Nutritional management of Crohn's disease

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Abstract: Nutritional care and therapy forms an integral part of the management of patients with Crohn's disease (CD). Nutritional deficiencies result from reduced oral intake, malabsorption, medication side effects and systemic inflammation due to active disease. Enteral nutrition has a role in support for the malnourished patient, as well as in primary therapy to induce and maintain remission. The use of parenteral nutrition in CD is mainly limited to the preoperative setting or for patients with intestinal failure, but does not offer any additional advantage over EN in disease control. Dietary modifications, including elimination–reintroduction diets and a low fermentable, oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet may improve symptoms but there are currently no data to suggest that these approaches have any role in the induction or maintenance of remission.

Keywords: Crohn's disease, enteral nutrition, intestinal failure, micronutrient deficiency, parenteral nutrition, protein energy malnutrition

Introduction

Crohn's disease (CD) is a chronic, relapsing, inflammatory disease, associated with malnutrition in 20–85% of patients [Goh and O'Morain, 2003], particularly, but not confined to, those with small bowel disease. Factors that compromise protein energy nutrition in CD include poor oral intake, malabsorption from active disease or following surgery, hypercatabolism due to active inflammation, and side effects from different treatment strategies. Deficiencies in micronutrients, vitamins and trace elements also occur, with iron deficiency the most common [Gisbert and Gomollon, 2008]. Vitamin D deficiency is also gaining increasing recognition, due to its role in bone health and other diseases [Christakos and DeLuca, 2011]. Recognition and treatment of malnutrition is essential since it is associated with complications, especially postoperative healing and septic complications.

Distinct from treatment of malnutrition is a role for nutrition as a primary therapy in CD. This was initially postulated in adults in 1973, when a small series of patients with CD treated with an elemental diet were demonstrated to have reduced Crohn's activity, in addition to improved nutrition [Voitk *et al*. 1973]. Since then, multiple trials and meta-analyses have attempted to assess the anti-inflammatory impact of enteral feed.

This review discusses common macro- and micronutrient deficiencies, the role for oral, enteral nutrition (EN) and parenteral nutrition (PN) and the evidence supporting nutrition as a primary therapy in CD.

Protein energy malnutrition

It is difficult to accurately establish the rate of malnutrition in CD due to widely differing definitions. Rates as variable as 20–85% have been published [Han *et al*. 1999; Harries and Rhodes, 1985; Gassull *et al*. 1986; Cabre and Gassull, 2001; Dieleman and Heizer, 1998], but these should be seen in the context of the prevalence of malnutrition in general acute inpatients of 34% [Russell and Elia, 2011]. In addition, a growing proportion of newly diagnosed patients are obese, reflecting the rise in obesity in the general population [Gerasimidis, 2011]. The largest published series by Nguyen and Munsell of 36,448 American inpatients with CD only detected a malnutrition rate of 6.1%; however, these data were based on ICD codes and therefore may be an underrepresentation [Nguyen and Munsell, 2008]. Nevertheless, the authors identified clear risk factors for malnutrition, such as fistulizing disease (odds ratio (OR) 1.65, 95% confidence interval (CI) 1.50–1.82) and bowel surgery (OR 1.37, 95% CI 1.27–1.48) [Nguyen and Munsell, 2008]. Notably,

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malnutrition was associated with an increased risk of in-hospital mortality (OR 3.49, 95% CI 2.89–4.23) and increased length of stay (11.9 *versus* 5.8 days, $p < 0.00001$) [Nguyen and Munsell, 2008].

As no single measure predicts overall nutritional status in patients with CD, a multidimensional approach has been proposed to include measurement of body composition, dietary intake, biochemical measures and muscle strength [Geerling *et al.* 1998]. However, this is clearly not practical for all patients in routine clinical practice and therefore the use of nutritional screening tools, such as the Malnutrition Universal Screening Tool (MUST) [Elia, 2003], which incorporates important measures such as body mass index [Mijac *et al.* 2010] should be applied to the general CD population to identify patients at risk of malnutrition. Selected patients should then undergo more detailed assessment, including dietary intake, anthropometric evaluation and measurement of vitamins and trace elements.

