Nutritional management of adults with inflammatory bowel disease: practical lessons from the available evidence

Melissa A Smith,¹ Trevor Smith,² Timothy M Trebble³

► Additional material is published online only. To view the files, please visit the journal online (<http://fg.bmj.com/content/3/3.toc>).

¹Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, UK

²Department of Gastroenterology and Human Nutrition, Southampton University Hospitals Trust, Southampton General Hospital, Southampton, UK

³Department of Gastroenterology, Portsmouth Hospitals NHS Trust, Portsmouth, UK

Correspondence to

Timothy M Trebble,
Department of Gastroenterology,
Portsmouth Hospitals NHS Trust,
Southwick Hill Road, Portsmouth
SO16 6YD, UK;
Tim.trebble@porthosp.nhs.uk

Accepted 10 April 2012

Abstract

Inflammatory bowel disease (IBD) is associated with impairment of nutritional status both anthropometrically and biochemically, which results from both qualitative and quantitative changes in dietary intake alongside disease activity. Dietary intervention to replace deficiency is essential and may also be used to treat active disease and to reduce symptoms. The evidence for dietary interventions in this area is reviewed and the following recommendations made:

- Assessment of nutritional status is an essential part of the investigation of all patients with IBD and deficiency should be actively sought.
- Any patient with macro- or micronutrient deficiency should be referred for dietetic assessment.
- Micronutrient deficiency (most frequently iron, vitamin B₁₂, folate and magnesium) should be replaced aggressively, parenterally if necessary.
- Significant improvement in gastrointestinal symptoms can be achieved by low-residue diets (for stricturing disease) and (always under dietetic supervision) management of lactose and other intolerances.
- Irritable bowel syndrome symptoms in patients with IBD can respond to low fermentable oligo-, di-, monosaccharide and polyol (FODMAP) diets, again this must be done under dietetic supervision.
- Active Crohn's disease can be treated by exclusive enteral nutrition (elemental/polymeric/alterated fat formulations all have equivalent efficacy).
- Enteral nutrition can maintain remission in Crohn's disease and in this context can be given alongside normal oral intake.
- Nutritional support does not have an established role in the treatment of active ulcerative colitis, other than in the management of malnutrition.
- Total parenteral nutrition should not be used unless intestinal failure occurs.
- There is insufficient evidence to support the routine use of Ω 3 fish oil, prebiotics and glutamine in the treatment of active IBD.

Introduction

Inflammatory bowel disease (IBD) is characterised by chronic relapsing inflammatory changes within the intestine that may lead to pathological changes to dietary intake, digestion and utilisation. This evidence-based review provides an overview of malnutrition in the two principal forms of IBD, Crohn's disease (CD) and ulcerative colitis (UC), and the role of nutritional measures in correcting deficiencies, reducing symptoms and modifying disease pathogenesis. This forms the basis of management in our units.

Nutritional status in IBD

Anorexia and weight loss were considered to be defining symptoms of active CD by Crohn,¹ and early studies by Harries noted an association of altered anthropometry with small-bowel CD but not colitis.²

The frequency of anthropometric malnutrition among IBD cohorts was noted to be higher where it is actively sought³ than in routine clinical practice,⁴ suggesting that this aspect of patients' management may be overlooked and, as with all indirect markers of disease severity, may be higher in hospital cohorts than population studies. Outpatient studies suggest that 14% of patients with CD (and 6% of patients with UC) have a body mass index of <18.5, with reduced skin-fold thickness (a measure of fat mass) and arm circumference (a measure of lean muscle mass)⁵ in up to 62%. Alterations in body mass and body composition in CD have been noted by others,^{5,6} particularly during disease activity. The evidence in UC is conflicting, although an association is seen with disease activity and disease of recent onset.⁵⁻⁷

The aetiology of malnutrition in IBD is probably multifactorial (table 1), with restricted dietary intake a prominent feature, and an association noted between reduced appetite and disease activity in CD.⁸ Dietary intake in patients with IBD differs qualitatively and quantitatively compared with the general population, with reduced intake of fruit and vegetables, but more refined sugar and fat (particularly animal fat).^{9, 10} This may suggest that patients need (or get less symptoms from) energy-dense foods or, alternatively, that a 'fast-food diet' has a role in the development of IBD.

