table 3: Clinical consideration of therapeutic diets and nutrient-based supplements for IBDs

Intervention	Discussion	Possible clinical application
Healthy diet	Unhealthful dietary practices could increase disease risk and severity. Minimally processed, semi-vegetarian, traditional dietary patterns can result in induction of remission and prevention of relapse.	Increase consumption of fresh fruits, vegetables, legumes and whole grains in line with dietary approaches such as the traditional Mediterranean-style diet. Limit red meat and include fish. Emphasise foods and food groups with prebiotic properties, such as fermented, high-fibre and phytonutrient-dense foods (e.g. natural yoghurt, fermented vegetables, root vegetables, green leafy vegetables, berries).
The IBD-AID diet	An AID developed for the treatment of IBD has been developed with some evidence to suggest it is an effective regime.	Consider the AID as a structured approached to personalising diet therapy in patients with IBD.
Personalised elimination diet	Elimination diets can help reduce symptoms by limiting exposure to foods that exacerbate inflammation.	An elimination diet can be based on food sensitivity testing, including IgG. Without testing, an elimination and re-challenge with major and/or suspected food allergens may still be useful.

NCGS	NCGS may be more frequent in patients with IBD, and could contribute to disease activity.	Consider a therapeutic trial with a gluten-free diet and re-challenge.
Coeliac disease	Coeliac disease has a significantly higher prevalence in IBD and should be ruled out with testing.	Coeliac disease can be treated with a gluten-free diet.
Additive-free diet	Experimental evidence suggests that industrial food additives may play an important role in the development of IBD, and a carrageenan-free diet may be effective.	Eliminate or reduce exposure to industrial food additives. A carrageenan-free diet could be trialled in select patients.
The SCD	Case reports and small preliminary clinical trials suggest important benefits of the SCD in patients with IBD, which may help induce and maintain remission.	The SCD could be considered in select patients, particularly treatment-resistant paediatric CD. The diet is restrictive and requires close professional supervision.
Increase intake of functional foods	Advise to increase intake of foods with anti-inflammatory effects, such as antioxidant- and omega-3 fatty acids-rich foods.	Advise patient to increase intake of polyphenol-rich fruits and vegetable foods and beverages, additionally increase intake of omega-3-rich foods, such as nuts, seeds, cold water fish and their oils, whole oats or oat fibre, and extra virgin olive oil.
Micronutrient deficiencies	Micronutrients deficiencies are widespread in IBD, and deficiencies can contribute to disease activity and co-morbidity.	A multivitamin and mineral supplement is a safe, inexpensive way to improve micronutrient intake. However, a multivitamin alone may not be sufficient to optimise intake, and laboratory screening for deficiency and to assess treatment response is recommended.
Vitamin D	Vitamin D treatment may help reduce disease activity and maintain remission.	Assessment of vitamin D status and subsequent supplementation in the case of deficiency. Higher doses of vitamin D [> 5000 IU (125 µg)] may be required to improve clinical symptoms and serum 25(OH)D3.
Probiotics	Some probiotic strains have shown benefit in mild–moderate IBD, and for maintaining disease remission.	Consider a probiotic supplement with demonstrated benefit in IBD. At least 2 months of treatment may be required to see benefit. If no response, another probiotic could be trialled. Avoid probiotics in severe, active IBD.
Prebiotics	Prebiotic supplements can help improve gut microbiota composition and may help maintain remission.	Consider supplementing with 10 g psyllium twice daily for at least 4 months in UC, and 15 g of FOS/inulin for at least 3 weeks in UC or CD.
Butyrate	Butyrate metabolism may be impaired, and contribute to mucosal barrier dysfunction and inflammation. Enteric-coated sodium or calcium butyrate salts have been used with some success in active IBD and to maintain remission.	Consider 4 g of enteric-coated or enhanced-delivery butyrate as an adjuvant to therapy in active IBD.
NAG	Experimentally, NAG has been shown to reduce intestinal inflammation and modulate the systemic immune system in autoimmunity.	Consider 6 g daily of NAG in active IBD.