Vitamin, macronutrient and micronutrient deficiency

Micronutrients refer to trace minerals and vitamins required in minute quantities, as opposed to macronutrients, required in larger amounts (fats, carbohydrates, proteins, calcium, phosphate and magnesium etc). Inadequate oral intake of dietary vitamins and micronutrients is prevalent in patients with CD [Rigaud *et al.* 1994; Pons *et al.* 2009; Gerasimidis, 2011]. Factors that contribute to decreased food intake, independently of disease activity, include loss of appetite, hunger and depressed mood [Rigaud *et al.* 1994]. An analysis of the 7-day dietary pattern of 74 patients with CD showed failure to meet recommended daily dietary intake of all nutrients, except vitamin B12, despite adequate protein/energy intake and a normal body mass index. This was particularly so with intake of vitamins A, C and E, folate, calcium and zinc, with prevalence rates of each deficiency exceeding 40%. These findings were independent of disease activity, although the study was not powered to assess this as a primary outcome [Aghdassi *et al.* 2007].

Consequences of micronutrient deficiencies range from overt clinical syndromes, including anaemia (due to deficiencies in iron, B12 and folate), osteomalacia (vitamin D), peripheral neuropathy (vitamin E), night blindness (vitamin A), beriberi (thiamine) and stomatitis or glossitis (vitamin B groups). In many cases, however, patients with micronutrient deficiencies present with nonspecific symptoms such as fatigue and depression.

Iron deficiency anaemia is the most common 'extra-intestinal' manifestation of inflammatory bowel disease (IBD), with prevalence rates ranging from 36% to 88% [Gisbert and Gomollon, 2008; Gerasimidis, 2011]. In a study evaluating the practice of iron replacement in patients with IBD in Europe, only 18–30% of 1173 patients with CD with iron deficiency anaemia received iron intravenously [Stein *et al.* 2011], whereas international guidelines [Gasche *et al.* 2007] advocate that the intravenous, rather than oral, may be the preferred route of iron administration. However, a prospective multicentre trial of 100 patients with CD or ulcerative colitis (UC) with iron deficiency demonstrated an improvement in iron levels and quality of life regardless of the route of administration [Gisbert *et al.* 2009]. Of the 78 patients with a haemoglobin between 10 and 12 g/dl (women) or between 10 and 13 g/dl (men) treated with oral iron, only 5% developed intolerance, necessitating a switch to the parenteral route. An explanation for the strikingly high rate of tolerance of oral iron in this study may be the relatively low dose used (equating to approximately 100 mg elemental iron). Indeed, when choosing the dose of oral iron to administer, it is important to recognize that a maximum amount of 10–20 mg can be absorbed from the gastrointestinal tract (proximal small bowel) [Rimon *et al.* 2005].

Vitamin B12 deficiency occurs in approximately one-fifth of patients with CD [Yakut *et al.* 2010; Headstrom *et al.* 2008], although this will clearly be higher in patients with loss of absorptive terminal ileal surface due to disease activity or after surgical resection. Although deficiency is thought to occur in all patients after resection of more than 60 cm of terminal ileum [Mowat *et al.* 2011], a small study of 42 patients with resections of between 20 and 60 cm demonstrated abnormal B12 absorption in 52%, highlighting the need to monitor these patients carefully [Duerksen *et al.* 2006]. Recent British Society of Gastroenterology guidelines suggest giving B12 replacement in all patients with ileal resections greater than 20 cm and yearly B12 measurements if less than 20 cm [Mowat *et al.* 2011].

Low serum and red cell folate levels have been reported in up to 28% of patients, particularly in those with active disease [Elsbourg and Larsen,

1979; Hoffbrand *et al.* 1968], though more recent studies using modern laboratory techniques put this much lower at 4.3% [Oldenburg *et al.* 2000]. In addition to poor intake and malabsorption, folate deficiency can also result from competitive inhibition from sulphasalazine use. There is a concern that folate deficiency may be associated with colorectal cancer in patients with UC or colonic CD, possibly secondary hyperhomocysteinaemia, which leads to DNA methylation and DNA instability [Phelip *et al.* 2008]. Observational studies suggest that folate supplementation may be associated with reduced colorectal neoplasia in IBD [Lashner *et al.* 1997], and the recently published British Society of Gastroenterology guidelines [Cairns *et al.* 2010] note that folate supplementation may be beneficial, especially in patients who may have folate deficiency due to sulphasalazine therapy, although these guidelines acknowledge that data supporting this statement are relatively sparse.