The data supporting an effect of increased resting energy expenditure, even during active disease, are conflicting.^{8, 11}

Table 1 The aetiology of malnutrition in IBD, adapted from Hartman⁷⁸

Mechanism	Cause
Reduced food intake	Anorexia, abdominal pain, nausea, dietary restriction
Malabsorption	Available absorptive surface area reduced and damaged by inflammation, resection, bypass and fistulae
Increased intestinal losses	Exudative enteropathy (protein), blood loss (iron), diarrhoea (K^+ , Mg^{2+} , Zn^{2+}), steatorrhoea (fat and fat-soluble vitamins)
Drugs	Altered absorption and utilisation. Examples include proton pump inhibitors (hypomagnesaemia and reduced iron absorption), bile salt sequestrants (reduced fat-soluble vitamin absorption)

Nutritional deficiencies in IBD and the role of nutritional intervention

For patients with IBD, a healthy balanced diet should be encouraged, sufficient to avoid macronutrient and micronutrient deficiencies and anthropometric malnutrition. This allows adequate metabolic, immunological and physiological function to maintain health, including wound and mucosal healing, appropriate response to secondary infection, pregnancy and growth. However, patients with IBD frequently restrict their diets, and in such circumstances, review by a trained dietician is considered an essential component of the multidisciplinary management of their disease,¹² and the routine recommendation of a multivitamin supplement may be appropriate.

Where additional oral, enteral or parenteral nutritional support is being considered (see below),

Table 2 Measures of nutritional status in IBD

Anthropometric	Biomedical
Weight	Ferritin*/TIBC*; transferrin saturation
Body mass index	Folic acid/vitamin B ₁₂
Skin fold thickness	Vitamin A*
Hand grip strength	Vitamin D
	Selenium*/zinc*/copper*
	Magnesium/potassium

*Acute phase reactants, measurements may be inaccurate in active disease. TIBC, total iron binding capacity.

* in Crohn's disease

Figure 1 Nutritional intervention in inflammatory bowel disease.

Table 3 Treating specific nutritional deficiencies

Specific deficiency	First-line replacement strategy	Second-line replacement strategy
Iron	Oral iron preparation (eg, ferrous sulphate or ferrous fumarate)	Intravenous iron preparation (eg, iron sucrose)
Folate	Oral folic acid	
Vitamin B ₁₂	Intramuscular hydroxocobalamin	High dose oral vitamin B ₁₂
Magnesium	Oral magnesium oxide/glycerophosphate	Intravenous magnesium preparations

additional anthropometric and biochemical evaluation is appropriate (table 2). This should be in addition to assessment of both disease activity and structural alteration (eg, fistula, stricture) allowing tailored intervention (figure 1). These assessments should be reviewed at regular intervals to assess the effectiveness of the intervention. Wherever possible, nutritional support should be through the oral/enteral route.¹³ Choice of specific supplement in this context is, in practice, largely determined by palatability, although consideration should also be given to cost and calorie requirement.

Perioperative nutritional support is a particular concern in patients with IBD as operating on patients in a malnourished state is known to be associated with poorer outcomes and therefore the use of nutritional support to attempt preoperative optimisation of nutritional status is advocated.¹³ It is in this context that total parenteral nutrition (TPN) is most frequently advocated, as the contraindications for enteral nutritional support often constitute indications for surgical intervention (although where the enteral route is available, this should always be preferred).¹³ There is, however, only limited published evidence for the benefit of parenteral (or enteral nutrition) in this context.

Specific micronutrient deficiencies in IBD

Restrictive or modified diets may lead to micronutrient deficiency, even in the presence of adequate protein-calorie intake.^{11–14} Identification of specific nutritional deficiencies should lead to confirmation that the results are not reflective of either an acute phase response (table 2) or a secondary disease. Where deficiency appears genuine, selective supplementation and monitoring is appropriate, (table 3).

Iron deficiency is considered the commonest micronutrient deficiency in IBD, and while prospective data are lacking, it has been reported in up to 39% of patients,¹¹ with 65% requiring iron replacement over the course of their disease.¹⁵ The associated anaemia is clinically important, with a significant, yet often unrecognised, impact on quality of life.¹⁶ Assessment is complicated by the fact that the most commonly used

marker of iron deficiency, ferritin, is an acute phase reactant. In active disease, transferrin saturation is a more suitable and accurate marker of deficiency.

Vitamin B₁₂ and folate deficiencies are also traditionally thought to be associated with IBD, although this appears to be restricted to patients with ileal disease or resection.¹⁷ Potentially important consequences of even mild vitamin B₁₂ and folate deficiency include the development of hyperhomocysteinaemia,¹⁸ which in other contexts is associated with thromboembolic complications and osteoporosis, while folate deficiency in pregnancy is known to be associated with birth defects.

Metabolic bone disease and fragility fractures are increased in patients with IBD¹⁹ compared with the general population. Although low calcium and vitamin D intake²⁰ and vitamin D deficiency have been demonstrated²¹ in IBD, this probably plays a minor role alongside inflammatory disease activity and corticosteroid usage. Reflecting this, calcium intake is not proportional to bone mineral density²⁰ and the results of calcium and/or vitamin D supplementation studies have been disappointing.^{22–23} However, low body mass index may increase the risk of osteopenia.²⁴

Hypomagnesaemia may occur in IBD primarily owing to high-volume diarrhoea, but also owing to poor absorption and restricted dietary intake. In most cases, this can be dealt with by oral supplementation (table 3). Where this causes unacceptable diarrhoea intravenous preparations may be required.