Glutamine	The use of glutamine in IBD is controversial.	There appears to be no significant benefit of glutamine in IBD.
Creatine	Creatine may help maintain gut epithelial integrity, and a single case report suggests benefit.	Consider 3–5 g of creatine 1–2 times daily (experimentally, in the absence of trial data).
Phosphatidylcholine	Phosphatidylcholine incorporates in the protective mucus layer, and has been shown to reduce disease activity and help maintain remission.	Consider 1–4 g of enteric-coated or enhanced-delivery phosphatidylcholine daily in UC.
CoQ10	A preliminary clinical trial suggests CoQ10 may help reduce UC disease activity.	Consider a trial of 200 mg daily for at least 8 weeks.
Omega-3 polyunsaturated fatty acids	EPA/ DHA have conflicting evidence of efficacy, but may improve gut histology, decrease disease activity, reduce requirement of corticosteroids and lower rates of relapse.	Consider supplementation with fish oil, at least 500 mg EPA daily, especially if inflammatory biomarkers are elevated. Emphasise omega-3 polyunsaturated fatty rich-foods such as cold water fish and linseeds. Avoid omega-6 polyunsaturated fatty acids in processed foods, baked goods and vegetable cooking oils, instead using extra virgin olive oil (cooking) or coconut oil (baking) in certain sub-sections of patients with IBD. The omega-3-index may help personalise therapy.
Curcumin	Curcumin is a safe and effective therapy for improving maintenance of remission of UC when given as adjunctive therapy along with mesalamine or sulfasalazine.	Consider 2 g of curcumin or curcuminoids daily given in two divided doses.
Boswellia	Boswellia may help induce remission in active IBD.	Consider 900 mg of Boswellia gum resin for at least 6 weeks.
Resveratrol	Resveratrol may reduce clinical disease activity, and systemic inflammation and oxidative stress.	Consider 500 mg once daily, particularly if biomarkers of oxidative stress and inflammation are elevated.
Aloe vera	Aloe vera may promote mucosal tissue repair and reduce inflammation.	Consider 100 ml twice daily of aloe vera inner-leaf gel for 4 weeks.
Silymarin	Silymarin may help maintain remission and reduce ESR in UC.	Consider 140 mg silymarin or placebo once daily for 6 months.

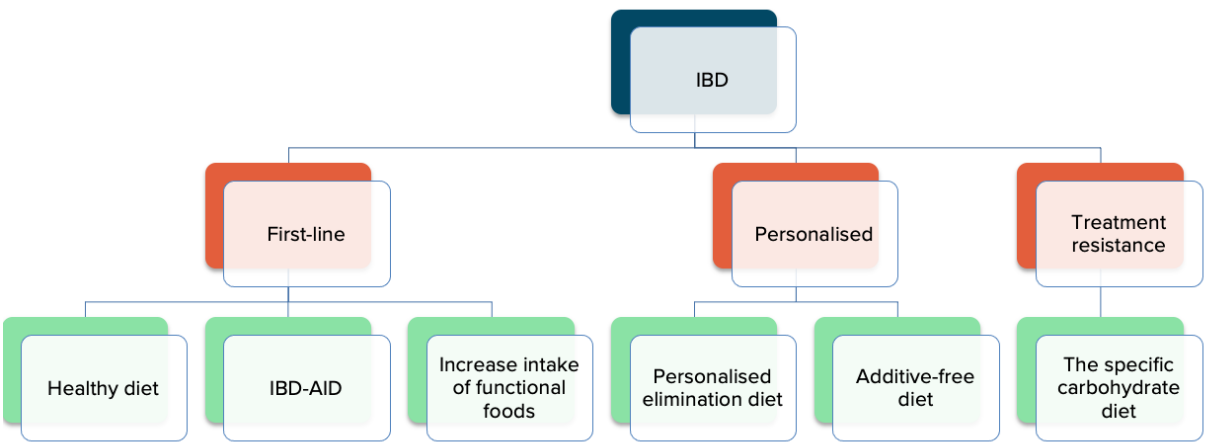
AID, anti-inflammatory diet; CD, Crohn's disease; CoQ10, coenzyme Q10; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ESR, erythrocyte sedimentation rate; FOS, fructooligosaccharides; IBD, inflammatory bowel disease; IgG, immunoglobulin G; NAG, N-acetylglucosamine; NCGS, non-coeliac gluten sensitivity; SCD, specific carbohydrate diet; UC, ulcerative colitis.

Some diets, including the AIP diet and genotype-guided diet, were excluded due to limitations in evidence. The low-FODMAP was excluded as it is for symptoms of IBS, not inducing and/or maintaining IBD remission.

Clinically, dietary interventions could be used in combination as part of rational decision-making with lower risk, higher likelihood of benefit dietary interventions forming part of a first-line dietary approach, while more personalised elimination diets could be considered on a case-by-case basis, and more demanding and restrictive interventions being reserved for treatment resistance (Figure 1).

Similarly, nutrient-based supplements with supportive evidence could be approached pragmatically, prioritising those generalisable across IBDs, then personalising based on IBD subtypes and potential clinical benefit (Figure 2).

Figure 1: Hypothetical approach to integrating different diets for IBD.