Malabsorption rather than dietary insufficiency is the likely main underlying mechanism leading to fat-soluble vitamin deficiencies [Kuwabara *et al.* 2009] which, in turn, can be associated with metabolic bone disorders [Kuwabara *et al.* 2009]. Vitamin D deficiency can, of course, result in osteomalacia. Studies of bone mineral density in patients with CD demonstrate variable rates of osteopaenia and osteoporosis, due to the definitions used, but all show significant reduction in bone health with osteopaenia rates of 23–77% [Abitbol *et al.* 1995; Bjarnason *et al.* 1997; Pigot *et al.* 1992] and osteoporosis rates of 17–30.6% [Bjarnason *et al.* 1997; Compston *et al.* 1987]. As stated, vitamin deficiencies, including vitamin K, are associated with reduced bone density, and other risk factors in IBD include corticosteroid use [Dear *et al.* 2001], jejunal involvement or bowel resection [Robinson *et al.* 1998], stricturing or penetrating disease [Cravo *et al.* 2010], and ongoing inflammation [Paganelli *et al.* 2007]. Vertebral fractures (often asymptomatic) have been demonstrated in 20–22% of patients with CD, including those under 30 years old [Klaus *et al.* 2002]. The exact pathogenesis is unclear but interesting data from 26 patients with CD in remission suggest suppressed bone formation with normal bone resorption, which may provide therapeutic avenues in the future [Schoon *et al.* 2001].

Depletion of vitamin A stores can occur in patients with CD in the absence of any clinical manifestations of this vitamin deficiency, such as night blindness [Bousvaros *et al.* 1998]. As vitamin A is stored entirely in the liver, serum vitamin A is a poor marker of body reserves [Rumi *et al.* 2000], thus making detection of deficiency difficult. Patients with primary sclerosing cholangitis are particularly at risk of deficiencies in vitamin A and other fat-soluble vitamins due to chronic cholestasis [Jorgensen *et al.* 1995]. However, deficiency of vitamin E leading to peripheral neuropathy is a rare clinical occurrence [Bousvaros *et al.* 1998].

Role of diet and Crohn's development

There have been several attempts to use epidemiological data to link dietary factors to onset of CD. A meta-analysis suggested a positive association between high intake of fat, polyunsaturated fatty acids, ω6 fatty acids and meat with risk of developing CD, while higher fruit and fibre intakes appeared to be protective [Hou *et al.* 2011]. However, data are very heterogeneous with predominantly retrospective dietary histories, so it is difficult to clarify the strength of any association.

Nutrition support

Oral nutritional supplementation

For patients with CD who are malnourished, or at risk of malnutrition, oral nutritional supplements (ONS) can be well tolerated, allowing individuals to meet their nutritional requirements with resultant improvements in anthropometry [Harries *et al.* 1983]. European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend up to 600 kcal/day in the form of ONS, suggesting this to be beneficial [Lochs *et al.* 2006].

Enteral tube feeding for nutritional support

If daily nutritional requirements are not adequately met by oral intake, alternative routes such as enteral tube feeding can be used in patients to achieve target intake. In a group of growth-retarded adolescents with CD, nocturnal tube feeding of 1–1.5 liters of non-elemental feed improved weight gain and growth [Aiges *et al.* 1989]. Continuous feeds are preferred to bolus regimes due to the reduced risk of complications [Lochs *et al.* 2006]. For patients requiring long-term enteral tube feeding, gastrostomy insertion is well tolerated in children and adults with CD [Anstee and Forbes, 2000; Cosgrove and Jenkins, 1997].

