Nutrition management in the adult patient with Crohn's disease

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Abstract

Malnutrition, nutrient deficiencies and osteoporosis are common in patients with Crohn's disease, regardless of disease activity. While the role of diet in the pathogenesis of the disease remains inconclusive, upon diagnosis, nutrition therapy plays an integral role in patient care. Successful nutrition intervention involves appropriate nutritional assessment, supplemental nutrition and individualised counselling and support.

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Introduction

Crohn's disease (CD) is a chronic and recurrent immune-mediated inflammatory disorder of the gastrointestinal tract.[1,2] Typically, patients suffer from chronic intestinal inflammation that follows a relapse-remitting pattern, as well as from a variety of complications (Table I) that may or may not involve the gut.[3,4] Disease activity can be classified by the Crohn's Disease Activity Index[5] (CDAI) (Table II), and usually, treatment includes various combinations of corticosteroid, anti-inflammatory (aminosalicylates), immune-modulating or biological therapy.[4] While the exact cause of CD is not known, it is thought to result from a complex interplay between intestinal bacteria and an environmental trigger in genetically susceptible individuals (Figure 1).[6]

The interaction between intestinal bacteria and environmental triggers creates an abnormal immune response in genetically susceptible individuals. The dysregulated immune response, driven by the intestinal microbiome, leads to alterations in mucosal barrier function, dietary antigen permeability and microbial clearance.

Numerous gene mutations that are associated with abnormal innate immune responses or impaired epithelial barrier function have been implicated. Specifically, mutations in the CARD15 or NOD2 gene on chromosome 16 result in improper bacterial product recognition, impairment of the innate immune response to commensal bacteria and damage to the intestinal mucosa.[7-13] The dysregulated immune response, driven by the intestinal microbiome, leads to proinflammatory cytokine production, particularly tumour necrosis factor-alpha (TNF-α), which directly contributes to both disease pathogenesis and malnutrition via alterations in mucosal inflammatory activity, epithelial permeability to dietary antigens and energy intake (appetite).[14,15]

Low-fibre, high-fat and high-sugar intakes have been implicated as some of the environmental triggers in disease development, although the role of a pre-illness diet in the pathogenesis of CD remains inconclusive.[16-18] However, upon diagnosis, nutrition therapy plays an integral role in patient care, regardless of disea se activity.

Malnutrition

Weight loss, low body mass index (BMI) and nutrient deficiencies have been well documented in patients with CD, especially during active disease. The degree of malnutrition depends upon the extent, severity and duration of the disease.[19] There is a higher incidence of protein energy malnutrition and specific nutrient deficiencies in small bowel, compared to colonic, disease.[20]

Individual or multiple mechanisms can contribute to malnutrition (Table III). However, anorexia, active inflammation and increased intestinal loss are reported most often.[21-26] Evidence suggests that in addition to improving nutrition status, nutritional therapy in CD functions to downregulate proinflammatory cytokine production, promote epithelial healing, modify gut flora, decrease gut permeability and antigenic load and promote an overall anti-inflammatory effect.[25]

European guidelines[27] recommend that 25-30 kcal (105-126 kJ)/kg ideal body weight (IBW)/day is optimal to meet energy requirements during active CD, although a recent systematic review[28] found that higher amounts of enteral nutrition (EN) [≥ 30 kcal (126 kJ)/kg up to 45 kcal (189 kJ)/kg IBW/day] may be associated with higher remission rates. Nonetheless, clinical judgement, based on recent clinical and surgical history, takes precedence in calculating actual requirements. Recommended nutrients to correct deficiencies and prevent bone loss in the case of active CD[29] are listed in Table IV.