Nutritional measures to improve symptoms in IBD

Dietary modification has been used to improve patients' symptoms and quality of life, regardless of IBD activity. Common interventions fall into four groups: exclusion diets, low-residue diets, dietary interventions for coexistent irritable bowel syndrome (IBS) symptoms and management of lactose intolerance.

Exclusion diets

Dietary intolerances are common in both UC and CD with studies suggesting frequencies greater than 60% compared with less than 15% in healthy controls.²⁵ Intolerances can be multiple and commonly reflect staples, including dairy products, vegetables, cereal products and fruit.^{25–26} Many patients independently identify food 'triggers' and restrict their diet accordingly, potentially leading to dietary deficiencies. All such patients should be referred for dietetic assessment. Trials of personalised exclusion diets and the LOFFLEX (low-fibre, fat-limited exclusion) diet as disease modifiers are discussed below.

Low-residue diets

A number of dietary constituents can induce symptoms in the presence of stricturing disease, including high-fibre foods (eg, nuts, seeds/pips, whole grains and fruit/vegetable skins) and foods that are difficult to break down mechanically—for example, meat, skin

and gristle.¹² Eliminating such foods from the diet may reduce frequency and severity of obstructive episodes, and this can generally be achieved without adverse nutritional consequences.

Dietary intervention for superadded IBS symptoms

IBS symptoms are common in patients with IBD even in disease remission,^{27 28} and are associated with an adverse effect on well-being²⁷ and quality of life.²⁸ Dietary and beverage avoidance is a key part of managing functional symptoms.²⁹ A recent study has suggested benefit in this group from avoiding fermentable oligo-, di-, monosaccharides and polyols (FODMAPs).³⁰ These poorly digested short-chain carbohydrates lead to increased gas production and fluid excretion in the gut, resulting in symptoms in susceptible individuals. The required diet is complex and requires formal dietetic advice and written supporting information, but can be effective in reducing symptoms.¹²

Lactose intolerance

Lactose intolerance is more common than would be expected in patients with IBD, even when ethnicity is taken into account.³¹ This increase is partly due to secondary intolerance, caused by the effects of the disease (and its treatment) on the small bowel, bacterial overgrowth and rapid small intestinal transit. However, there is also an increase in primary lactose intolerance. Additionally, many patients experience severe symptoms after the consumption of dairy products in the absence of true lactose intolerance.

In these two situations appropriate dietary modification is warranted. Replacement of milk with skimmed or lactose-free alternatives may be adequate for relief of symptoms, but replacement with soy or rice-based products may be necessary.²⁹ It is important to emphasise, however, that widespread prohibition of dairy products is not necessary and may be harmful.

Disease modification in IBD: the role of nutritional intervention

Enteral nutritional support has demonstrated efficacy as a therapeutic intervention in CD. The mechanism of its anti-inflammatory action is incompletely explained, but it is clear that its effect is much more than simple correction of nutritional deficiencies, and enteral nutrition may therefore be considered as a therapeutic option even where nutritional status is acceptable.

There is insufficient evidence to support the use of enteral nutrition as anti-inflammatory treatment in UC, and the following sections, therefore, refer exclusively to CD.

Enteral nutrition for induction of remission in CD

Enteral nutritional treatment for active CD is well established in paediatric practice, where it is generally considered first-line treatment and has been shown to be as effective as steroids in inducing disease remission,³² while avoiding the adverse effects of steroids and improving nutritional status, quality of

life³³ and growth.³⁴ In adult CD, evidence has been marginally less convincing and meta-analysis has concluded that steroids have slightly better efficacy in remission induction³⁵ albeit at the cost of considerable side effects. Enteral nutrition may be more effective in young adults³⁶ and where it is tolerated, high remission rates are seen. There are no serious adverse effects of enteral nutrition and it confers the benefits of mucosal healing^{32 33 37} and nutritional optimisation³⁴ which are not achieved by steroid treatment. Enteral nutrition is considered suitable treatment for CD whatever its distribution,^{32 38} although data in adults are lacking.

Comparative intervention studies of the different enteral formula diets are generally compromised by small cohort sizes. However, their conclusion, confirmed by meta-analysis,³⁵ is that the type of protein source—that is, amino acid (elemental) or protein (polymeric), does not affect remission rates^{35 39} and neither does the quantity or type of fat source used.³⁵

Considerable work has also focused on whether normal diet has to be completely stopped during enteral nutrition for a therapeutic benefit or whether supplementation/partial replacement is adequate. It appears that for disease remission there is a benefit from total cessation of the normal diet,³⁸ but this may not be necessary for maintenance of remission (see below).