Parenteral nutrition

There is no evidence that PN provides any benefit over EN as primary therapy for CD (or UC). PN is only indicated for nutritional support in patients with CD if nutrition cannot be optimized using oral or enteral routes alone. Examples may include intestinal failure (IF) due to short bowel syndrome resulting from multiple previous bowel resections or associated with high output stomas or fistulas. It is important that most patients should be allowed to continue oral intake if possible, despite the use of PN. In practice a mixture of oral, enteral and parenteral routes may be used together to achieve the best nutritional status [Woodcock *et al*. 2001].

Preoperative parenteral nutrition

PN may be used to improve nutritional status prior to bowel surgery to improve postoperative outcomes in the malnourished patient when the oral or enteral route cannot be used [Van Gossum *et al*. 2009]. ESPEN guidelines do not give any other specific guidance for the perioperative patient with CD, except to state use of PN should be considered as for any surgical patient [Van Gossum *et al*. 2009].

Postoperative parenteral nutrition

Postoperative PN is principally required for patients who develop IF, defined as 'obstruction, dysmotility, surgical resection, congenital defect or disease associated loss of absorption, characterised by the inability to maintain protein energy, fluid, electrolyte or micronutrient balance' [O'Keefe *et al*. 2006].

IF has been classified into three types [Lal *et al*. 2006]. Type 1 IF is transient and occurs in patients who develop a postoperative ileus and may require short-term intravenous nutrition, although this is often not needed. Type 2 IF describes patients with complex disease, often with septic, metabolic and nutritional complications, for which a multidisciplinary approach is essential, using the 'SNAP' algorithm (treat Sepsis, support Nutrition, demonstrate Anatomy and Plan future management) [Lal *et al*. 2006]. These patients may require long periods of PN, often in specialist centres or at home. Type 3 IF includes patients with more stable disease on long-term home PN, who may be candidates for intestinal transplantation.

Enteral nutrition as primary therapy

There is evidence to suggest that EN can induce and maintain remission in children and adults with CD [Zachos *et al*. 2007] but not with UC [Lochs *et al*. 2006]. Though corticosteroids are often used in adults to induce remission, it is important to recognize that these medications carry significant risks and do not necessarily lead to mucosal healing [Rutgeerts, 2001]. EN is often used as first-line therapy to induce remission in children [Lochs *et al*. 2006], not least because this approach is associated with growth and minimal side effects compared with steroids [Belli *et al*. 1988] and may be associated with mucosal healing [Borrelli *et al*. 2006], although this has not been confirmed [Afzal, 2004]. By contrast, EN may be underused as a primary therapeutic option in adults, partly due to compliance issues.

Induction of remission: enteral nutrition

Initial data suggesting a role for EN came from a small uncontrolled study of 13 patients who received an elemental diet to improve nutritional status prior to surgery [Voitk *et al*. 1973]. While weight gain and improved nutrition parameters were observed, there also appeared to be an anti-inflammatory effect. A further small series of patients with protein-calorie malnutrition due to extensive small bowel Crohn's demonstrated similar results with reduced protein and lymphocyte loss from the gut [Logan *et al*. 1981].

Since then, there have been multiple trials and meta-analyses evaluating the role of EN as primary therapy in CD, but often with small numbers and heterogenous groups of patients. With these caveats in mind, the most recent meta-analysis has demonstrated a significant benefit of steroids over EN for inducing remission in CD (OR 0.36, 95% CI 0.23–0.56, with number needed to treat of 4) [Zachos *et al*. 2007]. When only data for 'higher quality' studies were assessed (based on randomization, blinding and description of withdrawals and dropouts), there was no significant difference between steroids and EN. However, this finding should be interpreted with caution due to the low numbers of patients and the heterogenous nature of the studies included. Indeed, EN should be considered in appropriate patients. The challenge, however, is to know who these are: there are no trials comparing EN *versus* placebo; it is unclear how long exclusive EN is needed; and data are very heterogeneous with regards to response related to disease distribution

[Wilschanski *et al.* 1996; Afzal, 2009, Buchanan *et al.* 2009, Rubio *et al.* 2011].