Table I: Disease description, common symptoms and intestinal and extraintestinal complications of Crohn's disease[4]

Disease description	Common symptoms	Intestinal complications	Extraintestinal complications
• Affects all layers of the gastrointestinal mucosa • Inflammation is not continuous and may skip lesions • Surgery is not curative • The small bowel and colon are affected primarily, but the disease may present anywhere from the mouth to the anus • Fistulae and abscesses are common • The presence of confluent deep linear ulcers and aphthous ulcers • Fat wrapping and thickening of the intestinal wall are often diagnostic features that discriminate Crohn's disease from other conditions	• Chronic diarrhoea • Abdominal pain and cramping • Weight loss • Malaise • Anorexia • Fever • Vomiting • Constipation • Growth failure	• Haemorrhage • Bowel perforation • Intra-abdominal abscesses • Fistulae • Scarring and bowel narrowing • Bowel obstruction • Malignancy	• Arthritis • Ankylosing spondylitis* • Pyoderma gangrenosum* • Erythema nodosum* • Uveitis (iritis)* • Episcleritis* • Primary sclerosing cholangitis* • Osteoporosis • Nephrolithiasis and gallstones • Venous thromboembolism • Nonalcoholic fatty liver disease

- Ankylosing spondylitis: Chronic, inflammatory disease of the axial skeleton with variable involvement of the peripheral joints and nonarticular structures. Ankylosing spondylitis is a form of spondyloarthritis, a chronic, inflammatory arthritis in which immune mechanisms are thought to play a key role.
- Aphthous ulcer (canker sore): Type of ulcer that presents as a painful open sore inside the mouth or upper throat, characterised by a break in the mucous membrane.
- Episcleritis: Irritation and inflammation of the episclera, a thin layer of tissue that covers the white part (sclera) of the eye. It occurs without an infection.
- Erythema nodosum: Inflammation of the fat cells under the skin (panniculitis), characterised by tender, red nodules that are seen on both shins usually.
- Primary sclerosing cholangitis: Chronic liver disease that is caused by progressive inflammation and scarring of the bile ducts of the liver. The underlying cause of the inflammation is believed to be autoimmunity.
- Pyoderma gangrenosum: Condition that causes tissue to become necrotic, causing deep ulcers that occur on the legs usually.
- Uveitis (iritis): Swelling and irritation of the uvea, the middle layer of the eye. The uvea provides most of the blood supply to the retina.

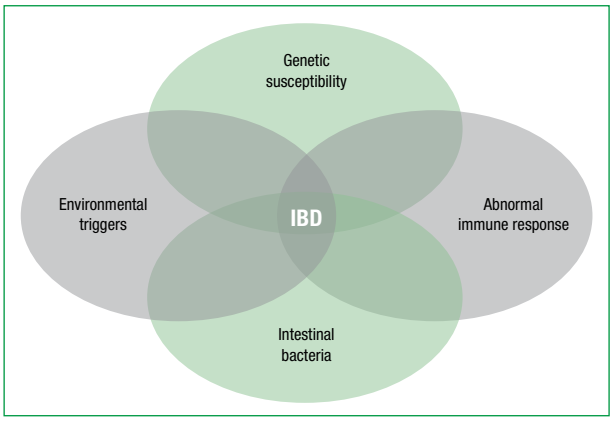
Table II: Crohn's Disease Activity Index used to classify disease activity

Score	Definition
CDAI < 150	Inactive or quiescent disease, i.e. remission.
CDAI 150-220	Mild disease characterised by < 10% weight loss and potentially increased C-reactive protein levels above the upper limit of normal, with no presentation of dehydration, fever, abdominal mass, tenderness or obstruction.
CDAI 220-450	Moderate disease characterised by weight loss > 10%, the presence of a tender mass (no overt obstruction), unsuccessful response to treatment and elevated C-reactive protein.
CDAI > 450	Severe disease characterised by intestinal obstruction, abscesses, elevated C-reactive protein and cachexia (body mass index < 18 kg/m²) in treated, yet persistently symptomatic, patients.

The Crohn's Disease Activity Index was developed by Best et al[5] in 1976 and consists of eight factors, each added up after adjustment with a weighting factor. Often used for research purposes, the score is then used to classify patient disease activity.

Table III: Aetiology of malnutrition in patients with Crohn's disease[21-24]

- Reduced food intake, anorexia and food aversions
- Active inflammation
- Reduced nutrient use
- Increased intestinal losses
- Malabsorption
- Increased elimination of nutrients due to oxidative stress
- Fistulae
- Surgical resections
- The side-effects of corticosteroids or other medication
- Metabolic abnormalities.