Enteral nutrition for maintenance of remission in CD

Published evidence for the efficacy of enteral nutrition in maintenance of remission achieved by drugs/surgery is the subject of a Cochrane systematic review,⁴⁰ which found only two eligible studies. One of these was not truly a study of maintenance of remission, but rather of the efficacy of enteral nutrition in steroid-dependency.⁴¹ The second study, by Tagaki *et al*, randomised patients with CD in remission (regardless of how that remission was achieved) to receive a normal unrestricted diet or half of their calorie requirement from enteral nutrition supplements. The trial was stopped early as a significant benefit of enteral nutrition supplements was demonstrated, despite weight gain and calorie intake being equivalent in the two groups.⁴² Other studies of inferior design show similar results.

Supplemental^{43–46} and cyclical enteral nutrition⁴⁷ have both been shown to improve maintenance of remission (both clinical and endoscopic),^{43 46} while consuming more than 900 kcal/day from supplements has been associated with decreased rates of readmission to hospital.⁴⁸

Use of enteral nutrition as an adjunct to other treatments

In clinical practice, enteral nutrition is often used as an adjunct to other treatments, but little experimental work has specifically examined this aspect of management. An audit of the use of infliximab in Japan showed, in subgroup analysis, that there appeared to be a significantly higher rate of remission with infliximab in those patients receiving concurrent enteral nutrition.⁴⁹ However, when supplemental enteral nutrition

during maintenance infliximab was studied prospectively, a statistically significant difference in relapse rate was not demonstrated. Relapse rates were lower in the enteral nutrition group, however, and a larger study might have demonstrated significance.⁵⁰

Parenteral nutrition

After the development of TPN there was early enthusiasm for its use as primary treatment in IBD which had failed to respond to conventional medical management.^{51 52} However, these studies and a subsequent meta-analysis suggested that, other than in intestinal failure, TPN had no advantage in inducing a maintained remission over other treatment modalities.^{53 54} Furthermore, there may be a detrimental effect through loss of mucosal barrier function and bacterial translocation, in addition to intravenous catheter-related complications. Of interest, however, the original studies suggested an improvement in CD symptoms during periods of bowel rest.

Similarly in UC⁵⁵, studies suggested that other than a temporary improvement in nutritional status, there is no significant alteration to the disease course or additional therapeutic benefit.^{56 57} TPN is therefore only recommended in UC when intestinal failure has occurred.

Modification of dietary intake

The role of dietary intake in modulating CD activity was examined in a large randomised study of a low refined sugar, high-fibre diet compared with an unrestricted sugar, low-fibre diet. This failed to demonstrate a significant difference in subsequent symptomatic disease course,⁵⁸ although smaller, retrospective studies have suggested some positive effects.

Formal and personalised exclusion diets, (identifying and avoiding dietary constituents that provoke symptoms) have been successful in maintaining clinical remission in CD over a 2-year period.⁵⁹ Woolner *et al* describe the use of a low-fibre, fat-limited exclusion (LOFFLEX) diet which achieved equivalent efficacy to that of traditional exclusion diets⁶⁰ while being more acceptable to patients (as it introduces a range of generally well-tolerated foods early on and avoids the need for continuing consumption of supplements). Other smaller, weaker studies support the value of elimination diets.²⁵ It is important to note that improvements documented in these studies are based on clinical symptoms, and it is not clear whether such diets are therefore just ameliorating functional symptoms (for which exclusion diets were developed) or having a disease-modifying effect.

A number of alternative diets have also been proposed for patients with IBD, although they have limited published supportive evidence and use in clinical practice. These include elimination diets for the avoidance of dietary allergens based on skin prick testing; gluten-free diet; specific carbohydrate diet; yeast-free diet; and microparticle diet (see Brown and Roy for a more comprehensive discussion).²⁵

Prebiotics

Prebiotics are dietary components that alter the composition and activity of the intestinal microbiota and include fructo- and galacto-oligosaccharides and inulin. They may be given in conjunction with probiotics when they are referred to as synbiotics. (Probiotics are not a truly nutritional intervention and are not therefore considered in detail here. They have an established role in the treatment of pouchitis¹³ but outside this indication, evidence is generally insufficient to support their use, although early data in UC are encouraging. For a detailed overview see Hedin *et al*⁶¹.)

A recently published randomised controlled trial has demonstrated that fructo-oligosaccharides are not effective in the treatment of mild/moderately active CD, with the treatment group demonstrating higher rates of abdominal symptoms and a trend towards lower rates of response and remission than the placebo group, although this failed to reach statistical significance.⁶² In UC there is a paucity of data on the use of prebiotics.

The use of synbiotics has also been studied. One pilot study using Synergy 1 (oligofructose and inulin with *Bifidobacterium longum*) in active UC showed promising changes in sigmoidoscopic scores and reductions in inflammatory cytokines in the gut mucosa, but failed to achieve a clinical improvement.⁶³ In CD, one small study using Synergy 1 improved symptoms in patients with active CD.⁶⁴ However, another small study failed to demonstrate any benefit of Synbiotic 2000 (a cocktail of five probiotic species and four prebiotics) over placebo in maintaining postoperative remission in CD.⁶⁵

Ω3 Fatty acids 'fish oil'

Animal studies and success in other inflammatory illnesses led to interest in the use of fish oil as a safe but effective anti-inflammatory treatment for IBD. However, while data remain conflicting, results have, on the whole, been disappointing, with meta-analysis showing, at best, a very small benefit.^{66 67} There are problems with the design of many of these trials including difficulty blinding patients against fish tasting interventions; the use of therapeutically active 'placebo' treatments and poor trial design.