EN as primary therapy has been evaluated in various formulations, including elemental and polymeric feeds. Elemental feeds consist of nutrition in its simplest form, for example, single amino acids, as opposed to oligopeptide 'semi-elemental' or full protein polymeric feeds. Elemental feeds were originally designed by the National Aeronautics and Space Administration (NASA) as easily digestible, water-soluble foods that produced smaller faecal bulk when consumed in space [Winitz *et al.* 1965]. There is clear evidence that elemental feeds have a primary anti-inflammatory effect in CD, with evidence of improved intestinal permeability [Teahon *et al.* 1991], reduced inflammatory cytokine production [Yamamoto *et al.* 2005; Sanderson and Croft, 2005] and mucosal healing [Yamamoto *et al.* 2005], although only when given exclusively [Johnson, 2006]. Various theories have been proposed as to how these benefits are rendered [O'Sullivan and O'Morain, 1998], but a definitive answer is lacking. The most popular theory was that elemental diets had a reduced antigenic load to the inflamed bowel compared with full protein feeds [O'Sullivan and O'Morain, 1998]. However, this may not be the case because polymeric feeds have since been found to be equally efficacious [Zachos *et al.* 2007; Grogan *et al.* 2012]. In addition, because polymeric feeds are more palatable than elemental feeds, the former tend to be used first line. It has been further suggested that the anti-inflammatory properties of enteral feeds relate to their fat content, with emerging evidence that lower fat feeds are more efficacious [Gassull *et al.* 2002]. Indeed modification of various dietary components, such as reducing long-chain triglyceride content [Zachos *et al.* 2007] or enrichment with fish oils [MacLean *et al.* 2005] have been evaluated but studies are small and results equivocal. For example, subgroup analysis in a Cochrane review of six studies did not demonstrate a statistically significant difference in remission rates between low and high long-chain triglyceride feeding formulae (OR 1.39, 95% CI 0.78–2.48) [Zachos *et al.* 2007].

Enrichment of enteral feeding with transforming growth factor β, a key regulatory peptide in immunoregulation, is a promising new development. Supported by evidence of efficacy from the paediatric literature [Rubio *et al.* 2011], there has only been one fully published trial in adult patients with CD [Triantafillidis *et al.* 2006]. In an uncontrolled observational study of patients with active CD given 4 weeks of exclusive Modulen IBD (Nestlé, Lausanne, Switzerland), 11 out of 29 patients were in remission [as defined by Crohn's Disease Activity Index (CDAI) < 150] and a further 8 had a response (CDAI drop > 50) [Triantafillidis *et al.* 2006]. Larger, randomized, controlled trials are clearly needed to verify these data.

In summary, EN can play a role in inducing remission in adult patients with CD, but further work is needed not just to define the phenotype of patients likely to respond, the duration of treatment required and the most beneficial formulae, but also to evaluate the putative mechanism by which EN modifies the inflammatory response. In addition, there is marked variation in use of EN between paediatric and adult gastroenterologists in the UK, reflected in the recent National Institute for Health and Clinical Excellence (NICE) guidance [NICE, 2012], and even between paediatric gastroenterologists in Europe and America, the latter with low uptake [Stewart, 2011]. This is unlikely to change without more robust data to support regular use of EN.

Maintenance of remission: enteral nutrition

While induction of remission can be achieved with EN, use of exclusive EN for longer term disease maintenance is more challenging due to compliance issues.

Uncontrolled, prospective data have suggested maintenance of CD can be prolonged by the addition of EN to an unrestricted normal diet [Koga *et al.* 1993; Verma *et al.* 2000]. These lent support to previous retrospective data in children and adolescents, demonstrating prolonged remission (and also improved growth) if patients received nocturnal nasogastric feeding [Wilschanski *et al.* 1996].

There have only been two randomized controlled trials assessing EN as maintenance therapy in CD [Verma *et al.* 2001; Takagi *et al.* 2006]. The first of these [Verma *et al.* 2001] gave 33 patients with steroid-dependent CD (two failed attempts to wean steroids) either an elemental or a polymeric diet to make up 30–50% of their requirements. Response was defined as successful withdrawal of steroids without a CDAI increase of more than 100 points to a score greater than 200 and avoidance of surgery; this was achieved in 14 of the 27 patients who tolerated the feed. Subsequently an

open-label extension allowed the 14 'responders' to choose whether or not to remain on enteral supplements. Of the seven patients who chose to return to an unrestricted diet, all relapsed within 4 months, requiring further steroids, whereas six of the seven patients who continued on enteral supplements remained in remission at 24 months.