IBD: irritable bowel disease

Figure 1: The interaction between intestinal bacteria and environmental triggers[6-8]

Previously, it was thought that once disease activity subsided, fat-free mass content would also improve.[30-33] The literature now suggests that patients in clinical remission may continue to present with changes in body composition, as significant reductions in lean body mass,[34] muscle mass[35] and muscle function[36-38] have been observed. In addition, when used alone, standard anthropometric and laboratory indexes, i.e. BMI or albumin, may not accurately represent nutrition status during remission.[39]

Rocha et al found that according to BMI, only 14% of outpatients with CD (n = 50) were malnourished, yet when combined with additional anthropometric parameters, 36% (n = 18) had fat mass depletion (triceps plus subscapula skinfold thickness), and 62% (n = 31) had muscle mass depletion (arm muscle area).[40] In a multicentre, prospective controlled study, Valentini et al reported that despite the fact that 76% of patients with CD (n = 94) are well nourished according to subjective global assessment, BMI and

Table IV: Nutrients that are important in active Crohn's disease[29]

Nutrient	Dose	Comments
Iron	60 mg/day	Supplemental elemental Fe, preferably ferrous sulphate or gluconate.
Calcium	1 000-1 500 mg/day	Calcium carbonate should be given with vitamin D to help prevent bone loss.
Vitamin D	800 IU/day or 50 mg/day	Cholecalciferol form. 25-hydroxy form calcidol.
DHA and EPA	1 g/day	To lower the use of anti-inflammatories.
Magnesium	300 mg/day elemental Mg	Magnesium oxide provides 60% of elemental Mg, while magnesium chloride/lactate provides 12%, but higher bioavailability.
Folic acid	800 mg/day	To prevent anaemia.
Vitamin B_{12}	1 mg orally/ intramuscularly	For patients with severe ileal disease.
Zinc	8 mg elemental Zn twice daily	As zinc carnosine.

DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid

plasma albumin values, body cell mass (measured by bioelectrical impedance analysis) and handgrip strength were significantly reduced when compared to controls.[41] Metabolic abnormalities might have also been present, during either active or inactive disease. Alterations in diet-induced thermogenesis, reductions in glucose oxidation[42,43] and increases in lipid oxidation[42-45] and resting energy expenditure[42,46-49] have been reported, compared to healthy controls. However, total energy expenditure was only slightly elevated when calculated in relation to fat-free mass.[33] While routine assessment of these parameters may not be feasible in the clinical setting, it is important that the dietetic professional is aware of possible underlying metabolic abnormalities, particularly during remission.

The trend of overweight and obesity in patients with CD, in combination with undetected malnutrition, is of recent concern. A preliminary study reported reduced hand grip strength and muscle stores in the absence of other signs of malnutrition in patients with quiescent CD. The majority of patients had normal or above normal BMI, of whom 40% were classified as overweight or obese.[50,51] In an outpatient case-control study, Guerreiro et al reported that 32% ($n = 78$) of outpatients with CD had a BMI > 25 kg/m², compared to 33.8% of controls, despite a significantly lower fat free mass (p-value < 0.05) and lower mean daily intake of macro- and micronutrients (p-value < 0.05).[52] More than half of the patients with CD in the study had muscle mass depletion in the absence of overt malnutrition. In fact, the most prevalent form of malnutrition in patients with CD was an excess in body weight in conjunction with inadequate dietary intake. None of the patients took corticosteroids within three months of the study.

Overweight in patients with CD has been shown to increase the risk of relapse to active disease[53] and the need for earlier surgical intervention,[54] and thus should not be seen as an indicator of health, as undernutrition impacts negatively on postoperative complications, clinical course and mortality.[27,55] Furthermore, adipose tissue produces bioactive molecules, including TNF-α, a known contributing factor in the inflammatory disease process.[51]

Currently, there is no gold standard in clinical practice for nutrition assessment in patients with CD. In general, BMI, unintentional weight loss, recent intake and iron studies are used to provide a preliminary overview of a patient's nutrition status.[20,39] More comprehensive assessment can be achieved using additional anthropometry and scoring systems, such as the Subjective Global Assessment[56] or Nutrition Risk Score,[57] although patient muscle mass and function are not evaluated in the latter assessments.