A study in CD by Belluzzi *et al* suggested a 33% reduction in risk of relapse with fish oil compared with placebo in patients with CD in clinical remission (but with raised inflammatory markers, suggesting a high risk of relapse).⁶⁸ However, no other study has been able to reproduce these results and the two largest randomised controlled studies suggest that there is no statistically significant reduction in CD relapse.⁶⁹ A Cochrane systematic review demonstrated a marginally significant benefit in the use of fish oil (RR=0.77, 95% CI 0.61 to 0.98, p=0.03), which is strengthened by including only those studies which use the enteric coated formulation, shown to enhance compliance.

Box 1 A summary of our recommendations

- ▶ Assessment of nutritional status is an essential part of the investigation of all patients with inflammatory bowel disease (IBD) and deficiency should be actively sought.
- ▶ Any patient with macro- or micronutrient deficiency should be referred for dietetic assessment.
- ▶ Micronutrient deficiency (most frequently iron, B₁₂, folate and magnesium) should be replaced aggressively, parenterally if necessary.
- ▶ Significant improvement in gastrointestinal symptoms can be achieved by low-residue diets (for stricturing disease) and (always under dietetic supervision) management of lactose and other intolerances.
- ▶ Irritable bowel syndrome symptoms in patients with IBD can respond to low fermentable oligo-, di-, monosaccharide and polyol (FODMAPs) diets; again this must be done under dietetic supervision.
- ▶ Active Crohn's disease can be treated by exclusive enteral nutrition (elemental/polymeric/alterated fat formulations all have equivalent efficacy).
- ▶ Enteral nutrition can maintain remission in Crohn's disease and in this context can be given alongside normal oral intake.
- ▶ Nutritional support does not have an established role in the treatment of active ulcerative colitis, other than in the management of malnutrition.
- ▶ Total parenteral nutrition should not be used unless intestinal failure occurs.
- ▶ There is insufficient evidence to support the routine use of ω-3 fish oil, prebiotics and glutamine in the treatment of active IBD.

In this analysis the number needed to treat to prevent a relapse at 1 year was five.⁶⁷ The authors concluded that fish oil should not be recommended to patients with CD, owing to its apparent inferiority to other treatments for the maintenance of disease remission.

Several studies have been conducted to assess the effects of fish oil supplementation on outcomes in UC, although there is a paucity of good randomised controlled data and the Cochrane Collaboration suggested that there is insufficient evidence to make any recommendations about the use of fish oil to induce remission⁷⁰ and that evidence suggests that fish oil is not effective in maintenance of remission in UC.⁶⁶ However, although trials failed to show benefits in hard end points such as achieving disease remission, several showed encouraging data for secondary end points, (eg, steroid-sparing effect,^{71 72} altered cytokine profile⁷¹) and a suggestion of short-term (up to 3 months) benefit of fish oil over placebo in maintaining disease remission.⁷³

Glutamine

In intensive care, supplementation with the amino acid glutamine has been successfully used to ameliorate the inflammatory response. It has been proposed that a glutamine supplement would have a beneficial impact on IBD, owing both to its general anti-inflammatory effects and effects specific to the gut, where it alters proteolysis and may help to preserve the integrity of the mucosal barrier.⁷⁴ Animal studies have been encouraging, but to date no clinical studies have shown any benefit of glutamine supplementation (either enterally^{75 76}

or parenterally)⁷⁷ in IBD, although each study contained only a small number of patients.

Conclusion

Nutrition remains an important concern for all clinicians dealing with patients with IBD. Nutritional deficiency should be sought and treated in all patients, particularly those who are inpatients. Patients should have access to dietetic services where nutritional problems are identified. Wherever possible, replacement/support should be given enterally. Enteral nutritional treatment is effective for the induction and maintenance of remission in CD, but has no disease-modifying role in UC. It is limited by palatability and acceptability to patients and, without continuing maintenance treatment, has disappointing relapse rates. Dietary modifications can help to reduce symptoms, again predominantly in CD. There is insufficient evidence to support the use of dietary supplements including Ω3 fish oil, prebiotics and glutamine in CD or UC.

A summary of our recommendations can be found in box 1. With the exception of vitamin B₁₂, oral replacement of micronutrients is always preferred where possible. However, tolerance of oral supplementation can be problematic with iron and magnesium supplements, which are commonly associated with gastrointestinal side effects.