The second paper by Tagaki and colleagues randomized a group of 51 patients with CD in remission to receive either a 'free diet' or half elemental diet [Takagi *et al*. 2006]. At 2 years, relapse rates were lower for those receiving enteral feed (hazard ratio 0.40, 95% CI 0.16–0.98) after multivariate adjustment for age, sex, disease duration, disease site and mean baseline CDAI.

As with induction of remission, identification of factors that predict which patients will respond would facilitate a targeted approach. A retrospective study of 145 patients in remission, with two-thirds receiving maintenance EN, identified penetrating CD (RR 3.89; 95% CI 1.58–9.62), colonic involvement (RR 3.10; 95% CI 1.39–6.90) and previous history of surgery (RR 2.48; 95% CI 1.16–5.33) to be factors that predicted recurrence [Esaki *et al*. 2006]. Recurrence rates were high (42/98 EN group *versus* 29/47 normal diet; $p = 0.047$), and it is difficult to assess the applicability of these data since remission was induced with PN and the only other therapy used was 5-aminosalicylic acid drugs.

While there are no studies comparing EN with immunomodulators for CD maintenance, one study has looked at the effect of using EN as an adjunct to biological therapy. EN provided at approximately half of the daily energy requirement over 56 weeks, in addition to infliximab maintenance therapy, did not alter clinical remission rates [Yamamoto *et al*. 2010], which may not be an unexpected finding given that EN tends to be used in relatively mild disease [Lochs *et al*. 2006], whereas infliximab is used in patients with CD at higher risk of relapse.

Postoperative recurrence rates of CD are high, with symptomatic recurrence rates of 20% and endoscopic recurrence rates of 73% of patients within 1 year following surgery [Rutgeerts *et al*. 1990]. A prospective, non-randomized trial studied recurrence in 40 patients with CD after either ileal or ileocolonic resection, using EN (*versus* normal diet) for disease maintenance [Yamamoto *et al*. 2006]. Maintenance of EN over 12 months was associated with reduced clinical (5% *versus* 35%, $p = 0.048$) and endoscopic (30% *versus* 70%, $p = 0.027$) recurrence compared with the non-EN group. Notably, all 20 patients with EN completed this study, which represents an unusually low dropout rate, likely reflecting patient selection preoperatively.

Concerns have also arisen as to whether long-term EN for CD maintenance may impair quality of life because of the restrictive nature of the dietary intervention or the need for repeated nasogastric tube intubations. Tagaki and colleagues found no difference in quality of life (as measured by the short IBD questionnaire) in patients maintained on EN *versus* those that continued a normal diet [Takagi *et al*. 2009]. Furthermore, multivariate analysis demonstrated EN to be independently associated with improvement of health-related quality of life in patients with CD with disease duration of over 10 years [Kuriyama *et al*. 2009].

Maintenance of remission: dietary modification

A variety of dietary modifications and measures have been evaluated in maintaining CD remission. For example, fish oils, which are a major source of ω3 fatty acids, have been shown to have specific anti-inflammatory properties in a variety of diseases [Wall *et al*. 2010]. However, a Cochrane review of six trials failed to demonstrate a clear clinical benefit of using fish oils in CD maintenance [Turner, 2009]. Though pooled results from all studies favoured the use of ω3 fatty acids (RR 0.77, 95% CI 0.61–0.98, $p = 0.03$), a combination of all studies showed statistically significant heterogeneity. In addition, due to a large dropout rate, 'estimated' rates of relapse were calculated, which were nonsignificant (RR 0.59, 95% CI 0.34–1.03, $p = 0.06$). Furthermore, combined results from the two largest and rigorous trials, EPIC-1 and EPIC-2, reported in the same manuscript [Feagan *et al*. 2008], failed to reach statistical significance (RR 0.88, 95% CI 0.74–1.05).