Osteoporosis

Osteoporosis occurs in up to 50% of patients with CD.[58] Contributing risk factors include corticosteroid use, inflammation, age, weight loss exceeding 10%, malabsorption, low dietary intake, activity, hormones and genetics. BMI < 20 kg/m² is an independent risk factor.[59-61]

Patients who have taken corticosteroids over the long term should be considered to be at risk of acquiring fractures.[62] However, not using the medication does not eliminate the risk of fractures,[63] as vitamin D malabsorption and elevated circulating cytokines may also act upon bone turnover rate.[61] Corticosteroids should be reduced when possible.[59] Calcium and vitamin D supplementation is recommended when steroid therapy is prescribed for longer than 12 weeks.[64,65] Very emaciated patients may also benefit from calcium and vitamin D supplementation. The provision of supplemental EN may also offer further benefit. A total of 1 000-1 500 mg calcium (dietary or supplemental) is recommended,[66,67] with an additional 800 IU vitamin D daily.[66] Patients with CD often avoid dairy products because of perceived intolerance. A dietary evaluation of calcium intake is essential. Lifestyle activities, such as regular weight-bearing exercise and the avoidance of smoking and excessive alcohol intake, should be promoted.

Anaemia

Anaemia of various origins occurs in up to 74% of patients with CD.[68] Anaemia is commonly caused by iron deficiency or anaemia of chronic disease (ACD), which involves alterations in erythropoiesis, iron homeostasis and red cell survival.[69]

Several factors, including malabsorption (duodenal and upper jejunal involvement), decreased dietary intake of iron-rich foods because of food aversions and inflammation, and chronic intestinal blood loss contribute to iron deficiency anaemia (IDA).[19,64,68] Studies that link disease location and activity with iron absorption are lacking. However, no difference was found in ferritin and haemoglobin levels between patients with CD and those with ulcerative colitis.[70] This suggests an alternate pathogenic factor besides small bowel absorption. Assessment of iron status is complex as inflammation increases serum ferritin levels (an acute-phase protein). IDA and ACD also often coexist.[64] Identifying the underlying cause is an important step before starting therapy, and diagnostic guidelines, based on the presence and absence of inflammation in anaemia,

and that allow individual reference values for iron stores, have been developed for clinical practice.[71,72] When providing supplemental iron, intravenous administration may be indicated as oral administration often leads to increased gastrointestinal side-effects, including diarrhoea, abdominal pain and nausea and potential worsening of inflammation.[71,72]

Vitamin B_6, vitamin B_{12} and folate deficiency

Deficiencies of vitamin B_{12} and folate have been reported in up to 48% and 54% of patients with CD, respectively.[36] Both folate and vitamin B_{12} are required to clear homocysteine via the homocysteine-methionine metabolic pathway,[73] and low levels of either nutrient lead to hyperhomocysteinaemia, a risk factor for prothrombotic states and thromboembolism.[74-76]

A well-known risk factor for developing vitamin B_{12} deficiency is resection of the terminal ileum or ileal CD.[68] Annual monitoring and parenteral supplementation are recommended in these patients.[77] However, vitamin B_{12} deficiency is not always due to intestinal resection.[78] Furthermore, deficiencies have been shown to occur despite additional supplementation.[39] Routine monitoring of vitamin B_{12} in all patients with CD may be warranted, especially those who are unresponsive to iron therapy or who are found to have macrocytic anaemia.[68]

Sulphasalazine treatment is a known risk factor for folate deficiency, although deficiencies also arise because of malabsorption and dietary insufficiency issues.[78] Subnormal vitamin B_6 levels have been observed, but are likely to be a result of malabsorption, rather than dietary insufficiency.[70] Routine monitoring and supplementation of these vitamins may be required.

Vitamin A deficiency

Low levels of circulating retinol-binding protein are associated with the acute-phase response,[79] and in the presence of zinc deficiency, secondary to the impairment of protein metabolism.[80] Deficiencies of vitamin A compromise the mucosal integrity and protective barrier function of the intestinal wall, leading to impaired gastrointestinal immune function and impaired resistance to pathogenic bacteria and antigens.[79,81]

Vagianos reported inadequate dietary intakes of vitamin A in 26% of patients with CD (n = 71). There was significantly lower median serum vitamin A in patients with active disease, compared to that in patients in remission.[70] Serum carotene was low in more patients with CD with active disease compared to those with inactive disease, and was significantly lower in patients with small bowel involvement [66 patients (76%), p-value = 0.006]. Lower serum carotene levels were significantly associated with longer disease duration (> 20 years). Routine multivitamin supplementation may be justified, regardless of disease type or activity.