Contributors MAS, TS and TMT were responsible for the manuscript production.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

References

1. Crohn BB, Yunich AM. Ileojunitis. *Ann Surg* 1941;113:371–80.
2. Harries AD, Jones LA, Heatley RV, *et al.* Malnutrition in inflammatory bowel disease: an anthropometric study. *Hum Nutr Clin Nutr* 1982;36:307–13.
3. Gassull MA, Abad A, Cabré E, *et al.* Enteral nutrition in inflammatory bowel disease. *Gut* 1986;27 Suppl 1:76–80.
4. Nguyen GC, Munsell M, Harris ML. Nationwide prevalence and prognostic significance of clinically diagnosable protein-calorie malnutrition in hospitalized inflammatory bowel disease patients. *Inflamm Bowel Dis* 2008;14:1105–11.
5. Rocha R, Santana GO, Almeida N, *et al.* Analysis of fat and muscle mass in patients with inflammatory bowel disease during remission and active phase. *Br J Nutr* 2009;101:676–9.
6. Jahnsen J, Falch JA, Mowinkel P, *et al.* Body composition in patients with inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2003;98:1556–62.
7. Geerling BJ, Badart-Smook A, Stockbrügger RW, *et al.* Comprehensive nutritional status in recently diagnosed patients with inflammatory bowel disease compared with population controls. *Eur J Clin Nutr* 2000;54:514–21.
8. Rigaud D, Angel LA, Cerf M, *et al.* Mechanisms of decreased food intake during weight loss in adult Crohn's disease patients without obvious malabsorption. *Am J Clin Nutr* 1994;60:775–81.
9. Reif S, Klein I, Lubin F, *et al.* Pre-illness dietary factors in inflammatory bowel disease. *Gut* 1997;40:754–60.

10. Yamamoto T, Nakahigashi M, Saniabadi AR. Review article: diet and inflammatory bowel disease—epidemiology and treatment. *Aliment Pharmacol Ther* 2009;30:99–112.
11. Vagianos K, Bector S, McConnell J, *et al.* Nutrition assessment of patients with inflammatory bowel disease. *JPEN J Parenter Enteral Nutr* 2007;31:311–9.
12. Lomer MC. Dietary and nutritional considerations for inflammatory bowel disease. *Proc Nutr Soc* 2011;3:1–7.
13. Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;53 Suppl 5:V1–16.
14. Filippi J, Al-Jaouni R, Wiroth JB, *et al.* Nutritional deficiencies in patients with Crohn's disease in remission. *Inflamm Bowel Dis* 2006;12:185–91.
15. Oldenburg B, Koningsberger JC, Van Berge Henegouwen GP, *et al.* Iron and inflammatory bowel disease. *Aliment Pharmacol Ther* 2001;15:429–38.
16. Gasche C, Lomer MC, Cavill I, *et al.* Iron, anaemia, and inflammatory bowel diseases. *Gut* 2004;53:1190–7.
17. Yakut M, Ustün Y, Kabaçam G, *et al.* Serum vitamin B₁₂ and folate status in patients with inflammatory bowel diseases. *Eur J Intern Med* 2010;21:320–3.
18. Romagnuolo J, Fedorak RN, Dias VC, *et al.* Hyperhomocysteinemia and inflammatory bowel disease: prevalence and predictors in a cross-sectional study. *Am J Gastroenterol* 2001;96:2143–9.
19. Bernstein CN, Blanchard JF, Leslie W, *et al.* The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. *Ann Intern Med* 2000;133:795–9.
20. Bernstein CN, Bector S, Leslie WD. Lack of relationship of calcium and vitamin D intake to bone mineral density in premenopausal women with inflammatory bowel disease. *Am J Gastroenterol* 2003;98:2468–73.
21. Pappa HM, Grand RJ, Gordon CM. Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease. *Inflamm Bowel Dis* 2006;12:1162–74.
22. Benchimol EI, Ward LM, Gallagher JC, *et al.* Effect of calcium and vitamin D supplementation on bone mineral density in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007;45:538–45.
23. Bernstein CN, Seeger LL, Anton PA, *et al.* A randomized, placebo-controlled trial of calcium supplementation for decreased bone density in corticosteroid-using patients with inflammatory bowel disease: a pilot study. *Aliment Pharmacol Ther* 1996;10:777–86.