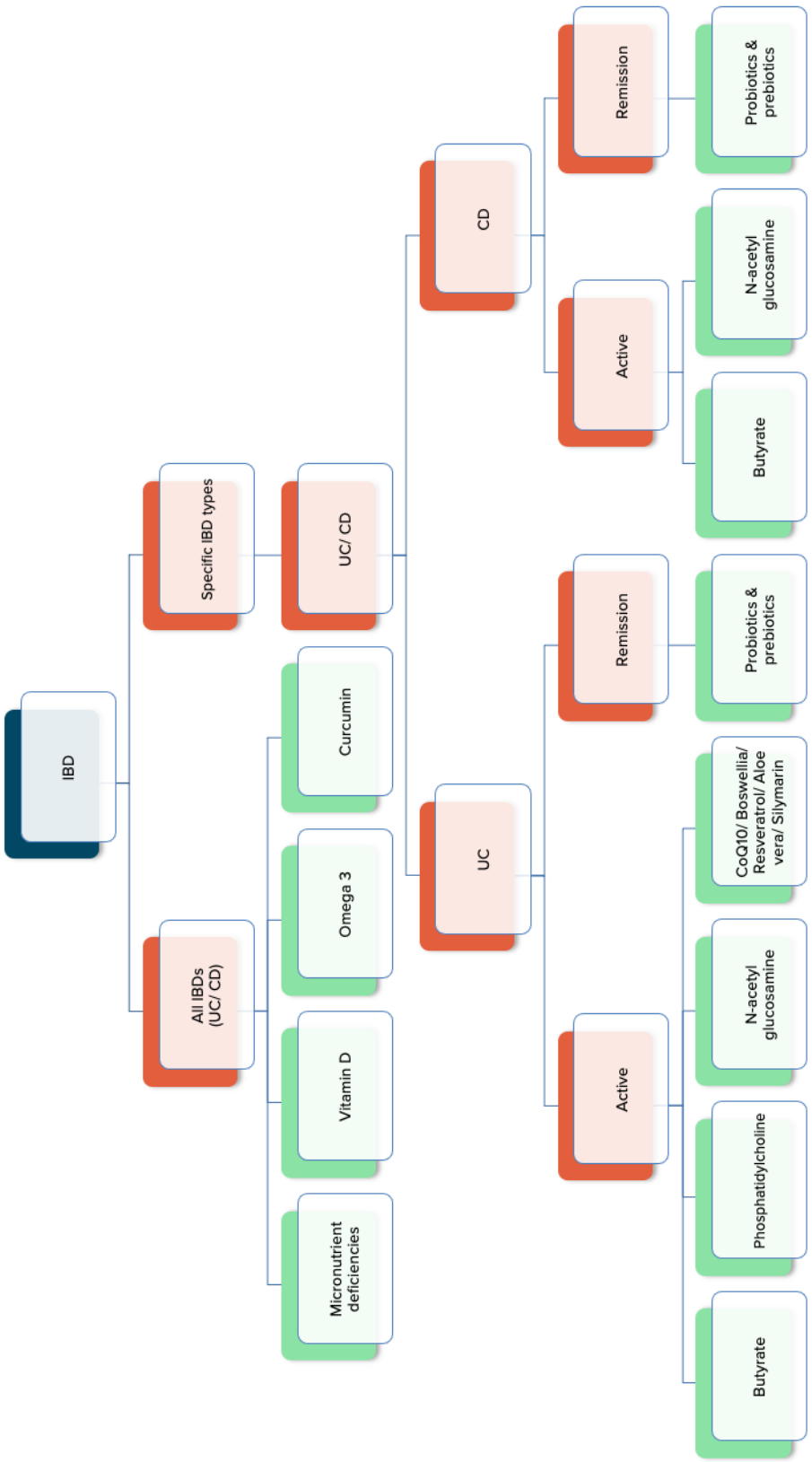


Figure 2: Hypothetical approach to integrating different nutrient-based supplements for IBD.

It must be emphasised that these are hypotheses, not guidelines, and several therapies are based on very limited research, preventing their routine use. The purpose of presenting nutritional therapies in this pragmatic, integrative model is to stimulate further investigation and research of multi-component, individualised clinical nutritional interventions for IBD.

Conclusion

Nutritional interventions clearly have great potential to reduce disease activity and maintain remission in IBDs. Diet is known to be a contributory factor to IBD development, and alterations in diet can modify the disease course. Adjuvant nutritional therapies could be used with conventional care or considered as alternative treatments in cases of drug intolerance or treatment resistance. Specific dietary approaches and nutritional interventions have some, albeit limited, clinical evidence to suggest they can modify gene expression, have anti-inflammatory effects, induce mucosal healing, normalise intestinal microbiota, reduce disease activity and/or help maintain remission. A pragmatic integrative model for the personalisation of nutritional therapy in patients with active or latent IBD, incorporating disease-modifying dietary recommendations and nutrient-based supplements holds promise, and deserves further investigation and research.

Acknowledgements

Author contributions: B. Brown carried out the literature review and formulated the manuscript.

Peer-reviewers and editors: the Nutritional Medicine Institute thanks the peer-reviewers and editors for their important contributions.

Funding: No funding was received for this work.

Declaration of interest: B. Brown has received consultancy fees from Pure Encapsulations, Sudbury, MA, USA.

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