Magnesium and zinc deficiency

Deficiencies of magnesium (14-33%)[36] and zinc (3-5%)[82] are often a result of chronic diarrhoea, high-output stoma or fistulae, short bowel syndrome, bacterial overgrowth and malabsorption.[36] Zinc depletion causes phosphorylation-mediated disruption of the junction complexes and cytoskeletal disorganisation in Caco-2 cells, resulting in neutrophil migration.[29] Zinc deficiency is associated with poor wound healing and fistulae formation, impaired membrane barrier function (both in vivo and in vitro), neutrophil migration and neutrophil accumulation in the intestinal lumen and epithelial crypts. This results in the formation of crypt abscesses.[29,83] Supplementation aids to reduce intestinal permeability, and recommended dosages of 8 mg elemental zinc twice a day, as zinc carnosine, for five days should be used when a deficiency is suspected.[29]

Exclusive enteral nutrition in active disease

Exclusive enteral nutrition (EEN) offers an alternative therapeutic approach with minimal side-effects, compared to corticosteroid or immunosuppressive therapy, when treating adults with CD.[84] In conjunction with improving overall nutrition status, growth and body composition, EEN has been shown to induce remission and mucosal healing, improve mucosal permeability, downregulate proinflammatory cytokines and reduce serum inflammatory markers.[20,85-89] Primary nutrition therapy has been compared to steroid therapy in several studies, including three meta-analyses and two Cochrane systematic reviews.[90-92] In terms of active disease, steroid treatment was more effective compared to EEN. There was no difference between elemental (free amino acids), semi-elemental (oligopeptides) and polymeric (whole protein- and glutamine-enriched) formulas to induce remission.[93,94] For this reason, the European Crohn's and Colitis Organisation[54] (ECCO) recommends EEN only as a primary therapy for those who refuse drug therapy, and as an adjunct therapy in corticosteroid-refractory or corticosteroid-dependent disease in adults. In children, a meta-analysis of 11 trials in 394 children with active CD demonstrated EEN to be equally effective as corticosteroid therapy [odds ratio (OR) 0.96, 95% confidence interval (CI): 0.6 to 1.14].[95] The ECCO recommends that both EEN and corticosteroids are effective in inducing remission, regardless of disease location or activity.[65]

However, it should be noted that compliance with liquid diets is often problematic in adult patients. Withdrawal rates can reach 39%,[92] compared to low dropout and high compliance rates in children. Potentially, this explains the difference in efficacy. Issues that surround taste dislike (particularly elemental feeds), taste fatigue, boredom and poor support from, and contact with, dietetic staff, are common.[96] Remission rates are as high as 80-85% in adult patients who do comply with a liquid diet.[97,98] Interestingly, Japanese guidelines[88] advocate nutrition therapy as first-line, and medication as second-line, therapy. This is important as corticosteroids often have limited efficacy in maintaining long-term remission and contribute to a range of side-effects, including osteoporosis.[99-101]

In a recent systematic review[28] that examined the efficacy of EN in the maintenance of remission, significantly higher rates were reported in both surgically and medically induced remission patients when studies compared outcomes between patients who received EN and those who did not. In addition, significantly higher reoperation-free rates at five years were found in the EN supplemental group. In all seven studies, EN was provided immediately after induction of

remission, either as an oral or nocturnal nasogastric feed in addition to ordinary foods, and was never the sole source of nutrition. In five studies, an elemental EN diet that was administered via nocturnal nasogastric feeding was provided, in three of which patients were instructed to take 50% of energy from enteral feeds and 50% from low-fat food (20-30 g/day). Overall, this provided 35-40 kcal/kg IBW/day.[28,102-108] The authors recommend that while polymeric feeds are often well tolerated orally during the day, nocturnal nasogastric tube feeds may be preferable when prescribing elemental formulas, because of poor palatability. Some international guidelines recommend polymeric feeds that are enriched with transforming growth factor-β_2 (TGF-β_2) as an alternative to elemental feeds.[109,110] TGF-β_2 is a protein that is secreted by the stomach and has been shown to exert anti-inflammatory properties. The protein reduces gastrointestinal inflammation, while its incorporation into polymeric feeds improves palatability and ultimately compliance.[109,110]

When offering liquid diets as a mode of therapy, whole-protein formulas may be advantageous in terms of cost, palatability and lower osmolarity.[111,112] Practical considerations include the composition of available formulas, patient motivation and understanding of the diet, in addition to patient tolerance to formula and taste preferences.