An 'elimination–reintroduction' diet was one of the earliest described modification diets evaluated for disease maintenance in CD. 'Elimination' involves remission induced by elemental feeds, followed by careful and slow 'reintroduction' of single food types to enable identification of those that precipitate symptoms. Evidence of efficacy of this approach derives from a trial of 93 patients who, after achieving remission with elemental

feed, were randomly assigned to either receive tapering steroids over 3 months with standard dietary advice or to reintroduction of a single food type per day, excluding those that induced symptoms [Riordan *et al.* 1993]. Relapse rates (as defined by Harvey-Bradshaw Index scores greater than 6) were high in both groups at 2 years, but were significantly better in the reintroduction group (62% *versus* 79%, $p = 0.048$). However, the latter group needed 12 visits to dieticians during the 2 year period, which has service cost implications. An alternative is the low-fibre, fat-limited exclusion (LOFFLEX) reintroduction diet, [Woolner *et al.* 1998] which involves a faster reintroduction phase of varied food types, instead of single food types, after EN-induced remission. The LOFFLEX approach was developed after observations that a patient with CD often developed symptoms after ingestion of foods that were high in fibre and fat. In an open-label study of this approach, in which patients chose which diet to use, 2-year remission rates for 76 patients were noninferior to a single-food type reintroduction diet (56% *versus* 59%), but with good compliance rates (8.3% noncompliant with LOFFLEX *versus* 14.3% with single-food type reintroduction) [Woolner *et al.* 1998].

An alternative dietary modification known as the 'FODMAP' (fermentable, oligo-, di-, monosaccharides and polyols) diet has also been evaluated in CD. Examples of FODMAP-containing foods include fructose (apples, pears, corn syrup), lactose (dairy products, soft cheeses), fructans and galactans (wheat, cabbage, broccoli, watermelon) and polyols (apples, apricots, cauliflower, sorbitol). Symptoms were assessed in 52 patients with CD at 3–6 months after initiation of FODMAP restriction, with an improvement in 56% [Gearry *et al.* 2009]. Though this was a retrospective questionnaire-based study, trials comparing a low-FODMAP diet with a control group or other diets have not yet been published. Furthermore, FODMAP diets are relatively restrictive, so concerns have been raised about nutrient deficiencies associated with these diets.

It is unclear whether dietary exclusion–reintroduction diets or FODMAP diets maintain remission through persistence of mucosal healing or are of predominant symptomatic benefit by alleviating 'functional' symptoms. FODMAP diets have been shown to be efficacious in patients with irritable bowel syndrome [Staudacher *et al.* 2011], and it is likely that they also reduce functional symptoms in patients with CD, possibly by reducing the osmotic load and bacterial fermentation associated with the food delivered [Gibson and Shepherd, 2010], rather than having a primary anti-inflammatory effect.

Conclusion

Nutritional deficiencies in patients with CD are common. It is important that use of malnutrition screening tools, such as MUST [Elia, 2003] is embedded into routine practice. In addition, there should be a low threshold to investigate for specific micronutrient deficiencies, particularly common abnormalities such as iron deficiency anaemia. IBD standards state all patients should have access to dieticians, both for nutritional support and consideration of primary therapy [IBD Standards Group, 2009]. Although the first IBD audit demonstrated low rates of uptake, more recent data suggest this has improved, at least when considering availability of dietitians, which is reported to be in 97% of hospital sites taking part in the audit [Royal College of Physicians, 2011].

Nutritional support should be provided by oral or enteral means wherever possible, reserving PN for patients with intestinal failure and, in rare cases, for perioperative optimization when oral nutrition or EN is unsuccessful.

For primary therapy, EN should be considered in patients with mild to moderate CD to induce remission. Polymeric diets are better tolerated than and as equally efficacious as elemental feeds, but the role of enriched feeds needs further clarification. Other unanswered questions are the optimal duration of exclusive EN and the phenotype of disease that will derive most benefit. Nevertheless, EN can be a very useful treatment in motivated patients. In addition, using EN as a third to half of diet appears to prolong maintenance of CD, although data are few. There is no role for PN to either induce or maintain remission.

Finally current dietary modifications do not provide any prognostic benefit but may be of value in addressing symptom control.

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