24. Andreassen H, Hylander E, Rix M. Gender, age, and body weight are the major predictive factors for bone mineral density in Crohn's disease: a case-control cross-sectional study of 113 patients. *Am J Gastroenterol* 1999;94:824–8.
25. Brown AC, Roy M. Does evidence exist to include dietary therapy in the treatment of Crohn's disease? *Expert Rev Gastroenterol Hepatol* 2010;4:191–215.
26. Jones VA, Dickinson RJ, Workman E, *et al.* Crohn's disease: maintenance of remission by diet. *Lancet* 1985;2:177–80.
27. Simrén M, Axelsson J, Gillberg R, *et al.* Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* 2002;97:389–96.
28. Minderhoud IM, Oldenburg B, Wismeijer JA, *et al.* IBS-like symptoms in patients with inflammatory bowel disease in remission; relationships with quality of life and coping behavior. *Dig Dis Sci* 2004;49:469–74.
29. MacDermott RP. Treatment of irritable bowel syndrome in outpatients with inflammatory bowel disease using a food and beverage intolerance, food and beverage avoidance diet. *Inflamm Bowel Dis* 2007;13:91–6.
30. Gearry RB, Irving PM, Barrett JS, *et al.* Reduction of dietary poorly absorbed short-chain carbohydrates (FODMAPs) improves abdominal symptoms in patients with inflammatory bowel disease—a pilot study. *J Crohns Colitis* 2009;3:8–14.
31. Mishkin S. Dairy sensitivity, lactose malabsorption, and elimination diets in inflammatory bowel disease. *Am J Clin Nutr* 1997;65:564–7.
32. Borrelli O, Cordischi L, Cirulli M, *et al.* Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol* 2006;4:744–53.
33. Afzal NA, Van Der Zaag-Loonen HJ, Arnaud-Battandier F, *et al.* Improvement in quality of life of children with acute Crohn's disease does not parallel mucosal healing after treatment with exclusive enteral nutrition. *Aliment Pharmacol Ther* 2004;20:167–72.
34. Thomas AG, Taylor F, Miller V. Dietary intake and nutritional treatment in childhood Crohn's disease. *J Pediatr Gastroenterol Nutr* 1993;17:75–81.
35. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007;1:CD000542.
36. González-Huix F, de León R, Fernández-Bañares F, *et al.* Polymeric enteral diets as primary treatment of active Crohn's disease: a prospective steroid controlled trial. *Gut* 1993;34:778–82.
37. Fell JM, Paintin M, Arnaud-Battandier F, *et al.* Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2000;14:281–9.
38. Buchanan E, Gaunt WW, Cardigan T, *et al.* The use of exclusive enteral nutrition for induction of remission in children with Crohn's disease demonstrates that disease phenotype does not influence clinical remission. *Aliment Pharmacol Ther* 2009;30:501–7.
39. Verma S, Brown S, Kirkwood B, *et al.* Polymeric versus elemental diet as primary treatment in active Crohn's disease: a randomized, double-blind trial. *Am J Gastroenterol* 2000;95:735–9.
40. Akobeng AK, Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007;3:CD005984.
41. Verma S, Holdsworth CD, Gaffer MH. Does adjuvant nutritional support diminish steroid dependency in Crohn disease? *Scand J Gastroenterol* 2001;36:383–8.
42. Takagi S, Utsunomiya K, Kuriyama S, *et al.* Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: A randomized-controlled trial. *Aliment Pharmacol Ther* 2006;24:1333–40.
43. Yamamoto T, Nakahigashi M, Saniabadi AR, *et al.* Impacts of long-term enteral nutrition on clinical and endoscopic disease activities and mucosal cytokines during remission in patients with Crohn's disease: a prospective study. *Inflamm Bowel Dis* 2007;13:1493–501.
44. Verma S, Kirkwood B, Brown S, *et al.* Oral nutritional supplementation is effective in the maintenance of remission in Crohn's disease. *Dig Liver Dis* 2000;32:769–74.