Elemental formulas may result in nausea and osmotic diarrhoea because of higher formula osmolarity, and these feeds must be introduced gradually over three to four days. Additional fluids should be provided to meet fluid requirements. In general, individuals who receive liquid diets may experience weight loss, hunger and diarrhoea, and volumes or concentrations should be adjusted accordingly.[112]

Formula composition

The amount of fat and the type of fatty acid that is present in formulas has been evaluated because of immunomodulatory and anti-inflammatory effects in the gut.[20,113] Favourable outcomes have been associated with the low-fat (predominantly medium-chain triglyceride) content (0.6-1.3% of total calories),[114] compared to the high-fat content (12-30% of total calories), particularly linoleic acid.[113-115] However, a 2007 Cochrane systematic review[94] examined the fat content variations in seven trials (n = 209) and found no significant difference between low-fat formulas (< 20 g/1 000 kcal) and high-fat formulas (> 20 g/1 000 kcal). Nevertheless, a trend, albeit nonsignificant, was noted that favoured very low-fat (< 3 g/1 000 kcal) and low long-chain triglyceride content.

Omega-3 fatty acids decrease proinflammatory gene expression and cytokine production[15] and have been shown to aid in the maintenance of remission in level-one studies. In a Cochrane systematic review and meta-analysis that examined six randomised control trials (RCTs) and two independent trials [Epanova Program in Crohn's Study 1 (EPIC-1) and Epanova Program in Crohn's Study 1 (EPIC-2)],[25] the pooled analysis of the six RCTs revealed statistically significant results [relative ratio (RR): 0.77, 95% CI: 0.61-0.98, p-value = 0.03 and RR: 0.71, 95% CI: 0.54-0.93, p-value = 0.002) of n-3 and enteric-coated n-3 supplementation, respectively. Conversely, findings from the two independent trials (EPIC-1 and EPIC-2) reported no clinical benefit. Despite the contradictory reports, when pooled together, marginally statistically significant results (RR: 0.77, 95% CI: 0.61-0.98) were found. The authors concluded that while enteric-coated n-3 therapy was considered safe and well tolerated,[116] existing data did not support routine supplementation to maintain remission in CD.[25,65] A primary limitation to the presumed benefit was attributed to the clinical heterogeneity between the studies and a publication bias suggested by funnel plot analysis, wherein small negative trials were underrepresented.[116] Moreover, based on the meticulous nature and large sample size of the EPIC trials (double that of the included six studies for pooled analysis), those results provided a more precise estimate of treatment efficacy and therefore could not recommend routine supplementation for remission maintenance. Further research is required to assess the effect of omega-3 fatty acids on proinflammatory cytokine production in CD.

Other nutritional agents, including glutamine, butyrate, curcumin (turmeric extract), ginsenosides (ginseng extract), lycopene and other flavonoids (generally found in fruits and vegetables) have been evaluated, based on potential anti-inflammatory, antioxidant, immunoregulatory and anabolic actions through interactions with gene expression.[15,117-121]

Total parenteral nutrition in active disease

In the past, bowel rest and the correction of nutritional deficiencies via total parenteral nutrition (TPN) was a recommended therapy in CD.[122,123] TPN is an invasive treatment therapy that carries an increased risk of infection, while prolonged gut rest may result in reduced intestinal integrity and villi atrophy. A landmark randomised control trial of 51 patients with active CD by Greenberg et al allocated patients to one of three groups: TPN and nil by mouth (n = 17), a defined formula diet via nasogastric tube (n = 19), and peripheral parenteral nutrition (PPN) plus supplementary oral diet (n = 15).[124] Remission occurred in 71% of patients on TPN, in 58% of patients receiving nasogastric feeds and in 60% of patients on PPN and the oral diet. After one year, of those who had achieved clinical remission, 42%, 55% and 56% maintained remission, respectively. The differences were not significant. While TPN is not a recommended therapy for inducing remission in patients with CD, the ECCO recommends the use of TPN for complex, fistulising disease and as a supplemental therapy when EN is contraindicated.[54] Starting with a continuous infusion and moving to cyclical delivery in stable or long-term patients may be preferable.[125] Despite the potential complications,[126] home TPN is a viable life-saving option for some patients and in select cases has proven to improve clinical outcome and eliminate the need for surgery.[125,127]

Diet to maintain remission

EN has shown a suppressive effect on disease activity and mucosal inflammatory cytokine levels, yet recommended duration of EN supplementation once remission is first achieved is unknown.[108] A 2009 Cochrane review[84] of EN in the maintenance of remission in CD examined two randomised control trials. The first, a Japanese study, showed that outpatients who received half their daily caloric requirements as an elemental feed, and half as a normal diet, had a lower relapse rate (35%) compared to those who consumed a

full normal diet (64% relapse rate).[128] The second UK-based study demonstrated no difference in the relapse rate, with regard to steroid therapy or surgery, of 33 adults when they were provided with 35-50% of nutrition requirements via a normal diet that was supplemented with either a whole-protein or semi-elemental sip feed.[105] The study did not compare the two feeds to a normal diet alone.

The review concluded that elemental or polymeric formulas might be used as an effective alternative, or as an adjunct treatment, to maintenance drug therapy during remission, yet optimal daily amounts are unknown. Interestingly, elimination diets have also been used to prolong remission after enteral feeding.[129,130] These diets help patients to identify problem foods and create an individualised, "safe" diet plan. Limitations of elimination diets are that they are often complicated and require significant self-discipline and patient support. The diet is a lengthy process as reintroduction of foods may take up to three months and reactions to foods are often missed because of the slow onset of symptoms as new foods are tested several times over one day only. Alternatively, the low-fibre, fat-limited, exclusion diet (LOFFLEX) offers a well-established option to the standard elimination diet and is as effective in maintaining remission compared to the standard elimination diet: 55.6% and 59.4%, respectively.[129] Patients are able to immediately reintroduce normally well-tolerated foods such as potato, rice, chicken or fish. while supplemented with nutritional sip feeds to ensure that nutritional adequacy for up to four weeks after remission is achieved initially. Thereafter, foods are individually introduced over four-day intervals until a complete normal diet is reached during a three- to four-week period. In light of the 2009 Cochrane review, in part, the success of the LOFFLEX diet may be because of prolonged use of EN in conjunction with a normal diet, in addition to the avoidance of poorly tolerated foods.[96] This suggests that the protracted use of supplemental EN is beneficial once remission is achieved. Nevertheless, this modified elimination diet offers a more acceptable option for patients as a wider variety of foods is permitted, making mealtimes less restrictive and more socially acceptable.

FODMAP

Up to 57% of patients with CD in long-standing remission report experiencing functional symptoms of abdominal pain, bloating, flatulence and diarrhoea, all of which impact on patients' overall well-being and quality of life.[131] Dietary restriction of fermentable oligosaccharides (fructans and galactans), disaccharides (lactose), monosaccarides (fructose) and polyols (FODMAP),[132] may aid in reducing these functional symptoms (Table V). FODMAP are osmotically active short-chain carbohydrates that are poorly absorbed in the small intestine and rapidly fermented by bacteria in the colon. While ingestion does not cause the gastrointestinal disorder, it may lead to luminal distension, inducing the sensation of bloating, abdominal pain and often motility changes, particularly in individuals with existing bowel disease.[132] As a low-FODMAP diet involves the avoidance of a wide range of foods, dietetic professional guidance is encouraged[133-135] as patients tend to pick and choose aspects of the diet and ignore the rest, defeating the purpose, effectiveness and possibly nutritional completeness of the diet.[132] Patients require individual consultation and ongoing support, in addition to written literature, particularly when adapting the diet to locally available foods and prepackaged products.[132,136] In order to identify the most problematic FODMAP foods, once eliminated, these foods are progressively introduced and tolerance is assessed, and,