45. Hirakawa H, Fukuda Y, Tanida N, *et al.* Home elemental enteral hyperalimentation (HEEH) for the maintenance of remission in patients with Crohn's disease. *Gastroenterol Jpn* 1993;28:379–84.
46. Yamamoto T, Nakahigashi M, Umegae S, *et al.* Impact of long-term enteral nutrition on clinical and endoscopic recurrence after resection for Crohn's disease: A prospective, non-randomized, parallel, controlled study. *Aliment Pharmacol Ther* 2007;25:67–72.
47. Matsueda K, Shoda R, Takazoe M, *et al.* Therapeutic efficacy of cyclic home elemental enteral alimentation in Crohn's disease: Japanese cooperative Crohn's disease study. *J Gastroenterol* 1995;30 Suppl 8:91–4.
48. Watanabe O, Ando T, Ishiguro K, *et al.* Enteral nutrition decreases hospitalization rate in patients with Crohn's disease. *J Gastroenterol Hepatol* 2010;25 Suppl 1:S134–7.
49. Tanaka T, Takahama K, Kimura T, *et al.* Effect of concurrent elemental diet on infliximab treatment for Crohn's disease. *J Gastroenterol Hepatol* 2006;21:1143–9.
50. Yamamoto T, Nakahigashi M, Umegae S, *et al.* Prospective clinical trial: enteral nutrition during maintenance infliximab in Crohn's disease. *J Gastroenterol* 2010;45:24–9.
51. Fischer JE, Foster GS, Abel RM, *et al.* Hyperalimentation as primary therapy for inflammatory bowel disease. *Am J Surg* 1973;125:165–75.
52. Ostro MJ, Greenberg GR, Jeejeebhoy KN. Total parenteral nutrition and complete bowel rest in the management of Crohn's disease. *JPEN J Parenter Enteral Nutr* 1985;9:280–7.
53. Issa M, Binion DG. Bowel rest and nutrition therapy in the management of active Crohn's disease. *Nutr Clin Pract* 2008;23:299–308.
54. Wiese DM, Rivera R, Seidner DL. Is there a role for bowel rest in nutrition management of Crohn's disease? *Nutr Clin Pract* 2008;23:309–17.
55. Mullen JL, Hargrove WC, Dudrick SJ, *et al.* Ten years experience with intravenous hyperalimentation and inflammatory bowel disease. *Ann Surg* 1978;187:523–9.
56. Dickinson RJ, Ashton MG, Axon AT, *et al.* Controlled trial of intravenous hyperalimentation and total bowel rest as an adjunct to the routine therapy of acute colitis. *Gastroenterology* 1980;79:1199–204.
57. Elson CO, Layden TJ, Nemchausky BA, *et al.* An evaluation of total parenteral nutrition in the management of inflammatory bowel disease. *Dig Dis Sci* 1980;25:42–8.
58. Ritchie JK, Wadsworth J, Lennard-Jones JE, *et al.* Controlled multicentre therapeutic trial of an unrefined carbohydrate, fibre rich diet in Crohn's disease. *Br Med J (Clin Res Ed)* 1987;295:517–20.
59. Riordan AM, Hunter JO, Cowan RE, *et al.* Treatment of active Crohn's disease by exclusion diet: East Anglian multicentre controlled trial. *Lancet* 1993;342:1131–4.
60. Woolner JT, Parker TJ, Kirby GA, *et al.* The development and evaluation of a diet for maintaining remission in Crohn's disease. *Journal of Human Nutrition and Dietetics* 1998;11:1–11.
61. Hedin CR, Mullard M, Sharratt E, *et al.* Probiotic and prebiotic use in patients with inflammatory bowel disease: a case-control study. *Inflamm Bowel Dis* 2010;16:2099–108.
62. Benjamin JL, Hedin CR, Koutsoumpas A, *et al.* Smokers with active Crohn's disease have a clinically relevant dysbiosis of the gastrointestinal microbiota. *Inflamm Bowel Dis* 2011 (In press).
63. Furrie E, Macfarlane S, Kennedy A, *et al.* Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. *Gut* 2005;54:242–9.
64. Steed H, Macfarlane GT, Blackett KL, *et al.* Clinical trial: the microbiological and immunological effects of synbiotic consumption - a randomized double-blind placebo-controlled study in active Crohn's disease. *Aliment Pharmacol Ther* 2010;32:872–83.
65. Chermesh I, Tamir A, Reshef R, *et al.* Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. *Dig Dis Sci* 2007;52:385–9.
66. Turner D, Steinhart AH, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2007;3:CD006443.
67. Turner D, Zlotkin SH, Shah PS, *et al.* Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009;1:CD006320.
68. Belluzzi A, Brignola C, Campieri M, *et al.* Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med* 1996;334:1557–60.
69. Feagan BG, Sandborn WJ, Mittmann U, *et al.* Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. *JAMA* 2008;299:1690–7.
70. De LM, de VR, Hommes DW, *et al.* Fish oil for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2007;4:CD005986.
71. Hawthorne AB, Daneshmend TK, Hawkey CJ, *et al.* Treatment of ulcerative colitis with fish oil supplementation: a prospective 12 month randomised controlled trial. *Gut* 1992;33:922–8.
72. Aslan A, Triadafilopoulos G. Fish oil fatty acid supplementation in active ulcerative colitis: a double-blind, placebo-controlled, crossover study. *Am J Gastroenterol* 1992;87:432–7.
73. Loeschke K, Ueberschaer B, Pietsch A, *et al.* n-3 fatty acids only delay early relapse of ulcerative colitis in remission. *Dig Dis Sci* 1996;41:2087–94.
74. Coëffier M, Marion-Letellier R, Déchelotte P. Potential for amino acids supplementation during inflammatory bowel diseases. *Inflamm Bowel Dis* 2010;16:518–24.
75. Akobeng AK, Miller V, Stanton J, *et al.* Double-blind randomized controlled trial of glutamine-enriched polymeric diet in the treatment of active Crohn's disease. *J Pediatr Gastroenterol Nutr* 2000;30:78–84.
76. Den Hond E, Hiele M, Peeters M, *et al.* Effect of long-term oral glutamine supplements on small intestinal permeability in patients with Crohn's disease. *JPEN J Parenter Enteral Nutr* 1999;23:7–11.
77. Ockenga J, Borchert K, Stüber E, *et al.* Glutamine-enriched total parenteral nutrition in patients with inflammatory bowel disease. *Eur J Clin Nutr* 2005;59:1302–9.
78. Hartman C, Eliakim R, Shamir R. Nutritional status and nutritional therapy in inflammatory bowel diseases. *World J Gastroenterol* 2009;15:2570–8.