Table IV: High-FODMAP food source and suitable food alternatives[133]

FODMAP food source	Fruits	Vegetables	Dairy	Breads and cereals	Sweeteners
High FODMAP	Apples, apricots, cherries, lychees, peaches, pears, nashi pears, plums, prunes, mangoes, nectarines, sugar-snap peas, watermelon, custard apples, white peaches, rambutans, persimmons and tinned fruit in natural juice *Concentrated fruit sources:* Large servings of fruit, dried fruit and fruit juice	Artichokes, beetroot, Brussels sprouts, broccoli, cabbage, fennel, garlic, leeks, okra, onions, peas, shallots, avocado, cauliflower, mushrooms and snow peas	*Milk:* Cow, goat and sheep, and ice cream *Yoghurt:* Regular and low-fat *Cheeses:* Soft and fresh, e.g. ricotta and cottage	Wheat and rye when eaten in large amounts, e.g. bread, pasta, couscous, crackers and biscuits	Fructose, high-fructose corn syrup, sorbitol, mannitol, xylitol, isomalt and others ending in "-ol' *Honey*
Suitable FODMAP alternative	Bananas, blueberries, carambola, durian, grapefruit, grapes, honeydew melons, kiwi fruit, lemons, limes, mandarins, oranges, passion fruit, pawpaws, raspberries, rock melons, strawberries and tangelos	Bamboo shoots, bok choy, carrots, celery, capsicums, choko, choy sum, corn, eggplant, green beans, lettuce, chives, parsnip, pumpkin, silverbeet, spring onions (green only) and tomatoes *Onion and garlic substitutes:* Garlic-infused oil	*Milk:* Lactose-free and rice milk *Cheese:* "Hard" cheeses, including Brie and Camembert *Yoghurt:* Lactose-free *Ice cream substitutes:* Gelati and sorbets *Butter*	Gluten-free and spelt bread and cereal products	Any, except polyols *Honey substitutes:* Maple syrup and golden syrup

FODMAP: fermentable oligosaccharides, disaccharides, monosaccarides and polyols

in turn, the need to reduce or limit intake of specific FODMAP foods can then be identified.

Quercetin

Maintenance of epithelial barrier function and permeability is essential to prevent translocation by dietary antigens, microbes and other toxins.[15] Impairment of epithelial permeability (mucosal integrity) allows for an increased antigen and bacterial uptake that potentially drives the inflammatory response and induces epithelial lesions.[137-139] In CD, impaired mucosal integrity is common and characterised by alterations in the tight-junction protein content and composition, reductions in tight-junction strands and strand breaks.[139] Interestingly, recent research now suggests that the dietary flavonoid, quercetin, may enhance barrier function and reduce intestinal permeability by "sealing" tight-junction protein, claudin-4, in the Caco-2 cells.[139] The role of quercetin as a direct intestinal barrier-protective agent has been advocated.[139] Food sources that are rich in quercetin include apples, capers, green tea, pears, cherries, grapes, red onions, kale, broccoli, leaf lettuce and garlic.

Probiotics

Probiotics may aid in maintaining CD remission by enhancing the immune and epithelial function of the gut.[140] However, nonsignificant results from a meta-analysis, including eight randomised-control trials that examined probiotic efficacy for the maintenance of remission in CD,[141] and a Cochrane systematic review[142] that concluded that probiotic use cannot be recommended as effective therapy for the maintenance of remission in CD, do not indicate the use of probiotics in therapy currently. Treatment protocols, probiotic preparations, antibiotic use, disease behaviour and location, methods to induce remission and prior probiotic intestinal colonisation remain as limitations in previous study designs, potentially influencing probiotic efficacy.[142]

Summary

Nutritional support is considered to be an integral part of patient care in CD and should begin with individual patient assessment and take into consideration the potential limitations of standard anthropometric and biochemical indices. Unless contraindicated, EN should be used to aid in inducing remission. However, issues that surround patient tolerance and compliance may limit its implementation. After remission is achieved, the LOFFLEX and FODMAP diets can be used to transition and create individual patient diet plans. Throughout the disease course, preservation of bone stores and promotion of bone health is essential, including the assessment and supplementation of vitamins and minerals where clinically indicated.

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